CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-450

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL DIVISION: Neuropharmacological Drug Products (HFD-120)
BIOMETRICS DIVISION: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-450

DRUG NAME: Zomig (zolmitriptan) Nasal Spray

INDICATION: Treatment of migraine with/without aura in adults

SPONSOR: AstraZeneca Pharmaceuticals LP

DOCUMENTS REVIEWED: Cover letter and documents (CDER REC'D Dates: 27-Mar-2003, 17-Apr-2003 and 25-Apr-2003) including SAS data base

STATISTICAL KEY WORDS: χ^2-test, logistic regression, odds ratio, Bonferroni adjustment, spending function, interim analysis

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STATISTICAL REVIEW AND EVALUATION

1 Executive Summary of Statistical Findings

1.1 Recommendations and Conclusions

Based on the collective evidences and findings, in this statistical reviewer's opinion the interim data and results of study 311CUS/0022 support the sponsor's efficacy claim of ZOMIG® (zolmitriptan) 5 mg nasal with respect to the headache response endpoint for the adult patients with migraine, using first attack analysis. The data and results of the study show that the primary endpoint, 2 hour headache response, is statistically significantly improved in the treatment arm to the placebo arm for the intention-to-treat (ITT) population (p-value=0.0006).

There was no statistically significant differences demonstrated for Zolmitriptan Nasal Spray dose of 5.0 mg to placebo in the secondary variable of nausea at 2 hours post dose. There was statistically significant differences demonstrated for Zolmitriptan Nasal Spray doses of 5.0 mg to placebo in the secondary variable of photophobia at 2 hours post-dose. There was no evidence to demonstrate the statistically significant difference for Zolmitriptan Nasal Spray dose of 0.5 mg to placebo in phonophobia at 2 hours post-dose.

Those results are consistent with the original NDA submission of Zolmitriptan Nasal Spray. We therefore recommend Approval for the treatment of adult patients with migraine.

1.2 Brief Overview of Clinical Studies

The zolmitriptan nasal spray NDA 21-450 was submitted on February 27, 2002. In the action letter dated December 19, 2002, FDA classified the submission as 'approvable'. Additional information was requested from AstraZeneca to address concerns regarding the clinical efficacy of the commercial zolmitriptan nasal spray device. At a teleconference (February 11, 2003), FDA agreed that the provision of efficacy data from an ongoing, placebo-controlled clinical trial using the commercial zolmitriptan nasal spray device (311CUS/0022) was an acceptable approach.

This interim analysis consists of results from a subset of the Study 311CUS/0022 in 210 adult patients who treated the first headache attack with study medication and provided efficacy assessments. This sample size provided adequate power (for 2-hour headache response) to show superiority over placebo and confirm the clinical efficacy of the zolmitriptan 5-mg commercial nasal spray device.

The primary objective for this interim analysis is to evaluate the efficacy (as assessed by the 2 hour headache response) of zolmitriptan 5-mg nasal spray compared to placebo in the acute treatment of adult patients with migraine, using

first attack analysis. The primary endpoint is the 2-hour headache response of the first treated attack.

The sponsor planned an adjustment for Type I error for both the interim and final full studies. The alpha spending function methodology based on Hwang, Shih, and deCani (1990) γ-family approach was used to control the overall two-sided type I error rate at 5% for both the interim and final analyses. The 2-sided significance boundaries for the p-values were calculated and pre-specified to be 0.0027 and 0.0479 (based on $\gamma = -2$ and information fraction of t=15%) for the interim and the final analyses, respectively. That is, the statistical significance of the analysis results for the primary efficacy parameter of 2-hour headache response was tested against significance level of 0.0027 for the interim and 0.0479 for the final analyses, respectively.

The first 210 adult men and women who treated the first migraine attack with study medication, and who had an established diagnosis of migraine headache, with or without aura, as defined by IHS criteria were included in this analysis. This sample size provided approximately 90% power of showing a difference (at 0.27% two-sided level of significance) in headache response rate between the zolmitriptan 5-mg nasal spray dose and placebo at 2 hours after treatment. Calculations were based on the assumption that the headache response rate at 2 hours would be 39% for placebo and 69% for zolmitriptan 5-mg nasal spray.

Reviewer's Comments:

This statistical reviewer used EaSt 2000 statistical software to verify α adjustment for the interim and final analyses and summarized the results in Table 1. The calculation was based on the overall significance level = 0.05, power = 90%, proportion response of control = 6%, and proportion response of treatment = 11% which were used by the sponsor for sample size determination of the full study.

Table 1. α Adjustment for Interim and Final Analyses — FDA Analysis

Boundary to Reject H_0 (Δ)	Maximum Subjects (n)	For Interim Analysis (α)	For Final Analysis (α)
0.0	1307	0.0000	0.0500
0.1	1316	0.0000	0.0500
0.2	1331	0.0003	0.0498
0.3	1354	0.0014	0.0489
0.4	1386	0.0055	0.0454
0.5	1427	0.0144	0.0374

This statistical reviewer has the following comments.

- From Table 1, the boundaries to reject H_0 $\Delta = 0.0$ and 0.5 are corresponding to O'Brien-Fleming and Pocock boundaries, respectively. The α=0.0027 and 0.0479 of interim and final analyses used by the sponsor is corresponding to a boundary which is between 0.3 and 0.4.

- All requested maximum subjects for $\Delta = 0.0$ to 0.5 are smaller than n = 1592 which was planned by the sponsor for the full study.

- The number of planned looks is 2 which is including the final look.

1.3 Statistical Issues and Findings

Statistical Issues:

- In the primary analysis, the endpoint was defined as 2 hours. If there was a missing data at the endpoint, the last observation would be carried forward (LOCF), i.e., the last post-treatment measurement was used in the analysis. In the confirmatory analysis, missing data at each time point was not imputed and the analysis was based on only the subjects who completed measurements. The sponsor did not use LOCF algorithm for the primary efficacy analysis. This statistical reviewer used LOCF algorithm to confirm the sponsor's results.
- In the confirmatory analyses, the secondary efficacy variables: headache responses at the time point 1 hour and 4 hours supported the primary efficacy result. However, a comparative analysis for the usual migraine-associated symptoms of Nausea, Photophobia and Phonophobia did not support the primary efficacy analysis. Clinically, those symptoms are highly associated with migraine.
- There were multiple comparisons in the secondary analyses. The NDA submission did not adjust the overall significance level (α=0.05) for the comparisons of secondary endpoints.

Findings:

Table 2 gives the summary of efficacy results of primary endpoint, the 2-hour headache response of the first treated attack, for the ITT population. A total of 108 patients on the zolmitriptan nasal spray 5 mg arm and 102 patients on the placebo arm were included in the efficacy analysis. The number of patients with headache response at 2-hour were 76 (70.4%) and 48 (47.1%) in the two arms, respectively. There was a statistically significant difference (p=0.0006) between the two treatment groups.

Table 2. Primary endpoint: Headache response at 2 hours — first attack (zolmitriptan nasal spray vs. placebo): FDA Analysis

	Zolmitriptan nasal spray 5.0 mg	Placebo
	(N = 108)[a]	(N = 102)
Patients evaluated at 2 h (n)[b]	108	100
Patients with headache response at 2 h (%)[c]	76 (70.4)	48 (47.1)
p-value[d]	0.0006	
Odds ratio[e]	2.67	
95% confidence limits[e]	(1.5, 4.9)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients received trial medication and treated a migraine attack.

[b] Two patients from placebo group were not evaluated: One patient had missing data at 2 hour; the other patient had taken escape medication before 2 hours when migraine headache pain was mild.

[c] Headache response is as a reduction in headache intensity from moderate or severe to mild or none.

[d] P-value is calculated by chi-square test.

[e] Odds ratio and 95% confidence limits (CI) are estimated by SAS FREQ procedure.

Reviewer's Comments:

The sponsor's efficacy claim was based on the ITT population which was not including two patients randomized but not evaluated at 2 hour: One patient had missing data at 2 hour and the other patient had taken escape medication before 2 hours when migraine headache pain was mild. This statistical reviewer used LOCF algorithm for the efficacy analysis, which included the two patients.

2 Introduction

2.1 Overview

Zolmitriptan is a potent and selective 5-$HT_{1B/1D}$ receptor agonist that has been developed for the acute treatment of migraine headache with or without aura. It was originally produced in conventional oral tablet form, and in this form was approved for use in the acute treatment of migraine in the United States (NDA 20-768, approved November 25, 1997) and most of Europe. More recently, an orally disintegrating tablet of zolmitriptan (ZOMIG FASTMELT) has been developed and is used in some European countries and the United States (ZOMIG-ZMT, NDA 21-231, approved on February 13, 2001). This formulation dissolves rapidly in the mouth and dose not need to be swallowed with water, and may thus often more convenient dosing, particularly in the patients who suffer nausea and/or vomiting as part of a migraine attack.

2.1.1 Background

Migraine is a debilitating and recurring disease affecting approximately 18.2% of women and 6.5% of men in the United States population (Stewart et al 2001). The typical migraine is characterized by a throbbing headache that is usually unilateral, made worse by movement, and is often associated with nausea, vomiting, photophobia, and phonophobia. Attacks may be preceded by an aura in which transient focal neurological symptoms, usually visual disturbances, occur (Jensen et al 1986).

The pharmacotherapy of migraine includes prophylaxis to reduce the frequency and severity of attacks, but the incomplete effectiveness and potential side effects of prophylactic drugs mean that symptomatic treatment of attacks is the usual approach. Symptomatic treatment of migraine has been revolutionized in the last decade by the advent of the triptans. Zolmitriptan, a nonsulphonamide synthetic analogue of 5-HT acts as a selective agonist at the 5-HT$_{1B/1D}$ receptor subtype. In vitro studies have shown that zolmitriptan has a high affinity for both human 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors, with approximately a 10-fold selectivity for the former. Zolmitriptan is not recognized by other 5-HT receptors, with the exception of a modest affinity at the human 5-HT$_{1A}$ receptor, and is also devoid of pharmacological activity at a wide variety of monoamine receptors (zolmitriptan investigator's brochure [IB]).

Peripheral inhibitory effects on the trigeminovascular system, characterized by the vasoconstriction of the cranial blood vessels can be observed after the administration of zolmitriptan (Plosker 1994). Data from animal models have indicated that zolmitriptan has the ability to inhibit the trigeminovascular system at central sites because it can cross the blood-brain barrier and access the 5-HT$_{1D}$ receptor thereby inhibiting the activated central components of the trigeminovascular system within the trigeminal nucleus caudalis (Goadsby and Hoskin 1995; Mills et al 1995). Zolmitriptan is also thought to inhibit neuropeptide release after trigeminal activation (Goadsby and Edvinsson 1994).

Most triptans are taken orally, but absorption of some oral triptans is affected by the gastric stasis experienced by many migraineurs. Consequently, other, non-oral routes of administration are desirable. Compared with the oral route, intranasal may permit faster and more complete absorption, and avoid first-pass metabolism. These characteristics may be associated with faster onset of action, which would be valuable to all migraineurs, not just those who are unable to take treatments orally. Intranasal administration is also more acceptable to most patients than subcutaneous injection.

Zomig (zolmitriptan), developed as an oral tablet, and as an orally disintegrating tablet, was approved by FDA as being safe and effective for the acute treatment of

migraine attacks with and without aura in adults. The oral tablet has been approved for marketing in more than 75 countries worldwide. A nasal spray formulation is currently marketed as the commercial device in Austria, Germany, Sweden, and the United Kingdom.

2.1.2 Major Statistical Issues

The major statistical issues can be found in Section 1.3.

2.2 Data Sources

The data sets analyzed were submitted by the sponsor on March 27 and April 17, 2003. All data sets analyzed are electronic documents and located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "27-MAR-2003" and "17-APR-2003", respectively. The main data set for the efficacy analysis is "DIARYV" which describes the Diary card.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

This interim analysis was used for efficacy evaluation. The data was from an ongoing, placebo-controlled clinical trial using the commercial zolmitriptan nasal spray device (311CUS/0022) that FDA agreed to be an acceptable approach as the additional information for the approvable zolmitriptan nasal spray NDA 21-450. The interim analysis consists of results from a subset of the Study 311CUS/0022 in 210 adult patients who treated the first headache attack with study medication and provided efficacy assessments. All 210 patients consist of the ITT population for the primary efficacy analysis.

3.1.1 Interim Analysis of Study 311CUS/0022

3.1.1.1 Introduction

Study 311CUS/0022 was a multi-center, randomized, double-blind, parallel-group, placebo-controlled trial to compare the efficacy and tolerability of the zolmitriptan 5-mg nasal spray dose and placebo in the acute treatment of migraine. The trial is being conducted at 162 investigation sites in the United States. Evaluable patients were those who treated at least 1 migraine headache with trial treatment (up to 2 migraine headaches can be treated with study medication). Evaluable patients for the interim analysis were the first 210 patients from 36 centers who treated the first migraine headache and provided efficacy assessments.

3.1.1.2 Statistical Issues

The major statistical issues can be found in Section 1.3.

3.1.1.3 Study Objectives

- **Full Study Objective:** The primary objective of the study was to evaluate early efficacy (as assessed by the percentage of responders) of a zolmitriptan 5-mg nasal spray dose in the acute treatment of adult patients with migraine. The secondary objective of this study was to further evaluate the efficacy, safety, and tolerability of the zolmitriptan 5-mg nasal spray dose in the acute treatment of migraine.

- **Interim Analysis Objective:** The primary objective was to evaluate the efficacy (as assessed by the 2 hour headache response) of zolmitriptan 5-mg nasal spray compared to placebo in the acute treatment of adult patients with migraine, using first attack analysis. Secondary objectives were to evaluate headache response at 15 minutes, 30 minutes, 1 hour, and 4 hours using the first attack, and to evaluate the resolution of migraine-associated symptoms (nausea, photophobia, and phonophobia) at 2 hours.

3.1.1.4 Efficacy Endpoints

- **Full Study Efficacy Endpoints:** The primary efficacy endpoints were to be headache response at 15 minutes, 30 minutes, 1 hour, and 2 hours after initial treatment with trial medication. Headache response is defined as an improvement in migraine headache intensity from severe or moderate to mild or none. The primary analysis of the efficacy endpoints will be based on the first attack data.

- **Interim Analysis Efficacy Endpoints:** The primary efficacy measurement was headache response at 2 hours after initial treatment of the first attack with trial medication. Headache response was defined as an improvement in migraine headache intensity from severe or moderate to mild or none. In addition, the following secondary endpoints were assessed: headache response rate at 15 minutes, 30 minutes, 1 hour, and 4 hours after treatment resolution of non-headache symptoms of migraine (i.e., nausea, photophobia, and phonophobia) at 2 hours after treatment.

3.1.1.5 Sample Size Considerations

- **Sample Size for Full Study:** Approximately 1592 adult men and women who had an established diagnosis of migraine headache, with or without

aura, as defined by the International Headache Society (IHS) criteria were to be enrolled to obtain 1384 evaluable patients (692 patients per treatment group). Assuming a 13% rate of withdrawal and unevaluable patients (withdrawal rate from 311IL/0077), this sample size provided a 90% chance of showing a difference (at a 0.5% level of significance) in headache-response rate between the zolmitriptan 5-mg nasal spray dose compared to placebo 15 minutes after treatment. Calculations were based on the assumption that the headache response rate at 15 minutes would be 6% for placebo and 11% for zolmitriptan 5-mg nasal spray.

- **Sample Size for Interim Analysis:** For this Interim Analysis, a correction for Type I error for both the interim and final full study was planned. The alpha spending function methodology based on Hwang, Shih, and deCani (1990) γ-family approach was used to control the overall two-sided type I error rate at 5% for both the interim and final analysis. The 2-sided significance boundaries for the p-values were calculated and pre-specified to be 0.0027 and 0.0479 (based on γ=-2 and information fraction of t=15%) for the interim and the final analysis, respectively. That is, the statistical significance of the analysis results for the primary efficacy parameter of 2-hour headache response was tested against significance level of 0.0027 for the interim and 0.0479 for the final analysis.

- The first 210 adult men and women who treated the first migraine attack with study medication, and who had an established diagnosis of migraine headache, with or without aura, as defined by IHS criteria were included in this analysis. This sample size provided approximately 90% power of showing a difference (at 0.27% two-sided level of significance) in headache response rate between the zolmitriptan 5-mg nasal spray dose and placebo at 2 hours after treatment. Calculations were based on the assumption that the headache response rate at 2 hours would be 39% for placebo and 69% for zolmitriptan 5-mg nasal spray.

3.1.1.6 Stratification

There was no stratification for the full study.

3.1.1.7 Interim Analysis

The interim analysis results are presented in this statistical review.

3.1.1.8 Efficacy Analysis Methods

The sponsor described their statistical methods for the Interim Analysis as follows.

The Interim Analysis of the efficacy endpoints was based on the principle of intention-to-treat (ITT). The ITT population was all patients who used trial treatment and provided baseline and post-baseline efficacy data for the same efficacy parameter, for first attack migraine attack treated. The primary efficacy endpoint for this Interim Analysis was headache response at 2 hours. Headache response is defined as an improvement in migraine headache intensity from severe or moderate to mild or none.

The analysis plan for this Interim Analysis was based on the first attack data. For the primary endpoint of headache response at 2 hours, between-treatment group comparisons for the first attack were performed using the logistic regression method with treatment, region (mid-Atlantic, mid-West, New England, South, Southwest, West), and baseline intensity in the model. Due to the small sample size in the New England region, the statistical model did not fit properly; therefore, this region was merged with the nearest geographical region, the mid-Atlantic region, in the final model. The analysis results were presented in terms of odds ratios for the treatment effects, the associated 95% confidence intervals, and the corresponding p-values. The results of this statistical comparison were tested against a 2-sided significance level of 0.0027. No formal Interim Analysis was performed on headache response at 4 hours, 1 hour, 30 minutes, or 15 minutes, but a summary of response rates at these time points was provided.

Resolution of non-headache symptoms of migraine (nausea, photophobia, and phonophobia) were subjected to formal interim statistical analysis at 2 hours. The same logistic regression method with treatment, region, and baseline intensity in the model as for the analysis of the 2-hour response was used for these analyses. Since these were secondary analyses, nominal p-values were provided and no statistical adjustment for these secondary comparisons were made.

3.1.1.9 Sponsor's Results and Statistical Reviewer's Findings/Comments

The sponsor defined the ITT population as all patients who used trial treatment and provided baseline and post-baseline efficacy data for the same efficacy parameter, for first attack migraine attack treated. Therefore, the sponsor's efficacy claim was based on the ITT population which was not including two patients randomized but not evaluated at 2 hour: One patient had missing data at 2 hour and the other patient had taken escape medication before 2 hours when migraine headache pain was mild. This statistical reviewer used LOCF algorithm for the efficacy analysis, which included the two patients.

3.1.1.9.1 Baseline Characteristics

Table 3 shows the key baseline demographic characteristics for the ITT population by treatment arm. All characteristics showed balance between the two treatment arms .

A total of 210 patients with a history of migraine headaches were randomized into this study and included in the Interim Analysis. Of these, 108 patients received zolmitriptan and 102 received placebo. All 210 patients treated a migraine attack with at least 1 dose of study medication and provided at least 1 set of baseline and post-baseline assessments.

Table 3. Demographic characteristic --- ITT population

Demographic characteristic	Treatment group	
	Zolmitriptan 5-mg nasal spray (N = 108)	Placebo (N = 102)
Age (y)		
Mean	38.6	40.4
Sex, number of patients (%)		
Women	89 (82.4)	87 (85.3)
Men	19 (17.6)	15 (14.7)
Race, number of patients (%)		
Caucasian	72 (66.7)	69 (67.7)
Black	28 (25.9)	29 (28.4)
Hispanic	4 (3.7)	4 (2.9)
Asian	2 (1.9)	1 (1.0)
Other[a]	2 (1.9)	0
Average number of attacks per month[b]		
Mean (SD)	3.7 (1.1)	3.6 (1.1)
Range	2 - 6	2 - 6

The sponsor's results confirmed by the statistical reviewer.

[a] Other includes any special subgroups.

[b] This applied to the 3 months prior to study entry.

3.1.1.9.2 Primary Efficacy Analyses

Table 4 gives the summary of efficacy results of primary endpoint, the 2-hour headache response of the first treated attack, for the ITT population. A total of 108 patients on the zolmitriptan nasal spray 5 mg arm and 102 patients on the placebo arm were included in the efficacy analysis. The number of patients with headache response at 2-hour were 76 (70.4%) and 48 (47.1%) in the two arms, respectively. There was a statistically significant difference (p=0.0006) between the two treatment groups.

Table 4. Primary endpoint: Headache response at 2 hours ---- first attack (zolmitriptan nasal spray vs. placebo): FDA Analysis

	Zolmitriptan nasal spray 5.0 mg	Placebo
	(N = 108)[a]	(N = 102)
Patients evaluated at 2 h (n)[b]	108	100
Patients with headache response at 2 h (%)[c]	76 (70.4)	48 (47.1)
p-value[d]	0.0006	
Odds ratio[e]	2.67	
95% confidence limits[e]	(1.5, 4.9)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients received trial medication and treated a migraine attack.

[b] Two patients from placebo group were not evaluated: One patient had missing data at 2 hour; the other patient had taken escape medication before 2 hours when migraine headache pain was mild.

[c] Headache response is as a reduction in headache intensity from moderate or severe to mild or none.

[d] P-value is calculated by chi-square test.

[e] Odds ratio and 95% confidence limits (CI) are estimated by SAS FREQ procedure.

Reviewer's Comments:

The sponsor's efficacy claim was based on the ITT population which was not including two patients randomized but not evaluated at 2 hour: One patient had missing data at 2 hour and the other patient had taken escape medication before 2 hours when migraine headache pain was mild. This statistical reviewer used LOCF algorithm for the efficacy analysis, which included the two patients.

3.1.1.9.3 Secondary Efficacy Analyses

Table 5 and Table 6 summarize the secondary efficacy analyses of the headache response at 15 minutes, 30 minutes, 1 hour, and 4 hours using the first attack, and the three migraine-associated symptoms: nausea, photophobia and phonophobia for ITT population.

Table 5 shows that there was no significant difference for headache response between zolmitriptan nasal spray 5.0 mg and placebo arms at the 15 minutes and 30 minutes (p-value=0.407 and 0.033, respectively) and there were significant differences between zolmitriptan nasal spray 5.0 mg and placebo at 1 hour and 4 hours (p-value=0.019 and <.0001, respectively). The probability of the type I error had a decreasing trend when the observed time was increased.

Table 6 shows that there were no significant differences for nausea, photophobia, and phonophobia symptoms between zolmitriptan nasal spray 5.0 mg and placebo at 2 hours (p-value=0.080, 0.026, and 0.170, respectively).

Table 5. Secondary endpoint: Headache response at each time point (zolmitriptan nasal spray vs. placebo): FDA Analysis

	Zolmitriptan nasal spray 5.0 mg	Placebo
	(N = 108)[a]	(N = 102)
15 minutes		
Headache response at the time point (%)[b]	18 (16.8)	13 (12.8)
p-value[c]	0.407	NA
Odds ratio (95% CI)[d]	1.38 (0.6, 3.3)	NA
30 minutes		
Headache response at the time point (%)[b]	40 (37.4)	24 (23.8)
p-value[c]	0.033	NA
Odds ratio (95% CI)[d]	1.92 (1.0, 3.7)	NA
1 hour		
Headache response at the time point (%)[b]	58 (54.7)	38 (38.4)
p-value[c]	0.019	NA
Odds ratio (95% CI)[d]	1.94 (1.1, 3.5)	NA
4 hours		
Headache response at the time point (%)[b]	84 (79.3)	52 (52.5)
p-value[c]	< .0001	NA
Odds ratio (95% CI)[d]	3.45 (1.8, 6.7)	NA

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients received trial medication and treated a migraine attack.

[b] Headache response is as a reduction in headache intensity from moderate or severe to mild or none.

[c] P-value is calculated by chi-square test.

[d] Odds ratio and 95% confidence limits (CI) are estimated by SAS FREQ procedure.

Table 6. Secondary endpoint: Nausea, photophobia and phonophobia at 2 hours (zolmitriptan nasal vs. placebo): FDA Analysis

	Zolmitriptan nasal spray 5.0 mg	Placebo
	(N = 108)[a]	(N = 102)
Nausea		
Patients with associated symptom at 2 h (%)[b]	19 (18.6)	28 (27.7)
p-value[c]	0.080	NA
Odds ratio (95% CI)[d]	0.56 (0.3, 1.1)	NA
Photophobia		
Patients with associated symptom at 2 h (%)[b]	37 (34.3)	50 (49.5)
p-value[c]	0.026	NA
Odds ratio (95% CI)[d]	0.53 (0.3, 1.0)	NA
Phonophobia		
Patients with associated symptom at 2 h (%)[b]	29 (26.9)	36 (35.6)
p-value[c]	0.170	NA
Odds ratio (95% CI)[d]	0.66 (0.4, 1.2)	NA

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients received trial medication and treated a migraine attack.

[b] Headache response is as a reduction in headache intensity from moderate or severe to mild or none.

[c] P-value is calculated by chi-square test.

[d] Odds ratio and 95% confidence limits (CI) are estimated by SAS FREQ procedure.

3.1.1.10 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Sponsor's Conclusion and Comments:

The proportion of patients who had a response at 2 hours after the initial dose in the zolmitriptan treatment group significantly exceeded the proportion of who had a response in the placebo treatment group (70.4% versus 47.0%, p=0.0005 [less than the pre-specified Interim Analysis boundary of α=0.0027]). The odds ratio of 2.84 indicates that patients treated with zolmitriptan had an approximately 3 times higher odds of having a response to treatment than patients treated with placebo.

Reviewer's Conclusion and Comments:

Based on the collective evidences and findings, in this statistical reviewer's opinion the interim data and results of study 311CUS/0022 support the sponsor's efficacy claim of ZOMIG® (zolmitriptan) 5 mg nasal with respect to the headache response endpoint for the adult patients with migraine, using first attack analysis. The data and results of the study show that the primary endpoint, 2 hour headache response, is statistically significantly improved in the treatment arm to the placebo arm for the intention-to-treat (ITT) population (p-value=0.0006).

3.2 Evaluation of Safety

No safety evaluation is included in this NDA statistical review.

4 Findings in Special/Subgroup Populations

There was no special/subgroup analysis in this NDA statistical review.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Statistical Issues:

- In the primary analysis, the endpoint was defined as 2 hours. If there was a missing data at the endpoint, the last observation would be carried forward (LOCF), i.e., the last post-treatment measurement was used in the analysis. In the confirmatory analysis, missing data at each time point was not imputed and the analysis was based on only the subjects who completed

measurements. The sponsor did not use LOCF algorithm for the primary efficacy analysis. This statistical reviewer used LOCF algorithm to confirm the sponsor's results.

- In the confirmatory analyses, the secondary efficacy variables: headache responses at the time point 1 hour and 4 hours supported the primary efficacy result. However, a comparative analysis for the usual migraine-associated symptoms of Nausea, Photophobia and Phonophobia did not support the primary efficacy analysis. Clinically, those symptoms are highly associated with migraine.
- There were multiple comparisons in the secondary analyses. The NDA submission did not adjust the overall significance level (α=0.05) for the comparisons of secondary endpoints.

5.2 Conclusions and Recommendations

Based on the collective evidences and findings, in this statistical reviewer's opinion the interim data and results of study 311CUS/0022 support the sponsor's efficacy claim of ZOMIG® (zolmitriptan) 5 mg nasal with respect to the headache response endpoint for the adult patients with migraine, using first attack analysis. The data and results of the study show that the primary endpoint, 2 hour headache response, is statistically significantly improved in the treatment arm to the placebo arm for the intention-to-treat (ITT) population (p-value=0.0006).

There was no statistically significant differences demonstrated for Zolmitriptan Nasal Spray dose of 5.0 mg to placebo in the secondary variable of nausea at 2 hours post dose. There was statistically significant differences demonstrated for Zolmitriptan Nasal Spray doses of 5.0 mg to placebo in the secondary variable of photophobia at 2 hours post-dose. There was no evidence to demonstrate the statistically significant difference for Zolmitriptan Nasal Spray dose of 0.5 mg to placebo in phonophobia at 2 hours post-dose.

Those results are consistent with the original NDA submission of Zolmitriptan Nasal Spray. We therefore recommend Approval for the treatment of adult patients with migraine.

Yong-Cheng Wang, Ph.D.
Mathematical Statistician
Date:

Concur: Dr. Jin
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This review consists of -- pages of text
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6 APPENDICES

No appendix is included in this review.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

MEDICAL DIVISION:	Neuropharmacological Drug Products (HFD-120)
BIOMETRICS DIVISION:	Division of Biometrics I (HFD-710)
STATISTICAL KEY WORDS:	χ^2-test, Logistic regression, odds ratio, multiple comparison, Bonferroni adjustment
NDA NUMBER:	21-450
DATE RECEIVED BY CDER:	February 27, 2002
DRUG NAME:	Zomig (zolmitripan) Nasal Spray
INDICATION:	Treatment of migraine with/without aura in adults
SPONSOR:	AstraZeneca Pharmaceuticals LP

DOCUMENT REVIEWED:

1. Cover letter (CDER REC'D Date: April 26, 2002) including doc file for review's aids, SAS data sets, and SAS codes for the primary efficacy results
2. Cover letter (CDER REC'D Date: June 27, 2002) including update data sets

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placebo in the secondary variable of phonophobia at 2 hours post-dose. There was no evidence to demonstrate the statistically significant difference for Zolmitriptan Nasal Spray dose of 0.5 mg to placebo in phonophobia at 2 hours post-dose.

4. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

4.1 Introduction and Background

Zolmitriptan is a potent and selective 5-$HT_{1B/1D}$ receptor agonist that has been developed for the acute treatment of migraine headache with or without aura. It was originally produced in conventional oral tablet form, and in this form was approved for use in the acute treatment of migraine in the United States (NDA 20-768, approved November 25, 1997) and most of Europe. More recently, an orally disintegrating tablet of zolmitriptan (ZOMIG FASTMELT) has been developed and is used in some European countries and the United States (ZOMIG-ZMT, NDA 21-231, approved February 13, 2001). This formulation dissolves rapidly in the mouth and dose not need to be swallowed with water, and may thus often more convenient dosing, particularly in the patients who suffer nausea and/or vomiting as part of a migraine attack.

4.2 Data Analyzed and Sources

The data sets analyzed were submitted by the sponsor on February 27, 2002. The SAS code for the format library of data sets was submitted by the sponsor on April 26, 2002. All data sets analyzed are electronic documents and located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "27-FEB-2002" and "26-APR-2002", respectively. The main data set for the efficacy analysis is "DIARYV" which describes the Diary card.

4.3 Statistical Evaluation of Evidence on Efficacy

4.3.1 Sponsor's Results and Conclusions

Table 1 summarizes the sponsor's results the primary efficacy parameter the headache response at 2 hours post treatment in comparison of each dose of 5.0 mg, 2.5 mg, 1.0 mg, and 0.5 mg zolmitriptan administered via intranasal route with placebo. By Bonferroni procedure for the multiple comparisons, there are statistically significant differences between each of dose 5.0 mg, 2.5 mg and 1.0 mg zolmitriptan administered via intranasal route with placebo ($p < 0.0001$ for all three doses). There is not significant difference between 0.5 mg zolmitriptan administered via intranasal route with placebo ($p = 0.022$).

Since the sponsor included the patients of 2.5 mg oral zolmitriptan group in logistic regression model when they compared efficacy of 5.0 mg, 2.5 mg, 1.0 mg, and 0.5 mg zolmitriptan administered via intranasal route with placebo, the sponsor's results were biased. This statistical reviewer conducted different analyses and report results late.

Table 4. Migraine headache history (ITT population)

	Zolmitriptan nasal spray				Oral Zolmitriptan	Placebo[a]
Migraine characteristic	5.0 mg (N = 235)	2.5 mg (N = 224)	1.0mg (N = 236)	0.5 mg (N = 221)	2.5 mg (N = 229)	(N = 226)
Mean age (range) at onset of migraine attacks (years)	20.1 (2 – 48)	18.5 (4 – 45)	18.4 (3 – 49)	20.2 (3 – 48)	19.1 (3 – 49)	19.1 (2 – 54)
Mean number (range) of migraine attacks in last 2 months	5.6 (2 – 12)	5.7 (2 – 12)	5.7 (2 – 20)	5.5 (2 – 15)	5.4 (2 – 12)	5.5 (2 – 12)
Mean number (range) of days of non-migraine headache per month over last 6 months	1.7 (0 – 10)	1.8 (0 – 10)	1.6 (0 – 10)	1.8 (0 – 10)	1.7 (0 – 10)	1.9 (0 – 10)
Presence of aura (patients [%][b])						
Always	30 (12.8)	24 (10.7)	26 (11.0)	18 (8.1)	17 (7.4)	15 (6.6)
Sometimes	66 (28.1)	56 (25.0)	70 (29.7)	56 (25.3)	79 (34.5)	62 (27.4)
Never	139 (59.1)	144 (64.3)	140 (59.3)	147 (66.5)	133 (58.1)	149 (65.9)
Average duration of typical migraine (patients [%][b])						
0 to 12 hours	35 (14.9)	40 (17.9)	39 (16.5)	35 (15.8)	38 (16.6)	32 (14.2)
>12 and ≤24 hours	54 (23.0)	68 (30.4)	68 (28.8)	59 (26.7)	61 (26.6)	63 (27.9)
>24 and ≤48 hours	81 (34.5)	76 (33.9)	68 (28.8)	57 (25.8)	59 (25.8)	64 (28.3)
>48 hours	64 (27.2)	40 (17.9)	59 (25.0)	70 (31.7)	70 (30.6)	66 (29.2)
not recorded	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.4)	1 (0.4)
Photophobia (patients [%][b])	218 (92.8)	209 (93.3)	210 (89.0)	198 (89.6)	213 (93.0)	206 (91.2)
Phonophobia (patients [%][b])	198 (84.3)	182 (81.2)	196 (83.1)	174 (78.7)	179 (78.2)	193 (85.4)
Nausea (patients [%][b])	207 (88.1)	193 (86.2)	203 (86.0)	187 (84.6)	197 (86.0)	195 (86.3)
Somnolence (patients [%][b])	158 (67.2)	143 (63.8)	157 (66.5)	141 (63.8)	161 (70.3)	146 (64.6)

Sponsor's results confirmed by reviewer's analyses. N = Number of patients.

[a] The placebo treatment group includes treated with placebo nasal spray and oral placebo.

[b] Percentage were calculated using the number of patients exposed in treatment group as the denominator.

4.3.3 Statistical Reviewer's Findings

This statistical reviewer performed own efficacy analyses. There are some issues between the sponsor's and the statistical reviewer's analyses. (1) The sponsor included the patients of 2.5 mg oral zolmitriptan treatment group in the logistic regression model when they compared the efficacy of 5.0 mg, 2.5 mg, 1.0 mg, and 0.5 mg zolmitriptan administered via intranasal route with placebo. This was not a statistically comparable analysis. (2) Since the sponsor did not define any procedure for multiple comparisons, the statistical reviewer used Bonferroni procedure for multiple comparisons. Based on the overall significance level 0.05, the adjusted significance level by Bonferroni method was 0.0125. (3) The sponsor used "Country" and "Baseline headache intensity" as the exposure variables (covariates). Therefore, their efficacy analyses were adjusted by those

Reviewer's analyses. NA = not applicable
[a] Patients received trial medication and treated a migraine attack of moderate or severe baseline intensity.
[b] Percentage of patients/attacks where response was recorded at each time point.
[c] Odds ratio and 95% confidence limits (CI) are estimated by logistic regression model with treatments only.
[d] P-value is calculated by logistic regression model with treatment variable only.

Table 9. Secondary endpoint: Meaningful migraine relief at each time point ---- first attack (zolmitriptan nasal spray vs. placebo, ITT population)

	Zolmitriptan nasal spray				Placebo
	5.0 mg (N = 235)[a]	2.5 mg (N = 224)	1.0mg (N = 236)	0.5 mg (N = 221)	(N = 226)
Meaningful migraine relief at each time point					
15 min					
M. Migraine relief rate[b]	3.7	2.4	3.8	0.5	2.1
Odds ratio (95% CI)[c]	2.01 (0.6, 6.6)	1.20 (0.3, 4.5)	1.83 (0.5, 6.2)	0.26 (0.0, 2.3)	NA
p-value[d]	0.252	0.790	0.330	0.224	NA
30 min					
M. Migraine relief rate	11.6	7.3	10.4	3.8	5.2
Odds ratio (95% CI)	2.28 (1.1, 4.9)	1.44 (0.6, 3.3)	1.89 (0.9, 4.2)	0.70 (0.3, 1.9)	NA
p-value	0.034	0.388	0.114	0.487	NA
45 min					
M. Migraine relief rate	19.5	13.7	18.5	9.2	9.4
Odds ratio (95% CI)	2.39 (1.3, 4.3)	1.53 (0.8, 2.9)	2.04 (1.1, 3.7)	1.03 (0.5, 2.1)	NA
p-value	0.004	0.190	0.022	0.937	NA
1 hour					
M. Migraine relief rate	35.3	25.4	26.1	18.5	15.1
Odds ratio (95% CI)	3.00 (1.8, 4.9)	1.74 (1.0, 2.9)	1.70 (1.0, 2.8)	1.26 (0.7, 2.2)	NA
p-value	< .0001	0.033	0.041	0.406	NA
2 hours					
M. Migraine relief rate	57.7	43.5	47.2	34.2	24.0
Odds ratio (95% CI)	4.41 (2.9, 6.8)	2.38 (1.5, 3.7)	2.83 (1.8, 4.4)	1.63 (1.0, 2.6)	NA
p-value	< .0001	0.0001	< .0001	0.037	NA
4 hours					
M. Migraine relief rate	76.3	60.8	63.3	47.3	27.7
Odds ratio (95% CI)	8.31 (5.3,13.1)	3.74 (2.4, 5.7)	4.34 (2.8, 6.7)	2.17 (1.4, 3.3)	NA
p-value	< .0001	< .0001	< .0001	0.001	NA

Reviewer's analyses. NA = not applicable
[a] Patients received trial medication and treated a migraine attack of moderate or severe baseline intensity.
[b] Percentage of patients/attacks where response was recorded at each time point.
[c] Odds ratio and 95% confidence limits (CI) are estimated by logistic regression model with treatments only.
[d] P-value is calculated by logistic regression model with treatment variable only.

Table 10. Secondary endpoint: Nausea improved at each time point ---- first attack (zolmitriptan nasal spray vs. placebo, ITT population)

	Zolmitriptan nasal spray				Placebo
	5.0 mg (N = 235)[a]	2.5 mg (N = 224)	1.0mg (N = 236)	0.5 mg (N = 221)	(N = 226)
Nausea improved from baseline at each time point					
15 min					
Nausea improved rate[b]	13.9	18.3	14.8	11.1	12.4
Odds ratio (95% CI)[c]	0.89 (0.6, 1.3)	1.16 (0.8, 1.7)	0.94 (0.6, 1.4)	0.89 (0.6, 1.3)	NA

p-value[d]	0.540	0.453	0.735	0.531	NA
30 min					
Nausea improved rate	24.8	30.8	22.3	22.9	20.6
Odds ratio (95% CI)	0.89 (0.6, 1.3)	0.99 (0.7, 1.5)	1.04 (0.7, 1.5)	0.92 (0.6, 1.3)	NA
p-value	0.549	0.959	0.826	0.654	NA
45 min					
Nausea improved rate	35.0	33.6	33.6	25.9	26.7
Odds ratio (95% CI)	0.65 (0.4, 1.0)	0.91 (0.6, 1.3)	0.86 (0.6, 1.3)	0.99 (0.7, 1.5)	NA
p-value	0.030	0.627	0.446	0.956	NA
1 hour					
Nausea improved rate	36.5	38.9	38.0	29.9	32.3
Odds ratio (95% CI)	0.64 (0.4, 1.0)	1.00(0.7, 1.5)	0.81 (0.6, 1.2)	1.02 (0.7, 1.5)	NA
p-value	0.028	0.999	0.274	0.922	NA
2 hours					
Nausea improved rate	43.7	44.4	43.8	37.8	39.1
Odds ratio (95% CI)	0.53 (0.3, 0.8)	0.74 (0.5, 1.1)	0.70 (0.5, 1.0)	0.88 (0.6, 1.3)	NA
p-value	0.002	0.144	0.075	0.526	NA
4 hours					
Nausea improved rate	47.7	49.0	47.1	40.9	42.2
Odds ratio (95% CI)	0.28 (0.2, 0.4)	0.44 (0.3, 0.7)	0.50 (0.3, 0.8)	0.68 (0.4, 1.0)	NA
p-value	< .0001	0.0003	0.002	0.075	NA

Reviewer's analyses. NA = not applicable

[a] Patients received trial medication and treated a migraine attack of moderate or severe baseline intensity.

[b] Percentage of patients/attacks where response was recorded at each time point.

[c] Odds ratio and 95% confidence limits (CI) are estimated by logistic regression model with treatments only.

[d] P-value is calculated by logistic regression model with treatment variable only.

Table 11. Secondary endpoint: Photophobia improved at each time point ---- first attack (zolmitriptan nasal spray vs. placebo, ITT population)

	Zolmitriptan nasal spray				Placebo
	5.0 mg (N = 235)[a]	2.5 mg (N = 224)	1.0mg (N = 236)	0.5 mg (N = 221)	(N = 226)
Photophobia improved from baseline at each time point					
15 min					
Photophobia improve rate[b]	22.4	19.0	18.9	8.3	13.7
Odds ratio (95% CI)[c]	0.62 (0.4, 0.9)	0.79 (0.5, 1.2)	1.02 (0.7, 1.6)	0.78 (0.5, 1.2)	NA
p-value[d]	0.026	0.279	0.930	0.249	NA
30 min					
Photophobia improved rate	39.4	31.4	35.6	19.1	22.2
Odds ratio (95% CI)	0.49 (0.3, 0.7)	0.65 (0.4, 1.0)	0.95 (0.6, 1.5)	0.78 (0.5, 1.2)	NA
p-value	0.001	0.044	0.796	0.264	NA
45 min					
Photophobia improved rate	50.9	41.3	46.8	25.0	33.3
Odds ratio (95% CI)	0.40 (0.3, 0.6)	0.59 (0.4, 0.9)	0.70 (0.5, 1.1)	0.77 (0.5, 1.2)	NA
p-value	< .0001	0.012	0.092	0.217	NA
1 hour					
Photophobia improved rate	52.1	51.5	54.3	34.5	47.3
Odds ratio (95% CI)	0.46 (0.3, 0.7)	0.55 (0.4, 0.8)	0.75 (0.5, 1.1)	0.81 (0.5, 1.2)	NA
p-value	< .0001	0.003	0.140	0.290	NA
2 hours					
Photophobia improved rate	63.8	61.0	64.8	50.0	57.1
Odds ratio (95% CI)	0.31 (0.2, 0.5)	0.46 (0.3, 0.7)	0.50 (0.3, 0.7)	0.65 (0.4, 0.9)	NA

p-value	< .0001	< .0001	0.0003	0.026	NA
4 hours					
Photophobia improved rate	66.9	67.4	70.1	52.7	64.7
Odds ratio (95% CI)	0.19 (0.1, 0.3)	0.25 (0.2, 0.4)	0.31 (0.2, 0.5)	0.44 (0.3, 0.7)	NA
p-value	< .0001	< .0001	< .0001	< .0001	NA

Reviewer's analyses. NA = not applicable

[a] Patients received trial medication and treated a migraine attack of moderate or severe baseline intensity.

[b] Percentage of patients/attacks where response was recorded at each time point.

[c] Odds ratio and 95% confidence limits (CI) are estimated by logistic regression model with treatments only.

[d] P-value is calculated by logistic regression model with treatment variable only.

Table 12. Phonophobia improved at each time point ---- first attack (zolmitriptan nasal spray vs. placebo, ITT population)

	Zolmitriptan nasal spray				Placebo
	5.0 mg (N = 235)[a]	2.5 mg (N = 224)	1.0mg (N = 236)	0.5 mg (N = 221)	(N = 226)
Phonophobia improved from baseline at each time point					
15 min					
Phonophobia improve rate[b]	18.0	16.9	6.7	6.8	4.7
Odds ratio (95% CI)[c]	0.82 (0.6, 1.2)	0.86 (0.6, 1.3)	1.03 (0.7, 1.5)	0.91 (0.6, 1.3)	NA
p-value[d]	0.294	0.447	0.868	0.637	NA
30 min					
Phonophobia improved rate	34.5	21.1	21.2	15.2	8.1
Odds ratio (95% CI)	0.64 (0.4, 0.9)	0.81 (0.5, 1.2)	0.86 (0.6, 1.3)	0.84 (0.6, 1.2)	NA
p-value	0.022	0.282	0.425	0.379	NA
45 min					
Phonophobia improved rate	42.9	36.8	30.6	24.0	13.0
Odds ratio (95% CI)	0.52 (0.4, 0.8)	0.56 (0.4, 0.8)	0.72 (0.5, 1.0)	0.75 (0.5, 1.1)	NA
p-value	0.001	0.003	0.082	0.138	NA
1 hour					
Phonophobia improved rate	45.0	44.4	35.9	28.6	23.6
Odds ratio (95% CI)	0.48 (0.3, 0.7)	0.55 (0.4, 0.8)	0.75 (0.5, 1.1)	0.85 (0.6, 1.2)	NA
p-value	0.0001	0.002	0.126	0.384	NA
2 hours					
Phonophobia improved rate	53.0	51.3	43.2	36.6	28.9
Odds ratio (95% CI)	0.33 (0.2, 0.5)	0.38 (0.3, 0.6)	0.51 (0.4, 0.8)	0.66 (0.5, 1.0)	NA
p-value	< .0001	< .0001	0.001	0.036	NA
4 hours					
Phonophobia improved rate	56.1	53.3	50.1	43.1	34.4
Odds ratio (95% CI)	0.22 (0.1, 0.4)	0.32 (0.2, 0.5)	0.36 (0.2, 0.5)	0.58 (0.4, 0.9)	NA
p-value	< .0001	< .0001	< .0001	0.009	NA

Reviewer's analyses. NA = not applicable

[a] Patients received trial medication and treated a migraine attack of moderate or severe baseline intensity.

[b] Percentage of patients/attacks where response was recorded at each time point.

[c] Odds ratio and 95% confidence limits (CI) are estimated by logistic regression model with treatments only.

[d] P-value is calculated by logistic regression model with treatment variable only.

4.4 Findings in Special/Subgroup Population

Since most of the patients enrolled in the treatment group of study were female (≥ 76.8%), there was no subgroup analysis for gender. Most of the patients enrolled in the study were Caucasians (≥ 98.3%), there was no subgroup analysis for race. The sponsor did not perform any subgroup analysis.

4.5 Statistical and Technical Issues

Method of Statistical Analysis

The major statistical issue in this submission is that an inappropriate statistical analysis procedure was employed by the sponsor. For the comparisons of placebo, the sponsor included the patients of the 2.5 mg oral zolmitriptan treatment group in the logistic regression model. For the comparisons of the 2.5 mg oral zolmitriptan treatment group, the sponsor included the patients of the placebo group in the logistic regression model. Therefore, the sponsor's results are not comparable for experimental treatment vs. placebo or experimental treatment vs. the 2.5 mg oral zolmitriptan treatment group.

Adjustment Procedure for Multiple Comparisons

This is a multiple doses study. There are 4 experimental treatment doses. Each experimental treatment dose will be compared with placebo or the 2.5 mg oral zolmitriptan treatment group. It is a typical multiple comparisons trial. The sponsor did not define any adjustment procedure for the multiple comparison tests. The sponsor concluded their results based on the unadjusted efficacy analyses.

Exposure Variables in Logistic Regression Model

The sponsor conducted the analysis for efficacy endpoints and included the exposure variables (covariates) "Country" and "Baseline headache intensity" in the logistic regression model. The sponsor's results for the efficacy analyses were adjusted by those two exposure variables.

Comparative Analyses for the Usual Associated Symptoms

The sponsor did not perform a comparative analysis for the usual associated symptoms of Nausea, Photophobia and Phonophobia. Clinically, those symptoms are highly associated with the treatments and should be included in efficacy analyses.

ITT Population

The sponsor defined the ITT population as that all patients received trial medication and treated a migraine attack of moderate or severe baseline intensity. It was not a typical definition for the ITT population that all patients take study medication and there is at

least a single post-dose efficacy assessment. There were 8 patients who had no post treatment efficacy assessment but they were included in ITT population by the sponsor.

Time Interval for the Endpoint

The sponsor used a 90 minutes time interval for the primary endpoint the 2 hour time endpoint assessment (91 to 180 minutes). This was a rather large time interval. The sponsor did not define any procedure to verify the time interval was acceptable.

Randomization for Gender

A higher percentages of female patients for the combined zolmitriptan (spray and oral) group (82.3%) compared to the placebo group (49.6%). The percentage of female patients was 84.7% for the 5.0 mg zolmitriptan nasal spray group, 76.8% for the 2.5 mg zolmitriptan nasal spray group, 86.9% for the 1.0 mg zolmitriptan nasal spray group, 80.5% for the 0.5 mg zolmitriptan nasal spray group, and 82.1% for the 2.5 mg oral zolmitriptan group. The randomization was not balanced for gender.

Randomization for Race

There were very high percentages of Caucasian patients for all zolmitriptan nasal spray, oral zolmitriptan and placebo groups. The percentage range for the Caucasian patients was 98.3% to 99.2%. The randomization did not present the distribution of race.

4.6 Statistical Evaluation of Collective Evidence

Table 5-12 clearly summarized the statistical results of the primary and secondary efficacy analyses and provided the evidence to support the overall conclusions. The Bonferroni procedure was used to adjust the multiple comparisons between each dose of 5.0 mg, 2.5 mg, 1.0 mg, and 0.5 mg zolmitriptan nasal spray and placebo. The odds ratio and its 95% confidence interval were used to present the association between zolmitriptan nasal spray and the placebo group.

4.7 Conclusion and Recommendations

This reviewer concluded the following efficacy conclusions. Since this is only one efficacy study and randomization were not to present the distributions of gender and national race, it might not be enough to represent for a wide-ranging population.

This clinical study demonstrated that drug Zomig (zolmitriptan) Nasal Spray, administered via the intranasal route in doses of 5.0 mg, 2.5 mg and 1.0 mg had significantly different efficacy than placebo in the primary variable of headache response rate at 2 hours after dosing. There were statistically significant differences demonstrated for the primary variable of headache response in (1) Zolmitriptan Nasal Spray doses of

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