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Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21450 (0040)

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Indication(s): Acute Migraine Treatment in Adolescents

Applicant: Astra Zeneca

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1. EXECUTIVE SUMMARY

Study D1220C00001 demonstrated a statistically significant effect of the 5 mg Zolmitriptan dose compared to placebo in terms of the primary efficacy endpoint, pain free at 2 hours in the study population of adolescents aged 12 to 17. In case there may be benefit risk considerations and given that the high dose was significant on efficacy it may be important to note that the middle dose 2.5 mg had a nominal p<.10 on the pain free at 2 hours post-dose as well as the headache response at 2 hours post-dose endpoints. An assumption of exchangeability of the placebo group before and after the interim is needed to have statistical validity of the final analysis results for the middle dose vs. placebo comparison since randomization was ceased to it after the interim analysis based on expected futility for it, but randomization continued to placebo. Therefore, for Zomig 2.5 mg more weight should be given to the interim estimates.

2. INTRODUCTION

2.1 Overview

ZOMIG® (zolmitriptan) is a selective 5-hydroxytryptamine$_{1B/1D}$ receptor agonist indicated for the acute treatment of migraine, with or without aura, in adults in 68 countries. In Europe, ZOMIG Nasal Spray is also approved for the treatment of acute migraine, with or without aura, in adolescents; this approval was based on data from Study D1221C00005. ZOMIG is available in 3 formulations in the United States (US): film-coated tablet, oral disintegrating film tablet [ZOMIG-ZMT]), and nasal spray. ZOMIG tablets and oral disintegrating film tablets contain 2.5 or 5 mg of zolmitriptan per tablet. ZOMIG Nasal Spray is an aqueous solution containing 50 mg/mL zolmitriptan and is available in doses of 2.5 or 5 mg.

On 14 October 2008, the Food and Drug Administration (FDA) determined that Study D1221C00005 did not meet the Pediatric Research Equity Act (PREA) obligation and issued a revised PREA commitment. After reaching an agreement with the agency regarding the study

design under a Special Protocol Assessment (SPA), a final protocol for Study D1220C00001 was submitted on 23 September 2010.

The purpose of this supplemental application is to provide the safety and efficacy data from Study D1220C00001 in order to address the 14 October 2008 PREA requirement to evaluate ZOMIG Nasal Spray for the acute treatment of migraine in pediatric patients aged 12 to 17 years. Study D1220C00001 was designed to be an adequate and well controlled Phase III, global, multicenter, parallel-group, double-blind, randomized, placebo-controlled study to compare the efficacy of ZOMIG Nasal Spray 0.5, 2.5, and 5 mg with placebo in the acute treatment of migraine headache in adolescents aged 12 to 17 years. This study also features several of the enrichment strategies used in previously successful adolescent triptan studies by requiring a history of ≥3-hour headache duration and a failed response to a single-blind placebo challenge.

This review will focus on data from Study D1220C00001 as data from Studies D1221C00005 and D1221C00004 have been previously submitted to FDA (NDA 21-450/S-005).

2.2 Data Sources

The derived and raw datasets for the key efficacy study `d1220c00001` were located in the following directories at the time of review.

`\\cdsesub1\evsprod\nda021450\0040\m5\datasets\d1220c00001\analysis\adam\datasets`

`\\cdsesub1\evsprod\nda021450\0040\m5\datasets\d1220c00001\tabulations\sdtm\`

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.2 Evaluation of Efficacy

3.2.1 Study D1220C00001

First subject enrolled: 7 October 2010
Last subject last visit: 31 October 2013

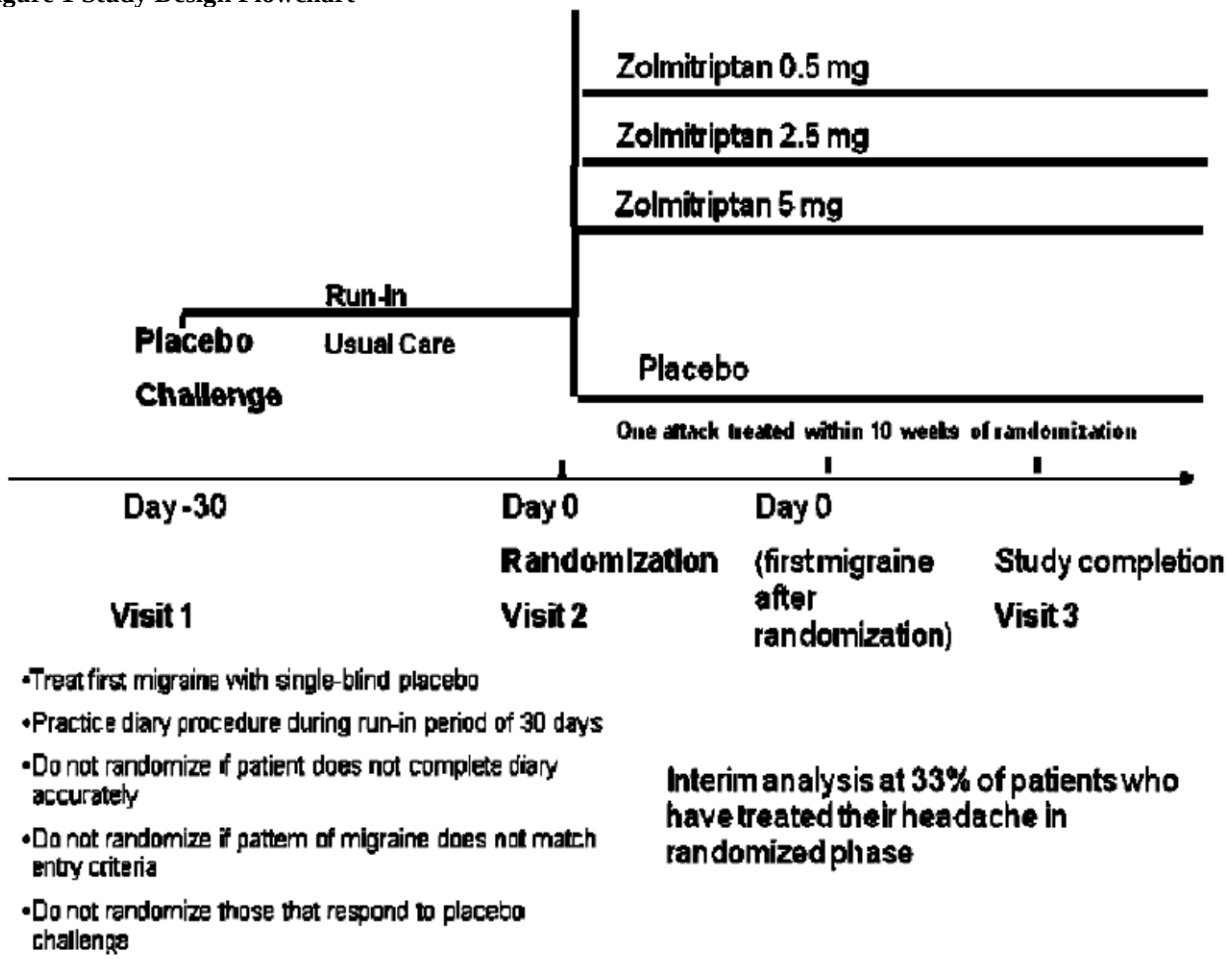
Primary objective

The primary objective of this study is to compare the efficacy of zolmitriptan nasal spray 0.5, 2.5, and 5 mg with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17 years), as measured by the primary endpoint (outcome variable) of pain-free status at 2 hours post treatment.

Study Design

This is a global, multicenter, double-blind, randomized, placebo-controlled study with a parallel group design and single-blind run-in period. The study was to comprise treatment of a single attack of migraine headache during the run-in period and placebo challenge with 1 dose of single-blind placebo. If the patient met conditions for randomization, a single attack of migraine headache was to be treated with 1 dose of zolmitriptan nasal spray 0.5, 2.5, 5 mg, or matching placebo in a blinded manner. Figure 1 summarizes the design.

Figure 1 Study Design Flowchart



Note: This figure was copied from page 29 of the sponsor's study report

Approximately 1000 patients were to be randomized at approximately 129 study sites in the US, Latin America, Europe, and South Africa. Adolescent patients, age 12 to 17 years with an established diagnosis of migraine, as defined by the IHS (International Headache Society) or IHS-Revised (IHS-R) criteria were to be enrolled in the study. Patients were to be screened for eligibility during Visit 1 (screening visit) after the informed consent and assent had been obtained. Medical history, migraine headache history and prior medication history were to be obtained, and a complete physical examination (including vital sign measurements), 12-lead electrocardiogram (ECG), laboratory assessments (clinical chemistry, hematology and urinalysis), urine drug screen, urine pregnancy test (for all females), and Columbia-Suicide Severity Rating Scale (C-SSRS) were to be performed. Eligible patients were to enter a 30-day run-in period beginning at Visit 1 to establish whether or not the patient had a headache pattern of appropriate severity and duration to qualify for the study. Patients were to be dispensed 1 dose of single-blind placebo and were to treat 1 episode of migraine headache. Patients were to not receive any double-blind, active study drug during the run-in period, but were to be permitted – with the exception of the placebo challenge – to treat their migraine(s) headache with their usual migraine treatment medications. For the placebo challenge, the patient's first migraine headache during the run-in period was to be treated with single-blind placebo. At 2 hours after treating

with single-blind placebo, if the patient's migraine headache had not responded (i.e., not reduced to mild or none), the patient could use rescue medication(s). For any subsequent migraine episodes, the patient was to use their usual acute migraine medication. During this run-in period, patients were to be asked to complete a diary of symptoms. Visit 2 (randomization) was to occur at the end of the 30-day run-in period. When the 30-day run-in period was complete, the patient was to come in to the study site for Visit 2. At this visit, patients were to only be randomly assigned if they did not respond to the placebo challenge, completed their diary correctly, and had the correct headache frequency required in the protocol criteria.

This study was to be established with a center-stratified randomization. Eligible patients were to be randomized in balanced blocks to receive zolmitriptan 0.5, 2.5, or 5 mg, or matching placebo in a 5:3:3:5 ratio. The actual treatment given to individual patients was to be determined by a randomization scheme that had been loaded into the interactive voice response system (IVRS) database. If a patient discontinued from the study, his/her patient or enrollment number was not to be reused, and the patient was not to be allowed to re-enter the study. Randomized patients who discontinued early from the study were not to be replaced.

A responder to placebo challenge is defined as mild or none in headache intensity at 2 hours. A non-responder to placebo challenge is defined as still moderate or severe headache intensity at 2 hours. Patients not treating a migraine headache with blinded placebo during the 30-day run-in period were to be considered screen failures.
At Visit 2, eligible patients with an established diagnosis of migraine (moderate or severe) who had met the criteria for randomization (no response to placebo challenge, headache characteristics consistent with the inclusion criteria, and ability to complete the study diary) were to be randomized to zolmitriptan nasal spray 0.5, 2.5, 5 mg, or matching placebo spray to treat a migraine headache. Paper patient diaries were to be provided to patients to record the severity of the headache (mild, moderate, or severe). Patients were to complete the diary for 24 hours for the migraine headache treated with the study drug, as well as record any Adverse Events (AEs) and medications taken at any time. Further dosing instructions were to also be provided during this visit.
Patients were to treat 1 migraine headache with 1 dose of zolmitriptan nasal spray 0.5, 2.5, 5 mg, or matching placebo within 10 weeks of randomization (Visit 2). Headache response is defined as a reduction in migraine headache pain intensity from severe or moderate at the time of initial treatment to mild or none at a specific assessment time.

Before taking the study drug, patients cannot have:
• Treated headache with other medication;
• Received any triptan, ergotamine or ergot-type medications (eg, dihydroergotamine or methysergide) in the last 24 hours; or
• Used opiates in the last 24 hours.
If headache pain persists after taking the study drug, approved rescue medication, as agreed by the treating physician, is permitted after 2 hours post-study treatment. Triptans and ergots are not allowed as rescue medications. Allowable drugs include non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics, analgesics (eg, opioids), and sedatives. Rescue medications were not to be provided by AstraZeneca (AZ).
After taking the study drug, patients may not:

• Sleep or nap for 2 hours;
• Use rescue medications for 2 hours;
• Use other triptan or any ergotamine or ergot-type medications (eg, dihydroergotamine or methysergide) for 24 hours.

Patients were to be allowed to continue throughout the study on medications normally taken for migraine prophylaxis, or to correct a long-standing condition provided the condition is stable in the investigator's opinion and that this ongoing treatment won't be adversely affected by study participation.

If there was no treatment with study drug within 4 weeks of randomization, patients were to return to the study site for the interim visit to review the study dosing instructions. Patients were to have approximately 14 weeks to complete the study, which consists of a 30-day run-in period followed by 10 weeks to complete treatment. Patients were to return to the study site after treating a single migraine headache within 2 weeks of using the study drug for the final study visit (Visit 3), or within 10 weeks after randomization (Visit 2) if no migraine headache was treated. At that time, end-of-study assessments (physical examination, vital signs, prior and concomitant medications, ECG, laboratory assessments, pregnancy tests for females, adverse event (AE) assessments, and C-SSRS) were to be performed. The nasal spray device was to be returned. Patient diaries were to be returned and reviewed.

Full analysis set

The full analysis set (FAS) includes all randomized treated patients who provide post-treatment efficacy data, classified according to randomized treatment. The analysis of all efficacy variables will be performed using the FAS.

Center Pooling

It was anticipated that some centers would randomize only a few patients. Therefore, within each country, centers with less than 16 randomized patients were pooled with the closest center(s) geographically until the number of randomized patients after pooling was approximately 16. For any country with less than 8 randomized patients, its centers were pooled with those of a geographically close country. The final pooling of centers was performed prior to database lock.

Handling of missing data

In general, the data for a visit or time point consisted of the actual recorded observation. This is observed case (OC) data, and if the observation was missing, it remained missing. Additional values were derived from the OC data to impute missing data for some efficacy endpoints. For the efficacy endpoints of pain-free status and headache response, a last observation carried forward (LOCF) value and a worst-case value were also derived at the 2-hour time point. The LOCF value was the corresponding 2-hour value or, if that value was missing, the last non-missing post-baseline value carried forward. The worst-case value was the corresponding 2-hour value or, if that value was missing, the value was set to non-response.

If time of rescue medication was missing, and date was also missing, then it was to be assumed that the rescue medication was taken at the earliest allowed time (2 hours 1 minute) after treatment. If the date was present, then time to rescue was to be set to be either 2 hours and 1 minute or calculated using the earliest time point on the date of rescue medication – whichever gave the larger time to rescue.

Primary efficacy analysis
The primary null hypotheses tested were that the LOCF pain-free rates at 2 hours for ZOMIG 0.5, 2.5, and 5 mg treated patients were no different from that of placebo-treated patients. A step-down approach was used for maintaining the type I error at 5% when comparing the pain-free rates for each of the 3 ZOMIG doses against placebo. Initially, ZOMIG 5 mg was compared with placebo. If ZOMIG 5 mg was significantly better than placebo at the 2-sided 5% level, then ZOMIG 2.5 mg was compared with placebo. If ZOMIG 2.5 mg was significantly better than placebo at the 2-sided 5% level, then ZOMIG 0.5 mg was compared with placebo. If any comparison between ZOMIG and placebo was not significant, then any lower doses of ZOMIG were not compared with placebo.
The primary variable was analyzed using a logistic regression model with LOCF 2-hour pain-free status as the response variable. Treatment was included as a fixed effect in the model and pooled center was included as a fixed factor.

The Statistical Analysis Plan indicated that if convergence issues occurred during model fit with pooled site treated as a fixed factor, then pooled center was to be considered a random (rather than fixed) factor to circumvent the problem. The estimate of the odds ratio and its 95% confidence interval (CI) were presented for each comparison, and the p-value was presented for each allowed comparison.

The primary analysis was performed on LOCF data using the FAS.
Similar supporting analyses, using worst-case data from the FAS and both LOCF and worst-case data from the per-protocol (PP) analysis set, were performed to check the robustness of the primary efficacy results.

Secondary efficacy analyses
The following secondary efficacy variables were analyzed for Observed Cases and/or LOCF using the FAS. All are binary (yes/no) variables except for incidence and time to use of rescue medication.
• Pain-free status at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment;
• Headache response at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment;
• Sustained headache response at 2 hours;
• Presence of associated symptoms of photophobia, phonophobia, nausea, or vomiting at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment;
• Resolution of associated symptoms of photophobia, phonophobia, nausea, or vomiting at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment;
• Use of rescue medication up to 24 hours post-treatment;
• Time to first use of rescue medication up to 24 hours post-treatment;
• Ability to perform normal activities at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment.
• Headache recurrence 2 to 24 hours post-treatment;
• Bilateral headache at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment; and
• Intensity increased by movement at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment.

For all the binary secondary efficacy variables, logistic regression methods similar to those of the primary efficacy variable were used. Frequency counts and percentages of patients were tabulated for each scheduled post-randomization assessment time point. Also, bar charts showing the percentages of patients who achieved pain-free status and headache response at each time point were produced.

The time windows for the post-treatment assessment for this study are defined in Table 4.

Table 4 Time windows

Nominal time[a]	Time window
15 minutes	1 - 30 minutes
1 hour	31 - 90 minutes
2 hours	91 - 150 minutes
3 hours	151 - 210 minutes
4 hours	211 - 360 minutes
24 hours	361 - 2160 minutes

[a] The nominal time is the protocol-specified assessment time.

If there were 2 assessments within a time window, 1 with an actual time and 1 with a nominal time (due to missing data), the assessment with the actual time was to be used in the analysis.

Determination of sample size

The sample size in this study was selected to demonstrate the efficacy of ZOMIG over placebo. Assuming a 2-sided test at an α level of 0.05, a sample size of 250 evaluable patients per group would provide 80% power to detect a clinically relevant difference of 0.11 between the ZOMIG 5 mg and placebo groups with regard to the primary outcome variable of pain-free status at 2 hours post-treatment. This calculation assumed a pain-free rate for placebo of 0.18 (as was observed in Study D1221C00005). By including 2 additional ZOMIG dose groups and using a 5:3:3:5 randomization ratio, a total of 800 evaluable patients was required. The sample size of 150 evaluable patients for the ZOMIG 2.5 and 0.5 mg groups would provide 67% power to detect a difference of 0.11 versus placebo. As 20% of randomized patients were expected to drop out of the study before treatment of a headache attack, approximately 1000 patients were to be randomized.

Due to the considerably higher placebo rates reported in previous adolescent migraine studies, a blinded interim sample size re-estimation analysis was planned to occur after approximately one-third of the planned patients had treated a migraine headache with randomized treatment. During the interim analysis, the blinded overall 2-hour pain-free rate was estimated. Depending on this blinded estimate of the pain-free rate, the sample size required could have been increased to as many as 1036 evaluable patients (approximately 1295 randomized patients).

Sample size Re-estimation

An interim analysis was to be performed based on the blinded data from approximately 267 evaluable patients to ensure that the total sample size provided sufficient power to detect a clinically relevant difference of 0.11 in the 2-hour pain-free response rate. The interim sample size re-estimation analysis was performed by an independent statistician who was not involved with this trial.

To estimate the number of patients required, the method described by Friede and Kieser 2006[1] was used. This method is based on the 2-treatment, continuity-corrected, chi-square test of equal proportions and required a blinded estimate of the response rate. The estimated sample size per group was calculated using the blinded estimate of the 2-hour pain-free rate along with the original sample size assumptions of a type I error rate of 0.05, a type II error rate of 20%, and a clinically relevant difference of 0.11. The calculated sample size per group was used for the ZOMIG 5 mg and placebo treatment arms. To account for the 5:3:3:5 randomization, the total sample size after the sample size re-estimation was to be (b) (4)

The maximum sample size required after the SSR was to be (b) (4) = 1036 evaluable patients. The sample size was not to be decreased from the original sample size even if the interim calculation suggested it. If the calculated sample size per group was ≤250, no adjustment to the sample size was made.

The Friede and Kieser 2006 article discussed the 2-sample parallel group design; however, in this case since pairwise comparisons will be the primary analysis, this method can be used for this 4-sample parallel group design. The relevant formula is as follows.

$$\mathrm{N/arm_{SSR}} = (2 + \theta + \frac{1}{\theta}) \cdot \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{2 \cdot (\Delta^*)^2} \pi \cdot (1 - \pi)$$

$\theta = 1$ *with a balanced design*

Δ^* *clinically relevant difference*

$z_{1-\alpha/2}$ 1.96 *with a* α *– level* $= 0.05$ *2 – sided*

$z_{1-\beta}$ 0.842 *with power*$(\beta) = 0.8$

π *the estimated total response rate*

The sample size re-estimation analysis was performed on 18 June 2012 and included 2-hour pain-free status data from 286 randomized patients. Based on the results of this blinded interim analysis, the calculated sample size per group was less than 250 patients. Thus, the original sample size assumptions were determined reasonable with no increase to the sample size

[1] Biometrical Journal **48** (2006) 4, 537-555: "Sample Size Recalculation in Internal Pilot Study Designs: A Review"

required. Further details of the interim sample size re-estimation analysis plan were specified in a separate charter document [17 December 2010].

After the blinded sample size re-estimation analysis, an unblinded futility analysis was discussed with the FDA and included in Protocol Amendment 3 (dated 6 September 2012). Based on the results of the interim futility analysis, determination of whether to stop enrollment to one or more randomized treatment arms was to be made.

Futility analysis
After confirmation of the total sample size required from the sample size re-estimation interim analysis, an additional interim analysis was performed to identify and discontinue randomization to any doses unlikely to demonstrate statistically significant improvements over placebo at the conclusion of the study. This interim futility analysis was performed on unblinded 2-hour pain-free response data by an independent statistician who was not involved with this trial.
The results from this interim analysis were determined according to whether the pre-set futility criterion had been met or not. An estimated difference in the 2-hour pain-free rate of 0.055 (i.e., 5.5%) or less between a Zolmitriptan nasal spray dose and placebo was defined as providing evidence of futility for that dose.
To assess for futility, a logistic regression model was fit with the 2-hour pain-free status as the response variable, treatment as a fixed factor, and center as a random factor. For each dose, the least squares (LS) mean difference versus placebo in the 2-hour pain-free rate was estimated. These LS estimates were then compared to the futility stopping boundary of 0.055. That is, an estimated difference in the 2-hour pain-free rate of 0.055 (i.e., 5.5%) or less between a ZOMIG nasal spray dose and placebo provided evidence of futility for that dose. The futility tests were conducted sequentially. First, the 0.5 mg dose was tested for futility. If this dose was determined to be futile, then the 2.5 mg dose was tested for futility. If the 2.5 mg dose was also determined to be futile, then the 5 mg dose was to be tested for futility. For any dose determined to be futile, no new patients were to be allocated to this treatment group with all ongoing patients randomly assigned to this treatment group continuing study participation until completion or discontinuation.

According to the sponsor the selected futility boundary and sequential testing procedure were discussed with the FDA in a Type C Meeting (Preliminary Comments correspondence dated 28 August 2012).

The interim futility analysis was performed on 5 October 2012. As a result of this analysis, the ZOMIG 0.5 and 2.5 mg dose groups met the futility definition with patient allocation to these 2 doses discontinued. After protocol amendment and Institutional Review Board (IRB) approval, all new patients were randomly assigned to either ZOMIG 5 mg or placebo in a 1:1 ratio with the total sample size adjusted to ensure approximately 250 evaluable patients into the ZOMIG 5 mg and placebo groups. Further details of the futility analysis were specified in a separate charter (see interim analysis futility charter [2 October 2012]).

The independent statistician was to determine the unblinded futility for the primary variable based on the futility criterion as described above. The independent statistician was to keep the interim analysis results confidential and ensure the blind was maintained for the AZ and

Quintiles study and project teams. Only the results of the futility analysis, i.e., an assessment as to whether the futility criterion had or had not been met for each dose, was to be communicated to the Astra Zeneca Zomig core clinical team members.

After database lock, Quintiles biostatistics group discovered that the actual randomization schedule was labelled as dummy and released during preparations for the interim futility analysis (5 individuals involved in the interim analysis but not otherwise on the main study team or the final analysis became aware and took steps to contain the information). An investigation revealed that no unblinding of any study-related personnel occurred. Although there was no evidence of unblinding, additional exploratory analyses were produced to assess for potential bias. These analyses examined key efficacy results for pain-free status and headache response for those patients randomized before conducting the futility analysis and separately for those randomized after. These analyses showed similar results before versus after the inadvertent release of the actual randomization schedule, supporting the conclusion that no bias had been introduced.

Data monitoring committee(DMC)
Separate external DMCs were constructed to perform the interim sample size re-estimation analysis and the interim futility analysis. Each DMC consisted of an external statistician independent of the study and project team. The DMC was to only communicate the decision on the total sample size to the project team.

The interim analysis charter (17 December 2010) and interim analysis futility charter (2 October 2012) provided detailed information on the remit, composition, and responsibilities of each DMC team member.

3.2.1.1 Patient Disposition

A total of 798 patients were randomized to the study: 288 to ZOMIG 5 mg, 99 to ZOMIG 2.5 mg, 115 to ZOMIG 0.5 mg, and 296 to placebo. Of the 798 patients, 82.3% received study drug, 90.4% completed the study and 9.5% discontinued from the study. Patient disposition was similar across treatment groups. All patients received their assigned treatment. Overall, the most common reason for study discontinuation was eligibility criteria not fulfilled (6.6%). No patients discontinued due to AEs.

Overall, of the 656 FAS patients, 3.8% (25/656) had at least 1 major protocol violation or deviation and were excluded from the PP analysis set. The most common protocol violation or deviation leading to exclusion from the PP analysis set was a study procedure deviation— patient sleeping within 2 hours after taking the study drug (2.3%). The percentages of FAS patients excluded from the PP population were numerically higher in the ZOMIG 2.5 and 5 mg groups (6.2% and 5.2%, respectively) than in the placebo and ZOMIG 0.5 mg groups (2.8% and 1.1%, respectively); patients in the higher two ZOMIG dose groups (2.5 and 5 mg) were twice as likely to have slept than those in ZOMIG 0.5 mg or placebo group. Only 0.9% of patients were incorrectly randomized after responding to placebo challenge during run-in.

The disposition of patients in this study is summarized in Table 1 and the sample sizes in the primary analysis set (FAS) as well as others are provided in Table 2. Note that patients who were randomized but did not treat an attack during the double blind study period are not included in the primary analysis. Slightly more randomized patients did not take drug in those assigned to drug groups than placebo {drug not taken/no migraine attack: placebo n=43 (14.5%) , 0.5 mg n=23 (20.0%), 2.5 mg n=18 (18.2%), 5.0 mg n=57 (19.8%), overall n=141 (17.7%)}. Most of the patients excluded from the FAS were due to the study procedure deviation of the patient sleeping within 2 hours after taking the study drug, with this deviation occurring more frequently in the ZOMIG 2.5 and 5 mg groups.

Table 1 Patient Disposition

		ZOMIG			
	Placebo n (%)	**0.5 mg n (%)**	**2.5 mg n (%)**	**5.0 mg n (%)**	**Total[a] n (%)**
Patients enrolled					1653
Patients randomized	296 (100.0)	115 (100.0)	99 (100.0)	288 (100.0)	798 (100.0)
Patients who were not randomized					855
Patients who took study drug	253 (85.5)	92 (80.0)	81 (81.8)	231 (80.2)	657 (82.3)
Patients who did not take study drug	43 (14.5)	23 (20.0)	18 (18.2)	57 (19.8)	141 (17.7)
Patients who completed study	269 (90.9)	98 (85.2)	86 (86.9)	268 (93.1)	721[b] (90.4)
Patients who discontinued study	26 (8.8)	17 (14.8)	13 (13.1)	20 (6.9)	76[b] (9.5)
Patient decision	2 (0.7)	1 (0.9)	0	2 (0.7)	5 (0.6)
Eligibility criteria not fulfilled	16 (5.4)	12 (10.4)	10 (10.1)	15 (5.2)	53 (6.6)
Death	0	0	0	0	0
AE	0	0	0	0	0
Severe non-compliance to protocol	1 (0.3)	0	0	0	1 (0.1)
Development of study-specific withdrawal criteria	1 (0.3)	0	0	0	1 (0.1)
Patient lost to follow-up	3 (1.0)	2 (1.7)	1 (1.0)	2 (0.7)	8 (1.0)
Other	3 (1.0)	2 (1.7)	2 (2.0)	1 (0.3)	8 (1.0)

AE adverse event.
[a] The "Total" column summarizes across all treatment groups.
[b] For 1 randomized patient receiving placebo (E1230101), the primary investigator did not complete the TERM page or sign the casebook. Thus, this patient was not counted as either completed or discontinued.
Note: Percentages are based on the number of randomized patients in each treatment group.

Note: This table was copied from page 48 of the sponsor's study report

Table 2 Analysis Sets (All Randomized Patients)

		ZOMIG			
	Placebo	0.5 mg	2.5 mg	5.0 mg	Total[a]
Patients randomized	296	115	99	288	798
Patients included in safety analysis set	253	92	81	231	657
Patients excluded from safety analysis set	43	23	18	57	141
Patients included in FAS	253	91	81	231	656
Patients excluded from FAS	43	24	18	57	142
Patients included in PP analysis set	246	90	76	219	631
Patients excluded from PP analysis set	50	25	23	69	167

FAS full analysis set; PP per-protocol.
[a] The "Total "column summarizes across all treatment groups.
Note: This table was copied from page 51 of the sponsor's study report

3.2.1.2 Baseline Demographics and Disease Characteristics

In general, baseline demographic data were similar across the treatment groups. Most patients enrolled in this study were white (93.1%). Overall, the mean age was 14.4 years (range 12 to 17 years) and the percentages of patients in the 12 to 14 and 15 to 17 age groups were similar. A higher percentage of females (61.8%) than males (38.2%) participated in the study. The mean weight and BMI at baseline were similar across the treatment groups.

The mean age of onset of first migraine attack was 10.5 years. By history, patients reported an average of 4.1 migraines/month (range of 2 to 30) and an average of 2.8 non-migraine headache days/month (range of 0 to 15). Most patients had a history of migraines lasting between 4 to 6 hours (42.4%) or greater than 8 hours (38.8%) in duration. In addition, most patients reported a history of migraine without aura (58.8%). Migraine symptoms of nausea, photophobia, phonophobia, and vomiting were reported by 86.3%, 86.8%, 79.3%, and 47.7%, respectively, of randomized patients overall.

The groups that actually treated a migraine attack after randomization (Table 3) and thus were included in the full analysis set still appear balanced according to common baseline demographics and disease characteristics although it's not possible to know with certainty that the groups are balanced across all such measured or unmeasured characteristics**.**

Table 3 Baseline Demographics and Disease Characteristics

Variable	Categories or Summary	Placebo	Zomig 0.5 mg	Zomig 2.5 mg	Zomig 5.0 mg	All groups
Age	Mean (SD)	14.3 (1.7)	14.7 (1.7)	14.7 (1.8)	14.5 (1.7)	
Age Group	12 - 14	138 (54.5)	41 (44.6)	38 (46.9)	114 (49.4)	331 (50.4)
Age Group	15 - 17	115 (45.5)	51 (55.4)	43 (53.1)	117 (50.6)	326 (49.6)
Gender	F	160 (63.2)	58 (63.0)	49 (60.5)	136 (58.9)	403 (61.3)
Gender	M	93 (36.8)	34 (37.0)	32 (39.5)	95 (41.1)	254 (38.7)
Race	AMERICAN INDIAN	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Race	ASIAN	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Race	BLACK OR AFRICAN AMERICAN	13 (5.1)	5 (5.4)	5 (6.2)	13 (5.6)	36 (5.5)
Race	OTHER	3 (1.2)	1 (1.1)	1 (1.2)	2 (0.9)	7 (1.1)
Race	WHITE	234 (92.5)	86 (93.5)	75 (92.6)	216 (93.5)	611 (93.0)
Age at onset	Mean (SD)	10.5 (3.2)	10.6 (3.5)	10.8 (2.9)	10.6 (3.0)	10.5 (3.1)
Duration	Mean (SD)	8.1 (1.1)	7.9 (0.9)	7.8 (0.9)	8.1 (1.0)	8.0 (1.0)
Avg. Number Non-Migraines	Mean (SD)	2.9 (3.4)	2.7 (3.3)	2.6 (3.1)	2.9 (3.7)	2.8 (3.5)
Avg. Number Migraines	Mean (SD)	4.1 (2.3)	4.3 (2.2)	4.1 (2.4)	4.1 (2.6)	4.1 (2.4)

3.2.1.3 Sponsor's Results

Table 4 presents the results of the primary analysis. The adjusted 2-sided p-values are shown only for the comparisons allowed according to the multiple testing procedure. The rates for pain-free status at 2 hours (LOCF) were numerically higher for all ZOMIG treatment groups compared to placebo. ZOMIG was significantly better than placebo for 5 mg ($p<0.001$), with about 30% of patients receiving ZOMIG 5 mg being pain-free at 2 hours vs. about 17% of those receiving placebo. The odds of a patient in the 5 mg group being pain-free at 2 hours was 2.18 times that of a patient in the placebo group.

Table 4 Pain-free status at 2 hours post-treatment-LOCF-primary analysis(FAS)

		Pain-free status at 2 hours (LOCF)		Treated group vs. placebo			
Treatment group	N	Yes n (%)	No n (%)	Adjusted odds ratio	95% CI	Unadjusted 2-sided p-value	Adjusted 2-sided p-value (step-down)
Placebo	253	42 (16.6)	211 (83.4)	-	-	-	-
ZOMIG 0.5 mg	91	20 (22.0)	71 (78.0)	1.37	(0.75, 2.50)	0.312	NA
ZOMIG 2.5 mg	81	20 (24.7)	61 (75.3)	1.76	(0.95, 3.26)	0.071	0.071
ZOMIG 5 mg	229	68 (29.7)	161 (70.3)	2.18	(1.40, 3.39)	<0.001	<0.001

CI confidence interval; FAS full analysis set; LOCF last observation carried forward; NA not applicable; OR odds ratio.

Note: The LOCF value is the corresponding pain-free status at 2 hours or, if that value is missing, the last non-missing post-baseline pain-free status carried forward.

Note: The percentages are based on the number of patients (N) in each treatment group and are calculated as 100% x (n/N).

Note: An OR of 1 indicates that, on the average, the odds of a patient in the treated group achieving pain-free status at 2 hours is equal to that of a patient in the placebo group. An OR greater (less) than 1 indicates that, on the average, the odds of a patient in the treated group achieving pain-free status at 2 hours is greater (less) than that of a patient in the placebo group.

Note: This table was copied from page 56 of the sponsor's study report

Headache response rates at 2 hours (LOCF) were numerically higher for all ZOMIG treatment groups when compared to placebo (39.1%): 44.0% for 0.5 mg, 53.1% for 2.5 mg, and 50.7% for 5 mg. ZOMIG 2.5 and 5 mg were significantly better than placebo (p=0.021 and p=0.010, respectively), but ZOMIG 0.5 mg was not significantly better (p=0.458). The odds of a patient with a headache response at 2 hours post-treatment in the 2.5 and 5 mg groups were 1.82 and 1.61 times, respectively, that of a patient in the placebo group.

For the symptoms of nausea and vomiting, no significant reductions in the presence of symptoms were seen for any ZOMIG dose at any time. For the symptom of sensitivity to light, nominally significant reductions were seen at 2, 3, and 4 hours for the ZOMIG 2.5 and 5 mg groups. For sensitivity to sound, nominally significant reductions were seen at 2 and 3 hours for ZOMIG 2.5 and 5 mg. ZOMIG 0.5 mg was not significantly better than placebo at any time point for either sensitivity to light or sound.

3.2.1.4 Reviewer's Results

This reviewer verified the sponsor's table summarizing the primary analysis.

During the treatment period, no patients took rescue medication prior to the 2-hour

timepoint (or prior to their 2-hour assessment). Several patients per group were reported to have slept within 2 hours after taking the study drug [4 (1.6%) placebo, 1 (1.1%) 0.5 mg, 2 (2.5%) 2.5 mg, and 8 (3.5%) 5 mg for a total of 15 (2.3%)]. There were three such 5mg patients who slept within or at 2 hours and who were still classified as responders. A sensitivity analysis imputing a value of not pain-free at 2 hours for these patients did not alter the significance of the primary result for 5 mg vs. placebo (p=0.0016).

Very few patients needed to have pain free status carried forward due to missing the 2 hour assessment (2 from placebo and 5 from the 5 mg Zomig group). Therefore, the effect of the LOCF method prespecified by the sponsor for handling missing assessments at 2 hours post-dose is minimal in this case. In fact, 5mg was still significant if these missing assessments were assumed failures (as in the sponsor's "worst case" analysis).

Overall the estimate of the variability between centers τ^2=0.579 +/- 0.280 S.E. appears to be significantly different from zero from the analysis of the logistic regression model with random effects for centers, thus justifying the need for center adjustment in the model of pain free status at 2 hours.

Note that there are at least two different ways to analyze a binary endpoint with a model assuming a random site effect and the analysis plan does not seem to have clarified the model sufficiently. This reviewer verified the first method (generalized linear mixed model/ GLIMMIX in SAS) which was presented by the sponsor in the study report [2.18 with 95% C.I. (1.40, 3.39), p=0.0006]. The second method undertaken by this reviewer attempts to average out of the likelihood the random site effect [2.23 (1.19, 3.26), p<0.0001] (marginal model/NLMIXED in SAS). The second method also produced similar results, as did a third approach excluding site effects altogether [2.12 (1.37, 3.28), p=0.0124].

Interim Futility Analysis

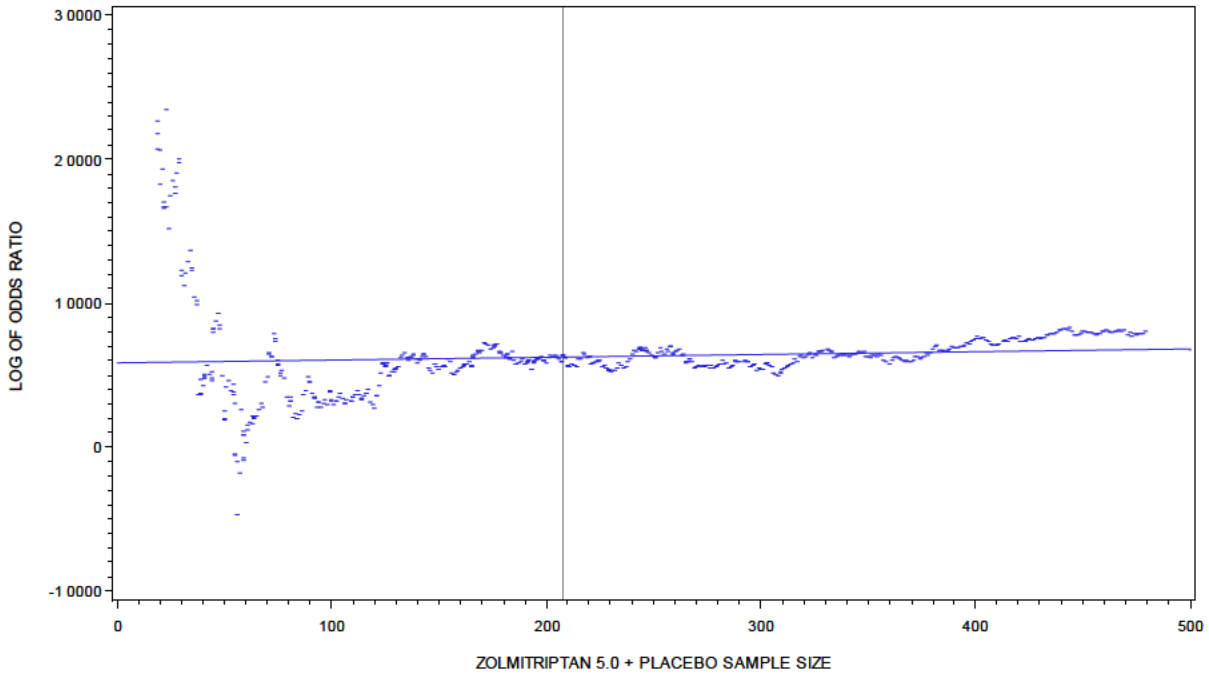
The planned Blinded Sample Size Re-estimation which was to be performed when 267 evaluable patients were available was conducted by an independent statistician on 6/18/12.
The result was that the original sample size was determined to be adequate.
The interim futility analysis was conducted on 10/5/12. Based on this analysis randomization to the two lower doses was stopped afterwards. There was no re-allocation of the remainder of the originally planned sample size for these groups to the ongoing groups.
The odds ratio of not pain-free at 2 hours for placebo to 5.0 mg was 1.7 at interim, p=0.075 (82% placebo non-pain free vs. 73% 5.0 mg non pain free at 2 hours).

The model for the probability of being pain free at 2 hours which is a logistic regression model is most readily interpreted in terms of the odds of being pain free at 2 hours, i.e., the probability of being pain free at 2 hours divided by the probability of not being pain free at 2 hours. This is because the traditional logistic regression model assumes that the logarithm of the odds (rather than the probability itself) is a linear combination of the explanatory variables, e.g., site and treatment group, in order to have better statistical performance. A 5.5% difference in pain free

rates which was the prespecified margin for interim futility corresponds to a difference on the log odds scale of log(.235/.765)- log(.18/.82)=.3361. Using the sponsor's primary analysis model with a random center effect this reviewer obtained interim estimated differences from placebo of .2081 and .3347 for 0.5 and 2.5 mg compared to placebo at the interim. Thus, both lower groups do seem to have met the futility criterion at the interim although there could be a slight difference between the sponsor's and the reviewer's cutoff date for inclusion of subjects in the interim analysis. This reviewer had a total of 419 subjects in the interim analysis.

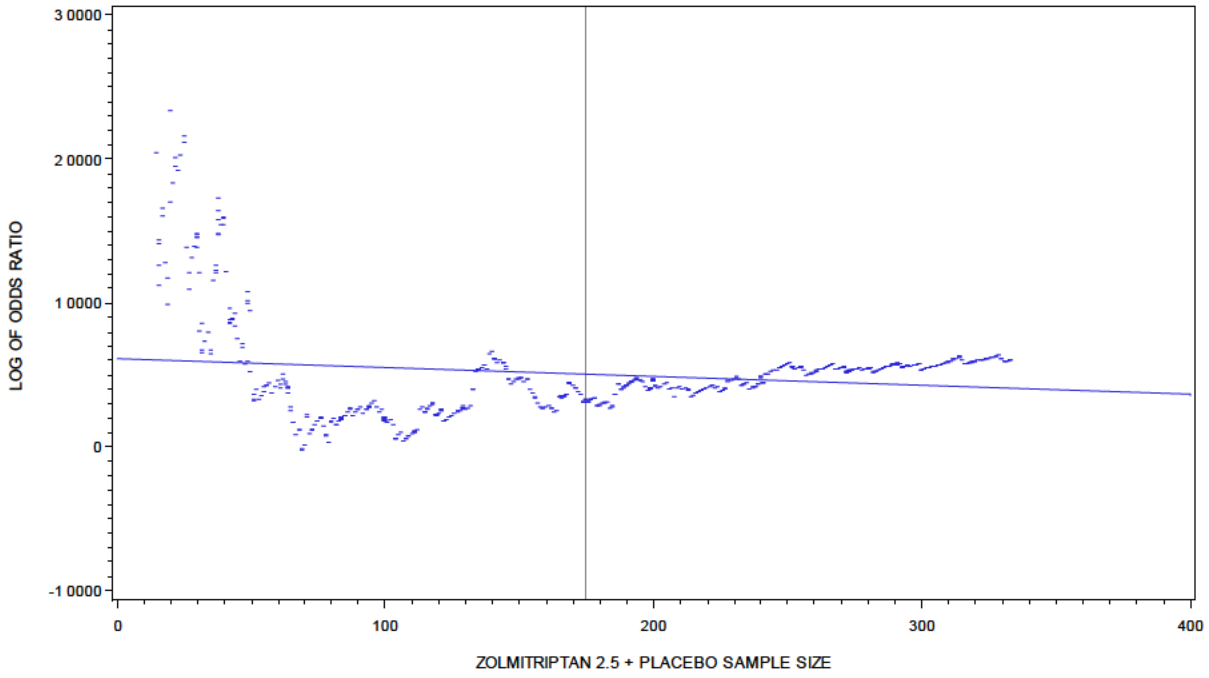
Figure 2 shows the log odds ratio of pain free at 2 hours between placebo and Zomig 5.0 mg as a function of the number of patients completed over time, i.e., calendar time. Such a figure could be useful for detecting operational bias arising from an interim analysis. The intersection with the vertical line corresponds to the interim analysis estimate. The estimate was reasonably stable around and after the interim.

Figure 2 Log of estimated Odds Ratio of pain free at 2 hours between 5.0 mg and placebo



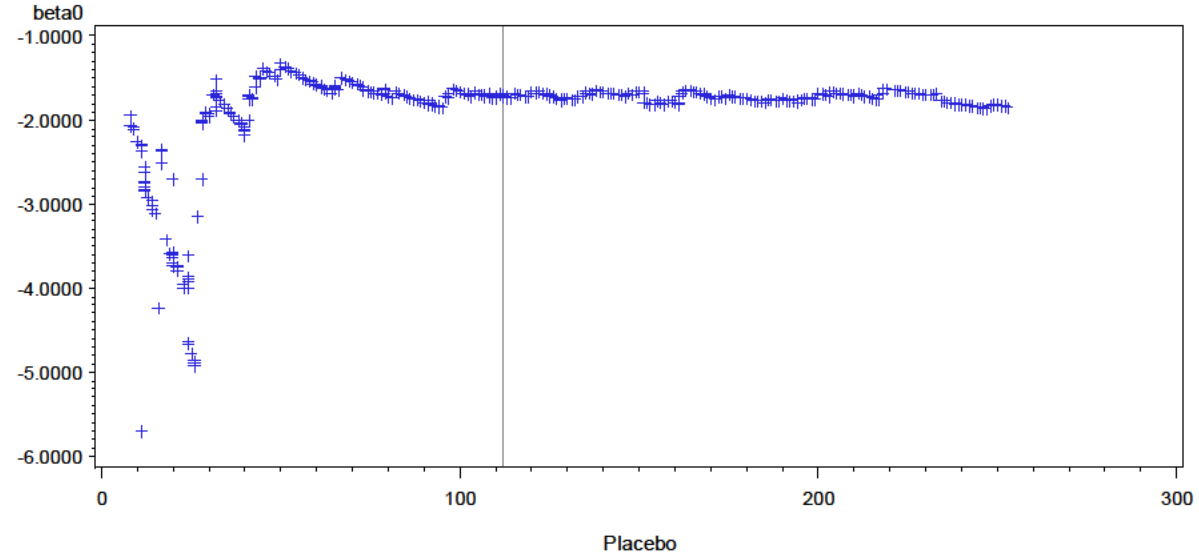
The same graph for the 2.5 mg group comparison is shown below. However, the full placebo group is not a concurrent control for middle dose (since it was ceased randomization to at the interim) so the post-interim comparison may not be statistically valid without an assumption that the later placebo subjects are exchangeable with the early ones.

Figure 3 Log of estimated Odds Ratio of pain free at 2 hours between 2.5 mg and placebo



The estimated log odds of pain free at 2 hours for the placebo group was also reasonably stable over the time period around and after the interim futility analysis as seen in Figure 4.

Figure 4 Placebo estimated odds pain free at 2 hours over Calendar Time



Using 12Oct2012 as a cutoff date for the interim (N=419) this reviewer obtained an odds ratio of

pain free at 2 hours for 2.5 mg vs. placebo of 1.40 (0.68, 2.89), p=0.3657. This can be translated into an estimated difference in proportions of 5.46%, just below the futility margin. In the same analysis an odds ratio of 1.72 (0.95, 3.14) was obtained for the high dose at the interim p=0.0747. The final analysis yielded an odds ratio of 1.76 for Zomig 2.5 mg vs. placebo. This can be translated into an estimated difference in proportions of 9.18%. The placebo percent pain free at 2 hours worsens only slightly for placebo after the interim: 18.0% before to 15.0% after. Another factor that may affect the treatment comparison is the random site effects in the model, e.g., there could be an impact on the treatment estimates of having more small sites at the interim and therefore more variable site effect estimates. The estimated variance of the random site effects decreases from 0.23 to 0.20 from interim to final analysis.

A likelihood ratio test comparing a model with adjustments for whether or not a patient completed before or after the interim futility analysis to a simpler model assuming no differences between patients before and after the interim found no compelling evidence that adjustments for the interim were needed: p=0.267. This test may be underpowered but at least it's lack of significance provides a little reassurance that the interim analysis did not introduce operational bias into the study conduct.

Therefore, in summary, there is no compelling reason to suspect that the interim futility analysis led to operational bias. However, there is still an additional issue with the validity of interpreting the middle dose results based on the final analysis since the middle dose was dropped (randomization ceased) at the interim but post-interim placebo patients with no contemporaneous middle dose parallel are involved in the test.

The secondary endpoint headache response at 2 hours post-dose was not too different between the interim and the final analysis [for the 2.5 mg vs. placebo comparison interim odds ratio: 1.68 (0.93, 3.02 p=0.0835; final odds ratio: 1.78 (1.07, 2.97) p=0.0258].

Figure 5 shows the log odds ratio of headache response at 2 hours between placebo and Zomig 2.5 mg as a function of the number of patients completed over time, i.e., calendar time. The intersection with the vertical line corresponds to the interim analysis estimate. The estimate was reasonably stable around and after the interim. The placebo proportion with headache relief at 2 hours decreased very slightly from 39.8% before the interim to 39.2 % after the interim. The Zomig 2.5 mg vs. placebo result may also depend slightly on the impact of the random site effects in the analysis model changing between the interim and final analyses (the estimated variance of the random site effects decreases from 0.065 to 0.063 from interim to final).

Figure 5 Log Odds Ratio of Headache Response at 2 hours between Zolmitriptan 2.5 mg and Placebo

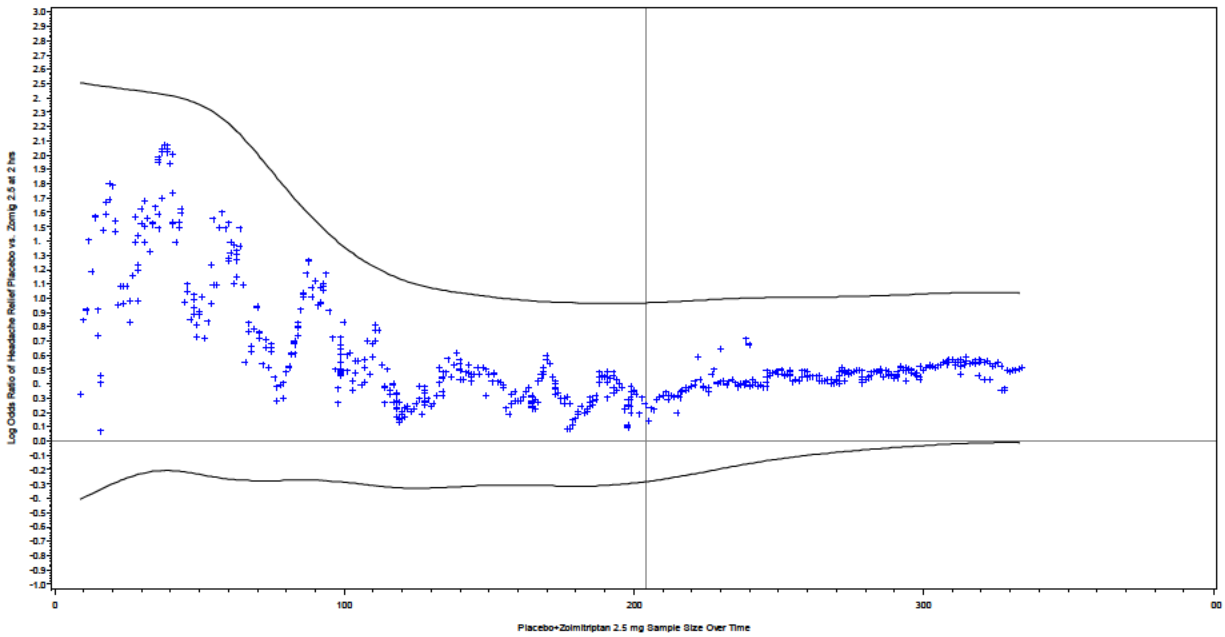
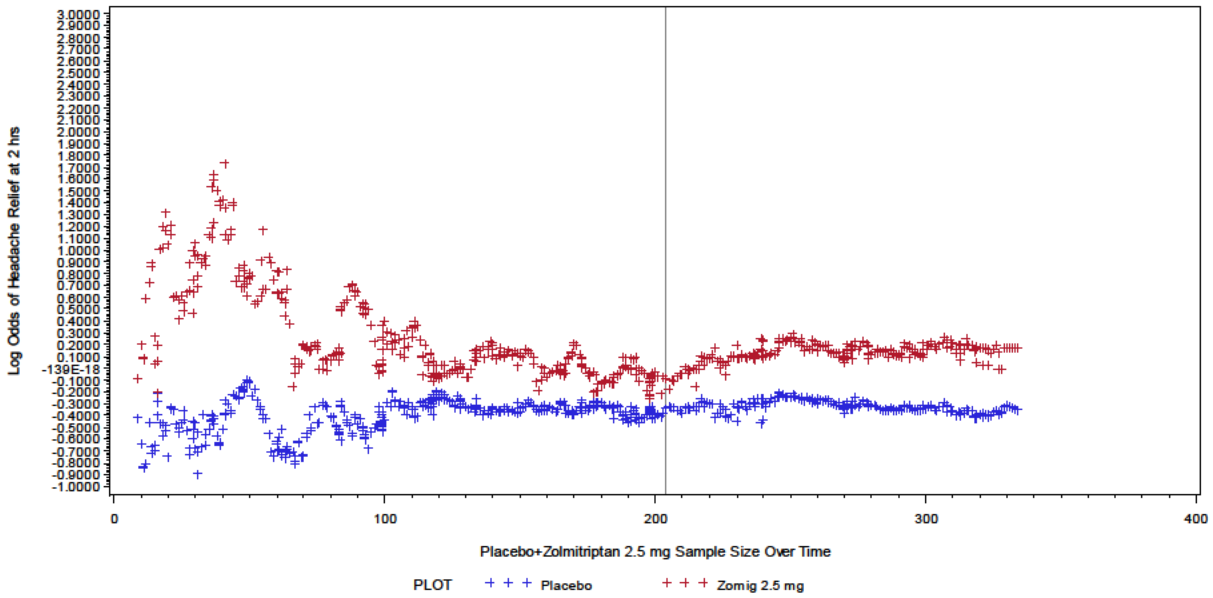


Figure 6 shows the log odds of headache response at 2 hours for placebo and Zomig 2.5 mg as a function of the number of patients completed over time, i.e., calendar time. The intersection with the vertical line corresponds to the interim analysis estimates. The estimates were reasonably stable around and after the interim.

Figure 6 Log Odds of Headache Relief at 2 Hours



3.3 Evaluation of Safety

Please see the medical officer's review for the evaluation of safety of the product.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Sixty one percent of subjects were female; ninety three percent were white, 5.5% were African American and 1.5% were "Other" (Asian American, Indian, or classified by the sponsor as Other); 87% were not of Hispanic ethnic origin. Ages ranged between 12 and 17 with an average of 14.5 and a median of 15.

Table 5 Proportions Pain Free at 2 hours by Gender Subgroup

	Description of Planned Arm								All
	Placebo		Zolmitriptan 0.5 mg		Zolmitriptan 2.5 mg		Zolmitriptan 5.0 mg		
	Pain Free (at 2hrs)		Pain Free (at 2hrs)		Pain Free (at 2hrs)		Pain Free (at 2hrs)		
	N	Prop	N	Prop	N	Prop	N	Prop	N
Sex									
Female	160	0.18	58	0.22	49	0.22	136	0.32	403
Male	93	0.15	33	0.21	32	0.28	93	0.27	254
All	253	0.17	91	0.22	81	0.25	229	0.30	657

Table 6 Proportions Pain Free at 2 hours by Race Subgroup

	Description of Planned Arm								All
	Placebo		Zolmitriptan 0.5 mg		Zolmitriptan 2.5 mg		Zolmitriptan 5.0 mg		
	Pain Free (at 2hrs)		Pain Free (at 2hrs)		Pain Free (at 2hrs)		Pain Free (at 2hrs)		
	N	Proportion	N	Proportion	N	Proportion	N	Proportion	N
Race									
AMERICAN INDIAN OR ALASKA NATIVE	1	0.00	.	.	.	.	.	.	1
ASIAN	2	0.00	.	.	.	.	.	.	2
BLACK OR AFRICAN AMERICAN	13	0.15	5	0.00	5	0.20	11	0.27	36
OTHER	3	0.33	1	1.00	1	1.00	2	0.50	7
WHITE	234	0.17	85	0.22	75	0.24	216	0.30	611
All	253	0.17	91	0.22	81	0.25	229	0.30	657

Table 7 Proportions Pain Free at 2 hours by Age

	Description of Planned Arm								All
	Placebo		Zolmitriptan 0.5 mg		Zolmitriptan 2.5 mg		Zolmitriptan 5.0 mg		
	Pain Free (at 2 hours)		Pain Free (at 2 hours)		Pain Free (at 2 hours)		Pain Free (at 2 hours)		
	N	Proportion	N	Proportion	N	Proportion	N	Proportion	N
Age									
12	47	0.11	15	0.33	15	0.20	38	0.42	116
13	49	0.20	12	0.17	8	0.50	35	0.23	105
14	42	0.10	14	0.43	15	0.00	39	0.21	110
15	47	0.19	14	0.21	13	0.46	37	0.30	111
16	37	0.19	20	0.10	12	0.17	51	0.31	121
17	31	0.23	16	0.13	18	0.28	29	0.31	94
All	253	0.17	91	0.22	81	0.25	229	0.30	657

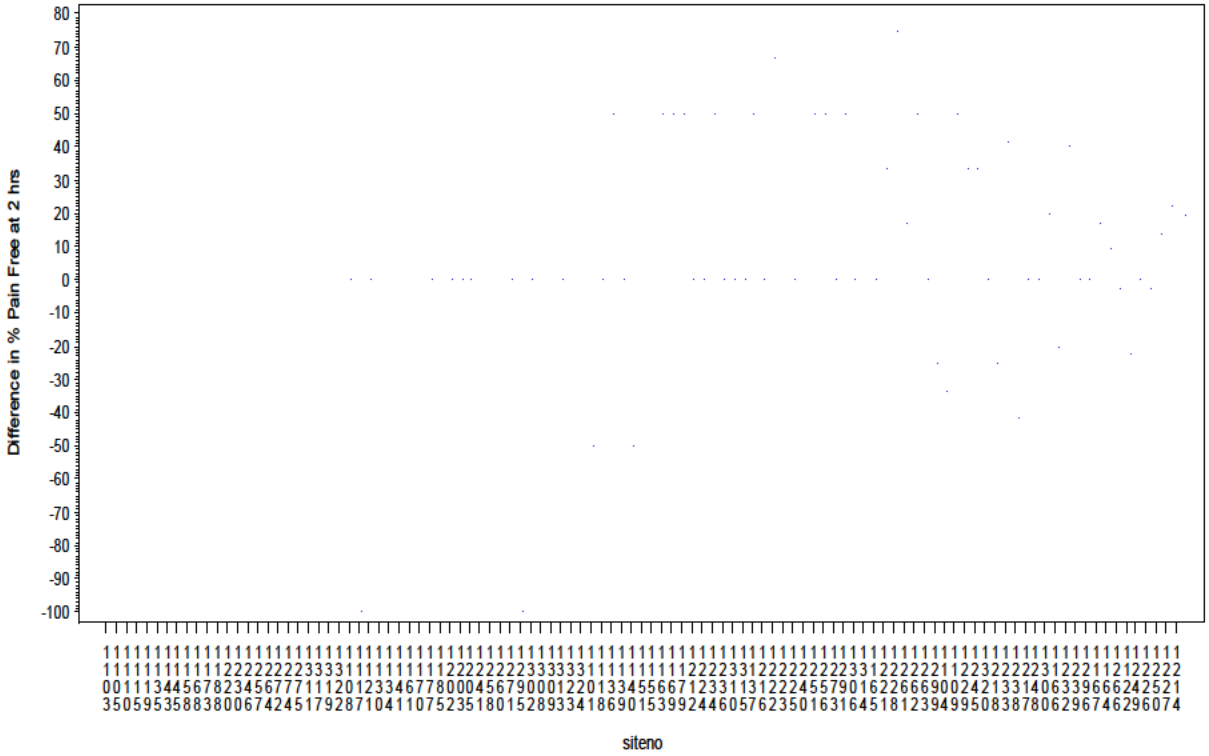
A test for any differential treatment group effects by gender was insignificant, p=.70.
A similar test for race categorized by the most frequent subcategory vs. Other (White vs. Other) was not significant, p=0.80. In addition, a test for an interaction between age subgroup and treatment: age>14 vs. age≤ 14 gave a nominally insignificant p-value of 0.12.
Odds ratios of pain free at 2 hours for high dose vs. placebo were fairly homogeneous across ages as well: a Breslow-Day test for equal odds ratios resulted in p=0.38, i.e., no compelling evidence that odds ratios varied across ages.
Therefore, in summary there is no compelling evidence that there were treatment group differences that varied by gender, race, or age subgroups.

4.2 Geographic Region

There were 129 study sites spread across the US, Latin America, Europe, and South Africa. Forty five (45) percent of patients enrolled in the US and the second biggest country was Hungary at 27%.

Figure 6 shows the observed differences in proportions pain free at 2 hours between the high dose and placebo at specific sites. The size of the plotting symbol is proportional to the number of patients randomized at the given site. Positive differences favor Zomig 5 mg. There is no compelling evidence that any one site is an extreme outlier or was responsible for the majority of the overall result.

Figure 6 Treatment Group Differences by Site



The effect for 5 mg on pain free at 2 hours in the US subgroup achieved nominal significance p=0.036, with an estimated odds ratio and 95% Confidence Interval of 1.7 (1.04, 2.89). Note that for this geographic region analysis model the random effect for sites was omitted since it would be redundant when the region effect is included.

4.3 Other Special/Subgroup Populations

No other special/subgroup populations are reported.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The study shows that the high dose 5.0 mg Zomig was significantly better than placebo in terms of pain free 2 hours after treating the migraine in the double blind period. The study procedures included an unblinded sample size re-estimation and an interim futility analysis based on the results of which randomization was subsequently ceased to the low and middle doses. Therefore, there is a statistical issue with the interpretation of the middle dose results when the data collected after the interim is included in the analysis since the middle dose was not randomized to after the interim analysis. In particular, placebo patients enrolled after the interim affect the test for the middle dose but they have no contemporaneous parallel in the middle dose cohort. Therefore, any trend in the placebo dose over time after the interim could potentially bias the test of the middle dose. The same is true for the lower dose which was also dropped due to a futility determination made at the interim. The results for the middle dose using all available data would need an assumption that there was no temporal dependence of the characteristics of the placebo group after the interim analysis in order to be statistically valid although perhaps it helps that the high dose group continued in parallel with the placebo group (so at least there was another concurrent arm and they were both blinded).

The SAP is dated November 18, 2013 which is after the interim analysis for futility (October 2, 2013) and, also, it references the outcome of the futility analysis. Since new previously unplanned changes to a final analysis plan, should not be made once an interim analysis has been performed the protocol was relied on to the extent possible for prespecified efficacy analyses.

5.2 Conclusions and Recommendations

Study D1220C00001 demonstrated a statistically significant effect of the 5 mg Zolmitriptan dose compared to placebo in terms of the primary efficacy endpoint, pain free at 2 hours in the study population of adolescents aged 12 to 17. In case there may be benefit risk considerations and given that the high dose was significant on efficacy it may be important to note that the middle dose 2.5 mg had a nominal $p<.10$ on the pain free at 2 hours post-dose as well as the headache response at 2 hours post-dose endpoints. An assumption of exchangeability of the placebo group before and after the interim is needed to have statistical validity of the final analysis results for the middle dose vs. placebo comparison since randomization was ceased to it after the interim analysis based on expected futility for it, but randomization continued to placebo. Therefore, for Zomig 2.5 mg more weight should be given to the interim estimates.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRISTAN S MASSIE
06/09/2015

KUN JIN
06/09/2015
I concur with the review.

KOOROS MAHJOOB
06/09/2015
I concur with the revew