CLINICAL REVIEW

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Reviewer Name	Teresa A. Podruchny
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(Proposed) Trade Name	
Established Name	Zomig (zolmitriptan) Nasal Spray
Therapeutic Class	Triptan
Applicant	AstraZeneca (AZ)
Priority Designation	S
Formulation	Intranasal spray
Dosing Regimen	Not Applicable at this time
Indication	Migraine
Intended Population	12-17 year olds

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EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Sponsor submitted one efficacy trial (D1221c00005) and requests that the study be used to fulfill PREA. I recommend that the Division consider the study inadequate to meet the terms of PREA as I do not believe the study data are definitively interpretable due to the imbalance in treatment groups secondary to the post-randomization exclusion of placebo-responders. This imbalance is noted in the FDA statistical reviewer's review (intent-to-treat (ITT) population, defined as all patients with post 2nd device efficacy data, 61 placebo and 81 zolmitriptan) and in the placebo response rate of 31% in the placebo-zolmitriptan group and about 23% in the zolmitriptan-placebo group for the 1st attack data (FDA statistical review pages 15 and 14 /19 respectively). In addition, the FDA statistical reviewer (Dr. S. Yan) noted a large number of imputations and complex imputation methods, poor compliance and poor data quality. As I understand it, an interpretable study is an expectation of PREA.

Even if the data were considered interpretable, Dr.Yan's review indicates that the data do not support an efficacy claim. Dr. Yan analyzed the 1st attack data three ways for the primary endpoint of 1-hour headache response. No analysis resulted in statistically significant results (p values of 0.15, 0.12, and 0.87). Her analysis of the 2-hour sustained response yielded a p-value of 0.0696. Due to concerns about the design, a worst-case-analysis was performed. Admittedly, this is a conservative and somewhat extreme analysis. The all-randomized treated (ART) worst-case-scenario analysis of 1st attack data is not statistically positive. The ART analysis results of the 1st attack data trend toward placebo.

This efficacy trial was the subject of much communication with the Sponsor (see the Regulatory History section of this review) and generally speaking, FDA and the Sponsor disagreed on the adequacy of the design, specifically on the post-randomization exclusion of placebo responders, and on the Sponsor's initial primary endpoint. The Sponsor also performed analyses that include an analysis of the originally proposed primary endpoint. The reader is referred to section 6.1.4 and Appendix 10.1.1 for further presentation and discussion of these data.

In addition to this trial not being definitively interpretable, as there are no approved products for adolescent migraine and clinicians do use triptans off-label in this population, it seems reasonable to ask the Sponsor to conduct another trial that is less complicated in design and statistical methodology. The Sponsor could consider a large placebo-controlled, parallel-group study, with any enrichment performed pre-randomization. Additionally, the Sponsor might consider other doses.

Whether the Sponsor has adequate safety exposure and data at single dose is unclear to me given that 40% of the ZNS is absorbed in the first 15 minutes and study D1221C0004 did not include an assessment this early (EKG was at 10 hours post-dose) and the study was small (n=15, 12 evaluable). EKG and vital signs early and at expected Tmax of the parent and metabolite should be monitored in a larger number of adolescents in any future safety study.

1.2 Recommendation on Postmarketing Actions

I recommend the Sponsor perform a double-blind, placebo-controlled, parallel group, study of migraine in adolescents. Any placebo enrichment should be done before randomization.

1.2.1 Risk Management Activity

I recommend consideration that the Sponsor provides background rates in future PSURs for some of the events seen in the cumulative exposure tables of the most recent PSUR and to provide product use (off-label) information by formulation for adolescents.

1.2.2 Required Phase 4 Commitments

If the Division agrees that the Sponsor's PREA obligation is not meant, the Sponsor will need to perform another study in the pediatric population.

1.2.3 Other Phase 4 Requests

None at this time.

1.3 Summary of Clinical Findings

Additional efficacy and safety information may be found in appendices 10.1.1-10.1.3 of this document.

1.3.1 Brief Overview of Clinical Program

The clinical program for the use of ZNS in adolescents was based on one efficacy study (D1221c00005) and a PK study of ZNS in adolescents and adults. Pediatric Exclusivity for the active moiety was granted previously based on a study in adolescents using the tablet formulation (NDA 20768).

1.3.2 Efficacy

Due to design and conduct flaws, the study is not definitively interpretable. If one chooses to interpret the study, I do not believe it is statistically positive based primarily on results of analyses performed by the FDA statistical reviewer and the Sponsor's own ITT data results.

1.3.3 Safety

There are no new obvious safety signals from the efficacy trial, D1221c00005, or the PK trial, D1221c00004, submitted with this application. The data in both studies are limited as described in section 7.2.4 of this review.

PSUR data in general and not limited to this application or product are challenging due to multiple factors, including the presence of potential confounders and insufficient information in many reports. I suspect that most of the serious, unlisted events noted in the detailed review of post-marketing data are probably within background. The Sponsor should provide background rates in future PSUR updates for serious and unlisted events.

Remarks from Consultative review dated July 2008 (J. Tonnig, M.D. M.P.H, R.Ph. OSE, Review of Triptans and Pulmonary Embolism/Deep Vein Thrombosis Events) indicate that, based on review of AERs cases, there did not appear to be a strong association between triptans and the development of DVT/PE. This review also noted that triptan labels may need greater standardization with respect to thrombophlebitis, deep vein thrombosis (DVT) and pulmonary embolism (PE).

1.3.4 Dosing Regimen and Administration

Not applicable to this supplemental NDA.

1.3.5 Drug-Drug Interactions

The PSUR included with the initial submission of this NDA supplement (covering period 3-7-06 to 3-6-07) states that interaction with inhibitors of the P450 isoenzyme CYP1A2 such as fluvoxamine, sertraline, and the quinolone antibiotics cannot be excluded. Section 4.5 of the Company's Core Data Sheet (CDS) describes that following cimetidine, the half-life of zolmitriptan was increased by 44% and the AUC by 48% and those of the active metabolite were doubled. Based on the overall interaction profile, an interaction with P450 CYP1A2 cannot be excluded. The CDS recommends dosage reduction with compounds of this type, such as fluvoxamine and the quinolone antibiotics.

Current U.S. labeling contraindicates use within 24-hours of treatment with another 5-HT1 agonist or ergotamine and has a precaution/warning for use with SSRIs or SNRIs, which would capture fluvoxamine (SSRI). CYP1A2 mediated metabolism is not noted in the label and ciprofloxin, a prescribed quinolone antibiotic, is not mentioned in current U.S. labeling. I recommend the Division formally consult the Office of Clinical Pharmacology and Biopharmaceutics, in an expeditious manner, regarding this information and potential changes to the label.

1.3.6 Special Populations

Pregnant women, nursing mothers, geriatric patients, and patients with hepatic or renal impairment were not the populations in the studies submitted with this supplement, therefore no new information about these populations was gained. The PSURs reviewed with this supplement state that there is no evidence of an increased risk of any adverse drug reaction in elderly patients or those with impaired organ function. The PSUR submitted in May, 2008 states that the profile and frequency of adverse events for patients 12-17 years is consistent with zolmitriptan use in adults. Also noted is that efficacy and safety have not been studied in children < 12 years old.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zolmitriptan is a selective 5-HT1B/1D receptor agonist labeled for the acute treatment of migraine, with or without aura, in adults. The product is available as an orally disintegrating tablet, a tablet, and a nasal spray. The tablet formulations come in 2.5 mg or 5 mg of zolmitriptan per tablet. The nasal spray (ZNS) contains 50mg/ml zolmitriptan and the unit delivers a dose of 5mg. The ZNS devices are intended to be single use devices.

Zolmitriptan in tablet formulation was approved in the US for adult use in 1997 with the orally disintegrating tablet approved in 2001 and the nasal spray in 2003. As of March 2008, zolmitriptan was approved in 93 countries for acute treatment of migraine with or without aura.

Migraine prevalence increases through the teen years. The Sponsor quotes recent publications as noting that one-year prevalence of migraine in 7-15 year olds is 11% diagnosed as per International Headache Society criteria. Clinical migraine features in adolescents can differ from those in adults. Children may have more bilateral headaches, especially younger children, and the duration may be shorter.

A Pediatric Plan was submitted to NDA 21450 for ZNS which included a PK study and an acute efficacy and safety study (studies D1221c0004 and D1221c00005 respectively). The Sponsor hopes to have fulfilled the Pediatric Research Equity Act (PREA) commitment for this NDA with these studies.

The design of the Sponsor's efficacy trial, D1221c00005, includes an enrichment of the population after randomization and is a crossover study. Both were issues with which the Agency did not agree and basically advised the Sponsor against, although the Sponsor had started the trials when the advice arrived (initial study outline/draft submitted June 2003, final draft submitted September 23, 2003, Advice Letter with comments dated October 30, 2003). The Sponsor decided to continue the trial. The disagreement over the post-randomization exclusion of subjects continued and there were a number of discussions or communications with the Company about this (see Regulatory History). The Sponsor argues, essentially, that the design is reasonable and the data can be interpreted. Their argument is summarized in the clinover.pdf document, which I paraphrase in the following paragraphs.

The Sponsor states that a number of triptan trials in this age group failed to achieve statistical significance on their primary endpoint although off-label use is present. The placebo-controlled trials failed at a 2-hour endpoint but endpoints such as 1-hour headache response suggest that triptans are effective (Sponsor references papers by K et al, 2004 and Winner P et al, 2000). The Sponsor posited that a number of factors likely contributed to the failed adolescent triptan trials and listed these as 1) a higher placebo response rate than in adults (50-65% v 34%), 2) the uniformity of diagnosis might have been affected by the differences in diagnostic criteria, and 3) delayed treatment since adult supervision is required. An AstraZeneca Advisory Board was

consulted to address the issues above. With regard to the placebo response rate, one potential design considered was a single-blind, placebo challenge pre-randomization in a double-blind (DB), placebo-controlled (PC) trial. The Company states it was not known whether the placebo responders were a fixed cohort and therefore this approach might fail to address the problem. The Company states that alternatively, a single-blind placebo challenge for each attack, followed by DB, PC treatment, would require randomization at the beginning of the trial as randomization at the point of non-response was not logistically feasible and would inevitably delay treatment. The Sponsor considered limiting the trials to a small number of sites with pediatric headache expertise in order to address diagnostic uniformity. The Sponsor stated this would limit enrollment thus making a two-attack cross over design preferable. The Sponsor states they chose a 1-hour primary endpoint to reflect shorter duration of adolescent migraines *(Reviewer's note: I think it is fair to say that generally it is thought adolescent migraine duration is shorter when compared to the duration of migraine in adults. Somewhat in contrast to this, in the efficacy trial submitted (D1221c0005), as per the migraine history demographic information, 58-61% of the treatment sequences had a history of migraine duration >8hrs-see Appendix 10.1.1.)*

The Sponsor states that an enrichment design that included a single blind placebo challenge within attack was supported by the AstraZeneca Advisory Board. The Sponsor states that by using a two attack cross over design, a patient responding to placebo for the first attack would not be withdrawn from the trial but would treat a 2nd attack as would patients who did not respond to placebo and that this approach would contribute to the understanding of whether the placebo responders were a fixed or variable group.

The Sponsor acknowledges that this design leads to the consideration that the comparison of treatments might be biased, but that since the placebo challenge applies equally to all patients and response to this cannot be expected to differentially influence the response to randomized treatment of those patients who are non-responders to placebo challenge, it is unlikely that bias will be introduced and that patients responding to the placebo challenge would be expected to behave as if they were missing at random. The Sponsor suggests that the robustness of such a design can be assessed by including patients as responders to their randomized treatment. The Sponsor states that a publication by Fergusson et al, 2002[1] on post-randomization exclusions indicates that excluding all randomized patients who do not receive the treatment will not bias the analysis providing that allocation to treatment group could not influence the likelihood of eligibility for inclusion in the analysis.

2.2 Currently Available Treatment for Indications

There are no approved therapies for acute migraine in children and adolescents (<18 years of age). The 2004 American Academy of Neurology (AAN) Physician Practice Parameter[2] for the pharmacological treatment of migraine in children and adolescents recommends that ibuprofen (for children >age 6 years) and sumatriptan nasal spray (for children >12 years of age) are effective and that acetaminophen is probably effective and can be considered for the acute treatment of migraine.

2.3 Availability of Proposed Active Ingredient in the United States

Zolmitriptan is marketed in the U.S. as a nasal spray as well as in two tablet formulations.

2.4 Important Issues With Pharmacologically Related Products

- Contraindications for triptan use include ischemic heart disease, coronary artery vasospasm, other significant underlying cardiovascular disease, cerebrovascular syndromes, uncontrolled hypertension, and hemiplegic or basilar migraines. Serious cardiovascular events, life-threatening cardiac arrhythmias and death, significant blood pressure elevations, and potentially life-threatening serotonin syndrome particularly in combination with SSRIs or SNRIs have been reported with these products. Labeling notes that gastrointestinal ischemic events and peripheral vasospastic reactions such as Raynaud's syndrome may be caused by 5HT1 agonists.
- Throat tightness, throat pain, dizziness, dry mouth, unusual taste, chest pain syndromes are associated with the use of triptans.
- Triptans are not to be used in combination with ergot-containing medications or MAO-A inhibitors.
- A one year post-pediatric exclusivity review covering the period from 12-13-2003 to 1-18-2005 was conducted by the Division of Drug Risk Evaluation (DDRE) of post-marketing adverse events for NDA 20768 (Zomig tablets) in children ≤ 16 years. The reviewers indicate that no remarkable safety concerns with the tablet or the orally disintegrating tablet formulations were found. (Review date March 2005)
- Recently, the Division recently decided to request that all marketed triptans include "seizure" in the 'Postmarketing Experience' section of the label.
- At the request of this reviewer, Dr. J. Tonning of the Division of Adverse Event Analysis I, Office of Surveillance and Epidemiology (OSE), reviewed the triptans for post-marketing adverse events of pulmonary embolism and deep vein thrombosis (review dated 7-10-08) and he performed a literature review. Dr. Tonning concluded that based on AERs cases reviewed, there did not appear to be a strong association between triptans and the development of DVT/PE. OSE did not recommend changes to labeling at this time for DVT/PE (with which I agree).
- Remarks from the consultative review described above suggest and describe examples indicating that triptan labels may need greater standardization with respect to thrombophlebitis, DVT, and PE.

2.5 Presubmission Regulatory Activity

(The reader is referred to the medical review of NDA 20768 (sequence 12, dated 12-2-03 by Dr. Prohaska), the medical review of submission PB 000 to NDA 21450/PU 37 IND 53848, signed 12-10-02, and the medical reviews for IND 53848 serials #50 and #53 (6-24-03 and 9-23-03 submission dates) for additional details regarding the pediatric studies, Written Request, and development plan.)

- November 25, 1997 Zomig Tablet (NDA 20-768) approved.
- September 2, 1998 Proposed pediatric clinical development plan submitted.
- March 26, 1999 Original Pediatric Written Request issued (for tablet).
- April 16, 1999 Sponsor's reply to Written Request submitted
- April 29, 2002 Pediatric Written Request Amendment issued (amended the timeframe of the Written Request, all other terms were to stay the same. Study reports of studies as per March 26, 1999 Written Request were to be submitted on or before September 30, 2003).
- July 3, 2002-Pediatric Written Request Reissue for NDA 20768-the initial Written Request was issued before the passage of the "Best Pharmaceuticals for Children Act" (BPCA). This letter describes changes under BPCA.
- August 15, 2002 Teleconference to discuss pediatric development program. A review by Dr. K. Prohaska (linked to IND53848 serial 50) indicates that there was some discussion about the proposed primary endpoint of 1-hour headache response and that this differed from the traditional 2-hour response. The Company's minutes of this teleconference were submitted on December 17, 2002 in serial 153 to the IND (Archival jacket volume 14.1). These minutes describe discussion between the Agency and the Company about the pediatric plan/exclusivity, the Pediatric Rule, and pediatric development of the both tablet formulations and the nasal spray. These minutes state that the Company requested a waiver of pediatric studies for Zomig-ZMT based on result of the Zomig tablet study and similar PK profile/efficacy between the two formulations and that FDA did not agree. The minutes note that FDA did agree to extend the deferral of pediatric studies for ZOMIG-ZMT until ZNS was evaluated in the adolescent population. Further, the minutes state that FDA agreed that the revised pediatric plan presented for ZNS was reasonable (a PK trial and an efficacy trial in adolescents) and that submission of the new ZNS pediatric plan would meet the FDA requirements to update the pediatric plan submitted in the ZNS NDA.
- November 25, 2002 revised Pediatric Development Plan for ZNS submitted. This included a synopsis of the PK study (15 adult and 15 adolescent migraineurs) that appears to have later become study D1221c0004. The Sponsor's cover letter indicates that upon completion of the PK study, the Sponsor would provide FDA with a protocol for the proposed efficacy study.
- December 19, 2002-Approvable letter issued for adult migraine ZNS application
- March 27, 2003- Sponsor submits a complete response to the December 19, 2002 action letter
- June 24, 2003- Sponsor submits a clinical study outline for the proposed adolescent efficacy and safety study, study D1221c00005.
- September 23, 2003 –the Sponsor submitted final protocol for protocol D1221 c00005.
- September 30, 2003- Approval letter issued for NDA 21450 for use of ZNS in the acute treatment of migraine with or without aura in adults. There were two phase 4 commitments concerning information **(b) (4)**
- September 30, 2003-sNDA for use of the tablet form in adolescent migraine under NDA 20768. In support of the pediatric exclusivity request, five studies were submitted.

- October 30, 2003 FDA advice letter issued with comments on study D1221c00005 and comments about the Pediatric Written Request. Study comments included-1) planned enrichment procedure and crossover design is unacceptable, believe trial results may be uninterpretable if there is an imbalance between sequences and concerns about unblinding due to local effects of zolmitriptan nasal spray, unacceptable to exclude early placebo responders after randomization. Division recommended a two attack, parallel design in which all patients treat first attack with placebo and then receive randomized treatment for 2nd attack. 2) primary endpoint of 1 hour response that may dissipate by 2 hours post dose is not clinically meaningful 3) request assess migraine recurrence out to 24 hours and 4) analyze associated symptoms .

Pediatric Written request comments: 1) The proposed adolescent efficacy study fails to "define a dose response" or a "no effect dose". FDA recommended including cohorts of 2.5 mg ZNS and 0.5 mg ZNS and for consideration of exploration of higher doses if the risk-benefit assessment was favorable. 2) The proposed adolescent efficacy study did not discuss an enrollment procedure to ensure enrollment of a similar number of adolescents between 12 -14 and 15 -17 years of age 3) The proposed adolescent efficacy study for Zomig Nasal Spray fails to use a "valid measure of headache response" and recommended evaluation of the 2-hour sustained headache response in addition to the 1 hour 4) The proposed adolescent efficacy study for Zomig Nasal Spray fails to evaluate effectiveness through hour 24. Letter recommended doing so.

- December 18, 2003-AZ submitted response to the Agency's October comments (serial 57 to IND 53848). From the Medical Officer's review of this package, it appears that Pediatric Exclusivity was granted in December to Zomig based on the adolescent development plan for Zomig Tablet. The Sponsor rejected the FDA's proposed trial design and believed that imbalance was not likely due to randomization, that the final analyses focused on within subject rather than between subjects comparison and therefore, statistical validity would not be affected by a sequence imbalance, and that there was no evidence that placebo responders were a fixed cohort of patients.
- December 2003-Pediatric Exclusivity granted to active moiety under NDA 20768
- January 7, 2004-teleconference between FDA and Company-FDA meeting minutes indicate the post-randomization exclusion of subjects continued to be problematic for the Agency as did the lack of an efficacy evaluation at 24 hours. The Sponsor asserted they expected drop-outs to be similar between cohorts and representative of the entire population. The Sponsor noted they understood FDA concerns but planned to continue the study and would attempt to address FDA concerns in the analysis of the study. Minutes note that the Sponsor was aware that FDA may find the study uninterpretable due to post-randomization exclusion.
- November 17, 2004-SAP for D1221c00005 was submitted. The Sponsor requested comments by 12-13-04. The Division advised that FDA could not guarantee review by that deadline and recommended the Sponsor wait for comments before unblinding data (Dr. Bastings' review of serial 57 to IND 53848).
- January 12, 2005- Comments on the 11-17-04 SAP for study D1221c00005 were sent by email. FDA comments included that there was no plan for dealing with possible problems in the event of significant numbers of drop-outs post randomization, that 2-hour sustained response must be a co-primary and win at 0.05, that key associated symptoms at the 2-hours sustained response should be co-primaries, any labeling claims for secondary endpoints would need agreement with the Division and replication, and that using an ITT population of patients who treat at least one attack may include patients with only one attack and that GEE could not solve this kind of problem.

- January 25, 2005- (serial 67 of IND) The Company submitted a response to 1-12-05 FDA
- March 1, 2005- A teleconference was held with the Company to discuss the submission. The following points were conveyed by FDA• That the proposed sensitivity plan would produce data that may not be interpretable and the use of GEE for missing data assumes randomness, which is not certain• FDA would accept a worst case scenario (WCS) analysis performed on either both periods or just the first attack, whichever the Company chose, but the Company should define this in advance of unblinding.• Send this worst-case analysis instead of the proposed sensitivity analysis.• FDA would not know how to interpret data on a subset of patients who provide data on both attacks• WCS analysis removes issue of missing data as there would not be any.• That the Division was re-considering whether associated symptoms have to be statistically significant in the pediatric population if they were significant in the adult population using the same drug. The Sponsor was to decide before breaking the blind to which group they would apply the worst-case scenario, both periods (the crossover design) or to those with the first attack (parallel group).
- March 16 and March 24, 2005- submissions in response to the March 01, 2005 teleconference. Data from attack 1 was to be used for the worst-case methodology. FDA considered the SAP acceptable.
- May 23, 2005-Comments resulting from the review of the March 2005 submissions sent to the Sponsor by email.
- October 25, 2005- The Company requested a meeting.
- April 19, 2006- FDA minutes (signed 1-18-07) indicate a teleconference was held between FDA and the Sponsor regarding the results of D1221c00005. The questions posed by the Company included whether FDA thought the trial demonstrated the efficacy of ZNS in adolescents. FDA indicated that based on answers to the other questions, FDA did not think so and noted that the first phase results of the study did not seem to support an efficacy claim. The Agency also noted that if the trial results were considered uninterpretable, then the PREA obligation may not be considered to be fulfilled. In terms of safety, the Company was advised that they would need to provide a rationale to support that the long-term safety data obtained with Zomig tablets are applicable to ZNS. An additional comment to the minutes notes that AZ could submit a pediatric supplement that would be considered for filing, but that the design issue would be considered a review issue.
- June 21, 2006- Dr. Luan's statistical review signed 7-6-06 indicate that the Sponsor submitted meeting minutes of the April meeting and requested responses to the questions discussed at the April 19, 2006 meeting. Statistical review of the 6-21-06 document was performed by Dr. Jingyu Luan. Her review indicates that AZ conducted additional analyses and simulations and AZ believed that the design and originally planned statistical approach were appropriate, that no evidence of systematic bias would be introduced due to the removal of placebo responders post-randomization, and that there was no increase in Type I error. Dr. Luan notes that AZ believed that based on their simulation results, substantial bias was introduced by the worst-case scenario and that Type I error was excessive and favored placebo. Dr. Luan did not agree that no major imbalance was observed as a result of the planned removal of placebo responders and noted the importance of randomization in clinical trials.
- 1-19-07-FDA emailed meeting minutes of the April 2006 teleconference to the Sponsor

2.6 Other Relevant Background Information

sNDA20768 (sequence 12) was issued a non-approvable due to failure to demonstrate efficacy in adolescents.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

Dr. T. C. Wu performed primary review for the OCPB. The interested reader is referred to his review for additional details. Dr. Wu's review states that review of the submitted PK study (D1221c00004) was performed and that the study report is acceptable from a clinical pharmacology and biopharmaceutics perspective with the qualification that final labeling language could be agreed upon between the Sponsor and the Division. **(b) (4)** I agree with this deletion.

Other OCBP labeling changes were to add information about propranolol use to the **(b) (4)** and "Drug Interactions" sections and deletions or modifications of language regarding **(b) (4)**

Dr. Wu's review summarized the pharmacokinetics of zolmitriptan and the active metabolite, 183C91, in adolescents and adults. His conclusions with respect to zolmitriptan, the active metabolite, and gender differences are below. *(The information below is either duplicated directly from Dr. Wu's review verbatim or is close to verbatim with small modification.)*

Zolmitriptan

- systemic exposure measures (AUC0-∞, AUC0-t, and Cmax) following a single intranasal dose of 5-mg zolmitriptan were similar based on geometric mean ratios (adolescents had 8-13% lower AUCs and 3% lower Cmax compared to that seen in adults). However, OCBP review notes that they do not consider the no-effect boundary of 0.5-2 for the 90% CIs of the exposure measures, pre-set by the sponsor, to be valid and adequately justified.
- The clearance in adolescents was 15% higher than adults. Female adolescents and adults had similar clearance values (geometric mean ratio of 1.03), corresponding to the similar exposure between these two populations. Male adolescents had an approximately 29% higher clearance on average, than adult male subjects, corresponding to approximately 22% lower exposure.
- The median Tmax was similar at about 2hours in both adults and adolescents. $T_{1/2}$ was slightly shorter at 3 hours in adolescents compared with 3.8 hours in adults.

- The median Tmax was 4 hours in female adolescents compared to 2 hours in female adults, although the ranges were similar.

For the active metabolite, 183C91:

- The systemic exposure was higher in adolescents than that seen in adults based on geometric mean ratios (adolescents had approximately 27- 32% higher AUCs and 17% higher Cmax compared to adults).
- Male adolescents and adults had similar Cmax values, while female adolescents had an approximately 36% higher Cmax than female adults. The reason for this is not clear, based on the limited metabolic information.
- Tmax was similar at about 4 hours in both adolescents and adults.
- $T_{1/2}$ was similar in both groups at 3.4 and 3.8 hours for adolescents and adults, respectively.

Gender differences in adolescent pharmacokinetics:

- In adolescents, female subjects had approximately 28-35% higher zolmitriptan exposure (AUCs and Cmax) than that observed in male subjects, similar to that observed in adults and also described in approved label for oral tablets. These higher exposure in female adolescents corresponds to an approximately 28% lower clearance.
- There are no significant gender differences for zolmitriptan with respect to the median Tmax (4 hours) or the $T_{1/2}$ (3.2 hours for females and 3.6 hours for males).
- The gender differences for the active metabolite in AUCs were less pronounced than that for the parent drug. However, Cmax of the active metabolite was approximately 39% higher in female adolescents.

3.2 Statistical Review

Statistical review of the sNDA submission was performed by Dr. X. Yan. The interested reader is referred to her review for additional details as needed. Dr. Yan concluded that the study failed to demonstrate that zolmitriptan was effective as treatment of acute migraine in the adolescent population. She states that neither one-hour response nor two-hour sustained response showed statistical significance regardless of the data set used.

Dr. Yan's review indicates that she had "extreme difficulties" in analyzing the data sets due to poor data quality, missing information, poor organization of the data, and various errors. She notes there appeared to be numerous imputed efficacy values that deviated from the statistical plan and describes discrepancies between the Sponsor and her in imputed data (p.12/17 of statistical review). She indicated that about 20% of the subjects had missing assessment time or had assessment time outside the 22-minute window for the placebo challenge. She questioned how/whether late assessment of the placebo challenge affected assessment for the randomized treatment. For the 1st attack, 16 were assessed after one hour and nine of them were assessed after 2 hours. The longest assessment time was 806 minutes.

Dr. Yan notes that the original protocol intended the primary endpoint to be 1-hour headache response in an enriched population using a crossover design. FDA comments on the protocol arrived after study initiation. FDA required the co-primary endpoints of 1-hour headache response and sustained headache response to 2 hours for those patients responding at 1 hour. She notes that FDA was concerned about dropping placebo responders post-randomization and concerned that there could be an imbalance between treatment groups due to dropping placebo responders post-randomization.

Dr. Yan's analysis of the response rate to placebo challenge yielded a 31% rate in the placebo/zolmitriptan (PZ) sequence for the first attack and 23.15% rate in the zolmitriptan/placebo (ZP) sequence for the first attack. For the second attack, the rates were 20.48% in the PZ sequence and 23.08% in the ZP sequence.

Dr. Yan performed analyses for both first and second attacks and a combined analysis of both attacks. She did not perform worst-case analysis because the three analyses described below and performed on the 1st attack data were negative. Dr. Yan's table displaying the data described in text below is reproduced below.

- Analysis 1 was performed based on the all randomized and treated population (ART) patient population using LOCF. All 208 treated patients were included. Subjects without assessment post 2nd device carried forward their assessment value of placebo challenge, which could be imputed. 62/100 (62%) subjects who took placebo were responders at one hour and 77/108 (71%) who were treated with zolmitriptan were responders. The logistic regression test yielded a p-value of 0.1538.
- Analysis 2 was a LOCF analysis that only carried forward values after the 2nd device. Dr. Yan states that this is the analysis that was originally intended for the study. A total of 142 subjects were included. Of these, five subjects did not take 2nd device but had assessments post 2nd device. A total of 31/61 (51%) of the placebo-treated subjects and 52/81 (64%) of zolmitriptan-treated subjected were responders at one hour. The p-value was 0.1254 from the logistic regression model.
- Analysis 3 was an analysis on observed cases (OC). A total of 131 subjects who had assessed value at 1 hour after 2nd dose were included. Of these, 28 (50%) of the 56 subjects treated with placebo and 49 (65%) of 75 subjects treated with zolmitriptan were responders at one hour. The p-value was 0.0866 from the test. *(Reviewer's note: in a telephone discussion with me on 10-10-08, Dr. Yan confirmed OC as all subjects with a 1-hour assessment after randomized treatment. The analysis was on the 1st attack data.)*

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

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

For the endpoint 2-hour sustained headache response, Dr. Yan notes that 115 subjects had values. Apparently, imputation was difficult due to missing values and the statistical reviewer found no imputation method reasonable. She believes only observed data are reliable and therefore, only used observed 2-hour response data in her analysis. 34% of the placebo- treated subjects and 52.3% of the zolmitriptan-treated subjects were responders at 2-hours (p=0.0696).

For the 2nd attack data, none of Dr. Yan's analyses produced statistically significant treatment difference results (ART p value= 0.3153, ITT p value= 0.2259, and OC p value= 0.2780).

Dr. Yan's analysis based on combining both attacks used only subjects who contributed data to both attacks. A total of 159 subjects were included in the 1-hour response (p=0.0312) and 71 in the 2-hour sustained headache response (p=0.1383).

Demographically, subjects generally were similar between the treatment sequences. 57% of the overall study group was female and 80% was Caucasian (10% Black, 9% Hispanic, <1% Asian). The average age was 14 years. Subgroup analyses by race were not performed as most subjects were Caucasian. Dr. Yan's table showing 1-hour headache response by gender and age for the ITT population (only patients with post-2nd device assessment are included) is duplicated below.

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

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

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Most of the clinical information came from the Sponsor in submissions to supplemental NDA 21450 with all of the new data from these submissions. The clinical review of the study 311CUS/0005 was utilized as this study also was submitted in support of the pediatric supplement for NDA 20768 as (zolmitriptan tablets) as part of the Exclusivity request and was reviewed by Dr. K. Prohaska for that NDA supplement.

4.2 Tables of Clinical Studies

TABULAR LISTING OF ALL CLINICAL STUDIES

Type of study	Study identifier	Primary objective of the study	Study design and types of control	Test product; Dosage regimen; Route of admin.	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type and location of study report	Site location (number of centers)
PK study	D1221C00004	To compare pharmacokinetics of zolmitriptan 5 mg nasal spray in adolescent migraineurs and in adult migraineurs between migraine attacks	2-center, open-label, nonrandomized, single-dose, parallel-group clinical pharmacology study	A single dose of zolmitriptan 5 mg in a nasal spray device	15 adults (≥18 years) and 15 adolescents (12 to 17 years, inclusive)	Adult and adolescent subjects with a history of migraine	Single dose	Completed; Full report included in this submission (Module 5.3.5.1)	2 centers in the US
Efficacy and Safety	D1221C00005	To evaluate the efficacy of zolmitriptan 5-mg nasal spray, as compared to placebo, for the acute treatment of migraine headache in adolescent subjects (aged 12 to 17 years)	Multicenter, double-blind, randomized, double-diamond, placebo-controlled, 2-way crossover study with a single-blind, placebo challenge (enriched enrollment)	A single dose of zolmitriptan 5 mg in a commercial nasal spray device administered double-blind at two migraine headaches	248 patients randomized; either zolmitriptan/ placebo (n=128) or placebo/zolmitriptan (n=120)	Migraine headache with or without aura (International Headache Society (IHS) and International Headache Society-Revised (IHS-R) criteria)	Randomization to 1 of 2 crossover sequences to treat 2 moderate or severe migraine headaches during a 12-week study period	Completed; Full report included in this submission (Module 5.3.5.1)	17 centers in the US

Type of study	Study identifier	Primary objective of the study	Study design and types of control	Test product; Dosage regimen; Route of admin.	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type and location of study report	Site location (number of centers)
Safety and efficacy	311CUS/0005	Phase I: To evaluate the efficacy of oral zolmitriptan across a range of doses for the treatment of a single migraine headache in adolescent patients (aged 12 to 17 years, inclusive). Phase II: To evaluate the safety of the long-term use of oral 5 mg zolmitriptan for the acute treatment of multiple migraine headaches in the same adolescents	This was a 2-phase, multicenter, study. In Phase I, patients were randomized to treat a single migraine headache with either 2.5 mg, 5.0 mg, or 10.0 mg zolmitriptan, or placebo. In Phase II (open-label period) patients treated multiple migraine headaches over a 12-month period with 5.0 mg zolmitriptan (tablet form).	In Phase I, patients took a single oral dose of 2.5, 5.0, or 10.0 mg zolmitriptan or matching placebo. In Phase II, patients took oral 5.0 mg zolmitriptan in an open-label fashion	850 patients randomised in Phase I were equally distributed among treatment groups: 2.5 mg (n=210) 5.0 mg (n=212) 10 mg (n=214) placebo (n=214)	Patients aged between 12 and 17 years (inclusive), with a minimum of 2 migraines per month (according to International Headache Society [IHS]-defined criteria) and a maximum of 10 migraine headaches or nonmigraine headaches each month.	Phase I: A single migraine headache was to be treated within 12 weeks of randomization. Phase II: Multiple migraine headaches were treated over a 12-month open-label period.	Completed; Full report included in this submission (Module 5.3.5.1)	40 centers in the US, 10 centers in Canada, and 23 centers in India, Finland, Germany, and UK

4.3 Review Strategy

My review focused on the studies described below and submitted with the sNDA, post-marketing data described below, zolmitriptan tablet information from labeling and other reviews, other medical or biopharmacology reviews as needed, and a brief look at published literature.

The Sponsor submitted three study reports with the initial sNDA submission; 311CUS0005, D1221c0004, and D1221c00005 and a Periodic Safety Update Report (PSUR) covering post-marketing information for the period from early March, 2006 to early March, 2007. During the review cycle (May 1, 2008), a second PSUR was submitted that covered the next year through early March 2008. The focus of the PSUR reviews was on cumulative serious unlisted events as per the PSUR submitted in May of 2008 and noting any recommendations for labeling. In general, the narratives of events were only referenced as indicated by the listing as most events happening once or a few times are likely not above the background rate given the exposure of the product. Therefore, these events would not lead to a change in labeling.

I did not re-review study 311CUS/0005 exhaustively, as it was reviewed as part of the review of the pediatric supplement submitted to NDA 20768. I did look at the adverse events described in the study report for the study and at the safety monitoring, specifically relative to EKG timing with Tmax and as noted, used the review of Dr. K. Prohaska of this study.

Although study D1221c0004 was also submitted to the NDA for 20768, it was not the main PK study for that NDA and was not a focus of detailed review at that time. I reviewed the study report for safety and for general information about the PK of the drug and the metabolite (full PK review deferred to the Office of Clinical Pharmacology and Biopharmaceutics' reviewer, Dr. T.C. Wu.)

Study D1221c00005 is the pivotal efficacy study for this supplement. In addition to utilizing formal FDA statistical review, the study report was used for safety and efficacy information. Datasets provided by the Sponsor were also explored or manipulated.

Information for tablet zolmitriptan was acquired from labeling, from Dr. Prohaska's review of the application for use of Zomig tablets in adolescents under NDA 20768, and from Dr. A. Jackson's (Office of Clinical Pharmacology and Biopharmaceutics) review of the study design of a proposed PK study of the nasal spray (Dr. Jackson's review of February 11, 2003 submission).

Additionally, I performed a limited search regarding the treatment of migraine in adolescents and perused or read a few selected abstracts or articles. The 2004 practice parameters published by the American Academy of Neurology regarding the pharmacological treatment of migraine headache in children and adolescents were read as was an article based on trial D1221c00005 (authors include two of the trial's investigators)[3].

4.4 Data Quality and Integrity

As the Division tended to believe the pivotal efficacy study was negative, no FDA inspection was performed for this supplement. Additionally, in terms of safety, the design of the study D1221c00005 was crossover with assessments at screening and after exposure of both study drugs. Thus, the interpretation of safety data in that study is limited.

A letter from the Division to the Company dated 1-22-07 indicates that inspections of bioequivalence studies in which the bioanalytical analysis was conducted by **(b) (4)** raised significant concerns about the validity of the reported results of these studies conducted in support of drug applications for marketing (from January 2000-December 2004). Study D1221c0004 was conducted between February 20, 2003 and April 13, 2003. The protocol indicates samples in this study were sent to **(b) (4)** for analysis.

The statistical reviewer noted difficulties analyzing the data due to poor quality, missing information (information not entered in the data by the Sponsor), poor organization of the data, and various errors. She noted that numerous efficacy values appeared to be imputed deviating from the rules set by the SAP.

The Sponsor submitted the entire study report for the previous adolescent tablet study. From a submission quality point-of-view, it would have been helpful for the Sponsor to summarize, in one place, the data and arguments to support using previous safety data to support this application.

4.5 Compliance with Good Clinical Practices

The submission contains a debarment certification signed by Donna Dea, Vice President of Regulatory Affairs at AstraZeneca (not dated) that states that she certifies, on behalf of

AstraZeneca Pharmaceuticals LP, that they did not use and will not use in connection with this NDA, the services of any person in any capacity debarred under section 306 (a) or (b).

The clinical study reports for studiesD1221c00005 and D1221c0004 each include a statement that the study was performed in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on bioethics.

4.6 Financial Disclosures

The Sponsor submitted certifications for studies D1221c0004 and D1221c00005. These certifications state that they have not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a) and that each listed clinical investigator required to disclose to the Sponsor whether the investigator had a proprietary interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b) did not disclose any such interest. Also, this statement includes that the Sponsor certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). The certification form for each study referenced is signed by Anthony F. Rogers, Vice President, Regulatory Affairs, AstraZeneca Pharmaceuticals LP on 8-23-07. The PIs listed for study D1221C0004 are P. Winner, DO (FL) and S. Linder, MD (TX) (initial sNDA application) and A. Henriksson, MD and J. Vouis, MD (6-26-08 submission). For study D1221C0D1221C00005, the PIs listed are E.D. Crisp, MD (TX), E. Goldstein, MD (GA), A. Hershey, MD (OH), T. Koch, MD (OR), D. Lewis, MD (VA), S. Linder, MD (TX), E. Pearlman, MD (GA), A. Pakalnis, MD (OH), A.D. Rothner, MD (OH), T. Rozen, MD (MI), P. Winner, DO (FL), M. Yonker, MD (DE), H. Abram, MD (FL), E. Vasconcellos, MD (FL), T. Sabo, MD (TX), W. McClintock MD, (VA), L.Mate, MD (FL), M. Fishman, MD (TX).

5 CLINICAL PHARMACOLOGY

This application included one PK study, D1221C0004. Formal review and data interpretation of this study is deferred to the OCPB reviewer Dr. T. C. Wu.

D1221C0004 dosed a single dose of 5 mg Zomig Nasal Spray (ZNS) and was conducted in 15 male and female adults and 15 male and female adolescents to obtain 12 evaluable adult and 12 evaluable adolescent subjects. The primary PK endpoint was AUC (0-∞) for zolmitriptan. Secondary PK endpoints were Cmax, Tmax, $T_{1/2}$, and AUC (0-t). The metabolite 183C91 was analyzed also. Placebo ZNS was used only to demonstrate the method to administer nasal spray.

Unless otherwise noted, most of the information in this section is as per the Sponsor from the study report for the study D1221c0004. Information for the tablet is taken from Dr. Prohaska's review of the application for use of Zomig tablets in adolescents under NDA 20768 and/or from Dr. A. Jackson's review of the February 11, 2003 submission (OCPB) of the study design of a proposed PK study of the nasal spray.

5.1 Pharmacokinetics

5.1.1 Zomig Nasal Spray

The study report for study D1221c0004 states that the geometric mean total exposures (AUC) to zolmitriptan in adolescents and adults were similar (40.9ng*hg/mL and 46.9 ng*hr/mL, respectively) with the 90% CI of the ratios (adolescent/adult) for AUC and Cmax within 0.5 – 2. There were no marked differences between adolescents and adults in the results of the analyses of secondary PK variables (Cmax, Tmax, $t_{1/2}$ for parent and metabolite and AUC for metabolite) and PK variables remained similar in adolescents and adults when the results were stratified by gender. PK data from the tablet is included in italics below for the ease of the reader. Also, Dr. Wu's review included a diagram (from the Sponsor originally) that illustrates the ZNS adult versus adolescent data. I include this diagram, duplicated from the Sponsor's submission, below.

Zolmitriptan

Parameter	**All Adolescent 95% CI n=15**	**All Adult 95% CI n=15**	**Ratio (Adol/adult) 90% CI**
Cmax (ng/mL) Geometric mean *Cmax tablet study 092 healthy vol*	6.2 (4.7, 8.2) *8.9*	6.4 (4.9, 8.5) *8.2*	0.97 (0.70, 1.34) *1.09 (0.89-1.33)*
AUC (hr*ng/mL) Geometric mean *AUC tablet study 092 healthy vol*	40.9 (30.0, 55.6) *47.8*	46.9 (34.5, 63.9) *42.7*	0.87 (0.61, 1.25) *1.12 (0.89-1.40)*
Tmax (hours)* Arithmetic mean or median (min,max)	2.0 (0.3, 4.0)	2.0 (1.0, 4.0)	
$t_{1/2}$ (hours) Arithmetic mean or median (min,max) *t1/2 tablet study 092 healthy vol*	3.0 (1.0, 4.8) *3.01*	3.8 (2.2, 5.5) *3.75*	

Data extracted from tables 11 of the CSR. Tmax in adolescent females was 4 while adolescent males were at 2. The adults are 2 regardless of gender. *Study 092 data taken from tables in sNDA review 20768 (see section 5.1.2 below). Tmax 30 minutes later in adolescents with the tablet when compared to adults (from Dr. Jackson's review dated 3-3-04-1.5 hours v 1 hour in adults)*

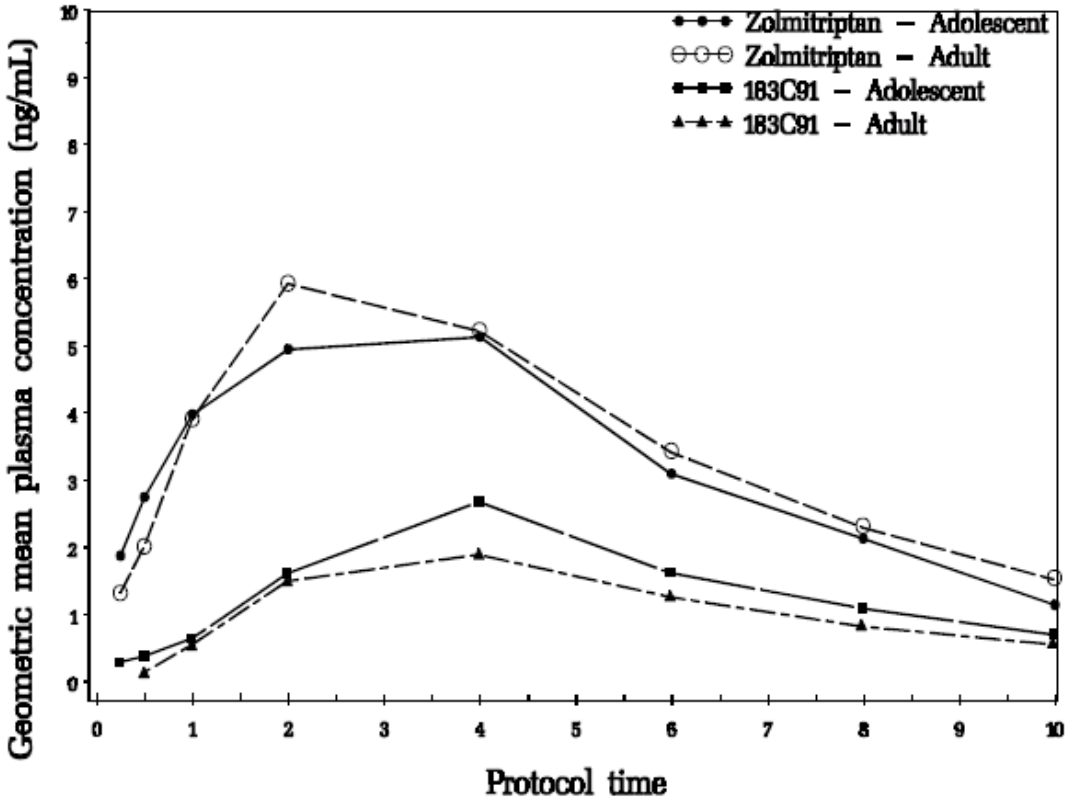
183C91

Parameter	**All Adolescent 95% CI n=15**	**All Adult 95% CI n=15**	**Ratio (Adol/adult) 90% CI**
Cmax (ng/mL) Geometric mean *Cmax tablet study 092 healthy vol*	2.4 (1.7, 3.4) *4.9*	2.1 (1.5, 2.9) *3.5*	1.17 (0.79, 1.72) *1.39 (1.17-1.65)*
AUC (hr*ng/mL) Geometric mean	20.4 (15.8, 26.5)	16.1 (12.7,	1.27 (0.94, 1.70)

AUC tablet study 092 healthy vol	*28.2*	20.5) *20.8*	*1.36 (1.15-1.60)*
Tmax (hours)* Arithmetic mean or median (min,max)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	
$t_{1/2}$ (hours) Arithmetic mean or median (min,max) *t1/2 tablet study 092 healthy vol*	3.4 (2.3, 5.7) *3.01*	3.8 (2.0, 5.9) *3.05*	

Data extracted from tables 12 of the CSR. Tmax is the same for both genders in both populations. *Study 092 data taken from tables in sNDA review 20768.*

Figure 1 Geometric mean plasma concentration for all subjects



5.1.2 Zomig Tablets

A memo from Dr. Jackson (OCPB-memo dated 4-15-04) and his review of the adolescent-adult PK study 311CIL/0092 (subjects were healthy volunteers not necessarily migraineurs) for sNDA 20768 indicate that systemic exposure to zolmitriptan appeared to be "slightly higher" in adolescents compared to adults. He noted that although mean Cmax, AUC (0-t), and AUC values were about 10% higher in the adolescents, the 90% CI for ratios were in the range of 0.89 to 1.43. In adolescents and adults, Cmax ranged from 3.7-20.3ng/ml and from 3.7 to 12.9 ng/ml

respectively and AUC values varied from 16.9-83.3 ng.h/ml in adolescents and 20.7 to 66.3 ng.h/ml in adults. Study 311 CIL/0092 of the oral tablet in adolescents and adults showed a slightly higher systemic exposure in the adolescent population with about 10% higher Cmax and AUC (0-t).

Tables displaying PK data from study 311CIL/0092 are duplicated in the appendix of this document. The metabolite 183C91 data indicate that exposure in adolescents is higher (AUC and Cmax) than in adults. Exposure to the metabolite 183C91 appeared higher in females than in males.

5.1.3 Conclusions based on the data above and OCBP review of PK data

Study D1221c 0004 PK data indicate that for the parent compound, in geometric mean terms, the exposure based on Cmax and AUC (hr*ng/mL) are similar or higher in adults than adolescents and the half-life is longer in adults (about 4 hours v 3). For the active metabolite, Cmax and AUC are higher in adolescents, although the half-life is a little longer in adults. The Sponsor notes that absorption is faster intranasally than orally with about 40% of the Cmax achieved within 15 minutes of intranasal dosing.

The OCBP reviewer indicates that the systemic exposure of the active metabolite is higher in adolescents than that seen in adults. For Cmax, the male adolescents and adults had similar values. However, Dr. Wu notes that for females, Cmax was about 36% higher in adolescents than in adults. Dr. Wu noted that the reason for this is not clear. Current U.S. labeling indicates that the $5HT_{1B/1D}$ potency of the active metabolite is 2-6 times that of the parent compound. Given the small numbers of subjects in this trial, the more rapid absorption, and the higher exposure to active metabolite, if the Sponsor performs another trial, I think there should be acquisition of EKG and vital sign data early (perhaps starting around 15 minutes) and through expected Tmax.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Company states they are not seeking an indication. The Company is requesting the Division to designate the PREA obligation for NDA 21450 fulfilled by study D1221c00005.

The Sponsor states in the cover letter that although they believe their study design is appropriate to address issues around adolescents, they acknowledge the Division's concerns regarding drafting appropriate language for inclusion in the DOSAGE and ADMINISTRATION of the full prescribing information and are not seeking a claim. The Company is clear, however, that they believe the studies submitted (PK, tablet Zomig in adolescents, and the ZNS Zomig study) are well controlled and had reasonable statistical analyses. **(b) (4)**

(b) (4)

6.1.1 Method

The clinical data from study D1221c00005 was submitted as the sole efficacy data for this supplement.

6.1.2 General Discussion of the Analysis and Endpoints

In the final protocol dated 8-6-03, the primary endpoint was the 1-hour headache response rate based on the ITT population. Only patients with efficacy data for both attacks were to be subject to statistical comparisons between placebo and zolmitriptan. The primary variable of 1-hour headache response was to be analyzed by the Generalized Estimating Equations (GEE) using the Alternating Logistic Regression (ALR).

The primary endpoint was changed subsequent to interactions with the Sponsor during which FDA expressed concern over issues of post-randomization exclusion and 2-hour sustained effects. The final SAP dated March 7, 2005 reflected changes made by the Sponsor as per FDA. This SAP indicates that there were two primary outcome variables, 1-hour headache response rate and 2-hour sustained headache response after randomized treatment using a worst case imputation for the placebo responders for the "FDA mandated" All Randomized-Treated (ART) population. The Sponsor intended other analyses using an ITT population with the ITT population defined at the patient level. To be in the ITT population a patient had to treat at least one moderate or severe migraine with randomized medication and provide at least 1 baseline and post-randomized treatment efficacy data for the 4 point intensity scale.

The primary analysis in the final SAP of March 2005 was to be the logistic regression analysis using the 1st period data (ART population). The factors in the model were treatment and region. Since there were only two treatment groups for the primary comparisons and there was a requirement for both variables to obtain significance, no multiplicity adjustment was performed. Some of the secondary efficacy endpoint analyses employed the GEE model using Alternating Logistic Regression on the ITT population.

6.1.3 Study Design

This was a multicenter, double-blind, randomized, double-diamond, placebo-controlled, two-way crossover study with a single-blind, placebo challenge to evaluate the efficacy of 5 mg zolmitriptan nasal spray in the acute treatment of migraine headache in adolescent subjects.

For each headache, subjects had access to three nasal spray devices, a device with the placebo challenge, and two devices with randomized study medication. Subjects were to use the 1st device, which contained placebo regardless of to what randomized group the subject was assigned, when migraine pain reached moderate or severe intensity. Subjects were to assess headache pain 15 minutes later. If the patient assessed the pain as mild or none, no other study

treatment was to be used. If the patient evaluated pain as moderate or severe, he/she was to use 2nd device, which contained the randomized treatment. If the headache pain continued at 2 hours after the 2nd device was used, the subject could use either the 3rd device, which contained another dose of the randomized treatment, or use an approved escape medication. Subjects could not enter information into the palm pilot if he/she was a placebo responder to the placebo challenge (use of the 1st device). A diagram illustrating the study design is included in Appendix 10.1.1 of this document.

6.1.4 Efficacy Findings

I describe briefly the efficacy findings as per the Sponsor's initial analysis with a 1-hour endpoint, as per worst-case-scenario analysis (WCS), and as per Dr. Yan's analyses. Additional details may be found in section 3.2 and Appendix 10.1.1 of this review.

As per the Sponsor, 128 subjects were in the randomized sequence of zolmitriptan/placebo (ZP) and 120 were in the placebo/zolmitriptan (PZ) sequence. 91 subjects in the ZP sequence and 80 in the PZ sequence were analyzed in the Sponsor's ITT population for efficacy. As per the Sponsor's analysis, for the first headache attack, 84 subjects were non-responders in the ZP group and 68 were non-responders in the PZ group. For the second attack, 60 were non-responders in ZP group and 66 were non-responders in the PZ group.

The Sponsor's headache response rate for *both* attacks (different # ITT subjects than noted above-see Appendix 10.1.1.13.3), at 1 hour, the p-value was 0.013 with response rates of 58.1% and 43.3%, zolmitriptan compared to placebo. P values by the Sponsor's analysis were positive at 15 minutes, 30 minutes, and 1 hour and not positive at 45 minutes, 1.5 hours or 2 hours (p=0.066, 0.06, and 0.06 respectively). *(Noted this is not the 2-hour sustained response rate.)* The % difference in responders between the placebo and zolmitriptan group ranged from about 11% to about 15%.

Using the worst-case scenario for the ART population, 1-hour headache response was 0.051 favoring placebo and the 2-hour sustained response p value was 0.236.

Dr. Yan's review indicates that, because the worst-case scenario is conservative, she performed OC and LOCF analyses. She notes that including a subject with missing data, especially the placebo responders, involves "substantial imputation in a complex scheme" (p.12 of the review). Dr. Yan notes that she followed the Sponsor's rules of imputation as specified in the SAP. She notes there were large discrepancies between her imputed data and the Sponsor's. Her analysis of placebo-response rates yielded 31 to 23 % of the PZ and ZP group respectively for the first attack and 20.48% and ~23% for the groups respectively for the 2nd attack.

Dr. Yan's results are summarized below.

- an analysis using the ART population and LOCF data with all 208 treated patients included. 62% of the placebo group and 71% of the zolmitriptan group were responders at 1 hour (p=0.1538)

- an LOCF analysis that only carried forward values after the 2nd device (she notes this is the analysis originally intended for the study) included 142 subjects. 51% of the 61 placebo-treated subjects and 64% of 81 zolmitriptan treated subjects were responders at 1-hour (p=0.1254)
- an OC analysis of 131 subjects, 28 of the 56 subjects treated with placebo and 49 of 75 subjects treated with zolmitriptan (65%) were responders at one hour (p=0.0866).
- For 2-hour sustained response, using observed data, 34% of placebo treated subjects and 52% of zolmitriptan treated subjects were responders (p=0.0696)
- analyses of 2nd attack data yielded no significant p-values
- For the combined both headache attacks, at 1-hour, Dr. Yan confirmed a p-value of 0.0312. For the two hour sustained response analysis, 71 subjects were included (p value= 0.1383).

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Dr. Yan's opinion is that the study failed to demonstrate that zolmitriptan is effective as a treatment of acute migraine headache in the adolescent patient population with neither 1-hour headache response nor 2-hour sustained response showing a treatment effect that reached statistical significance regardless of what dataset she used. Her analyses seem reasonable to me and therefore, combined with the Sponsor's ITT data, I conclude that the study, if interpretable, is not positive. I question/disbelieve the interpretability mainly because of the unbalanced groups (not balanced in the ITT population with 61 subjects in the placebo group and 81 in the Zomig group as per Dr.Yan's review). Additionally, the statistical reviewer found the datasets difficult to analyze due to poor data quality, missing information, and poor organization of the data and noted that numerous efficacy values appear to be imputed differently from the rules in the SAP. From my look at the dataset of violations submitted by the Sponsor, there seemed to be a fair number of subjects with deviations considered major deviations. Finally, the Sponsor's ITT results displaying the data from 0-2 hours in this enriched population are not impressive, in my opinion, with the 1-hour time-point statistically positive, but others not positive statistically.

Overall, I think the study cannot be interpreted definitively due to the exclusion of placebo responders post-randomization and the data quality/compliance issues. If the study data are considered interpretable, the study is not positive for the first attack data as analyzed by Dr. Yan.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

There were two studies in the submission with new safety data, the PK study, D1221c0004, and the efficacy study, D1221c00005. Neither study is optimal for definitive safety data as there is no placebo group in the PK study, it is a small study, and it seems EKG and vital signs assessments were not timed to be necessarily at Tmax (EKG at 10 hours post-dose). Also, there is faster absorption with the nasal spray than via the gastrointestinal mucosa with about 40% of the maximum Cmax achieved within 15 minutes of intranasal dosing (clinover.pdf, p.19/29). Assessments in study D1221c00005 were collected after subjects were exposed to both products in a crossover design.

These are single dose studies with an active moiety known to the Division and studied in a longer term study in the tablet formulation. Based on this knowledge, it seems unlikely that a single dose study would have uncovered any findings with specific regard to laboratory data or most of the physical exam with the exception of the nasal exam.

(Additional safety information may be found in appendices 10.1.1-10.1.3 of this document.)

7.1.1 Deaths

There were no reported deaths in either study.

7.1.2 Other Serious Adverse Events

There was one serious adverse event of hyper-anticoagulation (adult subject) in the PK study, study D1221c0004. As described, the event is not related to the study drug and was seemingly related to the heparin concentration used in flushes during multiple attempts at intravenous line placement.

There were no reported serious adverse events in studyD1221c00005.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

There were no discontinuations in study D1221C0004.

In study D1221c00005, 25 subjects in the zolmitriptan/placebo sequence and 24 in the placebo/zolmitriptan sequence discontinued the study early. “Protocol noncompliance” was the

most frequent reason for discontinuation with lost to follow-up second most common. As per the submission,

Zolmitriptan/Placebo (n=128)
Discontinued (n=25)
Felt trial med ineffective (n=2)
Lost to follow-up (n=10)
Protocol noncompliance (n=11)
Informed consent withdrawn (n=2)

Placebo/Zolmitriptan (n=120)
Discontinued (n=24)
Lost to follow-up (n=9)
Protocol noncompliance (n=13)
Informed consent withdrawn (n=2)

7.1.3.2 Adverse events associated with dropouts

There are no reported adverse events leading to discontinuation in these two studies.

7.1.3.3 Other significant adverse events

For study D1221c0004, one event was reported as moderate (headache in adolescent) and two events are reported as severe (coagulation time prolonged and headache-in adult with the serious adverse event) (Table 11.3.2.4 of the study report.)

For study D1221c00005, 3% of the zolmitriptan group and 1.09% of the placebo group experienced a severe event. Based on the dataset ADE.xpt for this study, there were several events for each group categorized as "moderate" (21 zolmitriptan and 8 for the placebo group) and 10 categorized as "severe" (8 zolmitriptan and 2 placebo). Seven events categorized as severe occurred within 24 hours of using the zolmitriptan device (five were burning or bad taste in the throat, one nasal burning, and one was vomiting) and two events categorized as severe occurred within 24 hours of using the placebo device (randomized placebo-one was dizziness and one was nasal congestion). Moderate events in the zolmitriptan group included one event of "difficulty breathing" and several of nausea, dizziness, or burning throat/nose. Moderate events for the placebo group included a postural dizziness, numbness on the right forehead, and nasal congestion. Except for the nasal congestion, all of these events are noted as recovered in the dataset.

7.1.4 Other Search Strategies

The adverse event dataset for study D1221c00005 was used as needed and referenced in this review.

7.1.5 Common Adverse Events

In study D1221C00005, the most common AE with zolmitriptan use was dysgeusia in 6.5%, followed by nasal discomfort (2.5%). The most common AE term with placebo use was also dysgeusia (2.72%) followed by "pharyngolaryngeal pain" (ADE terms "sore throat") in 1.63%. A higher proportion of females when compared to males reported adverse events within 24 hours of use of both zolmitriptan (22% v 9%) and placebo (13% v 6%) (clinover.pdf p.26/29).

In study D1221c0004, the most common adverse event reported was dysgeusia (80% of adolescents and 60% of adults). Headache was reported in 20% of both age groups, dizziness in 13.3% of both age groups, and rhinorrhea in 6.7% (n=1) of adolescents and 13.3% of adults (n=2). More adults reported pharyngolaryngeal pain (n=3 or 20%) as compared to no adolescents. Nasopharyngeal events occurred in 3 adolescents (four events) and 6 adults (seven events).

7.1.5.1 Eliciting adverse events data in the development program

D1221c00005- adverse events were collected for 24 hours post dosing with SAEs recorded throughout the trial, within 7 days after the last dose of trial treatment, or until the termination visit, whichever occurred last. Adverse events could be symptoms, signs, abnormal laboratory or EKG findings and were to be assessed regardless of presumed causality. Pregnancy was not an adverse event unless it was thought that the product interfered with the effectiveness of contraception.

Patients received a symptom log to record any additional medications taken and unusual experiences that may occur during the study. At the final visit, investigators were to review the logs to determine if any events were to be considered adverse events and then captured on the CRF. (p 827/4494).

D1221c0004: Adverse events were collected from the time of administration of placebo nasal spray for training purposes at visit 1 through 24 hours after treatment with zolmitriptan 5 mg nasal spray at visit 2. Pregnancy was not considered an adverse event unless it was suspected that the investigational product may have interfered with effectiveness of a contraceptive product. Significant abnormalities identified by the designated cardiologist were to be assessed by the investigator as possible adverse events and/or cause for discontinuation.

7.1.5.2 Incidence of common adverse events

7.1.5.3 Common adverse event tables

Only data fromD1221c00005 are presented in this section as it allows for placebo comparison. Non-serious adverse events generally were collected only for the 24 hour window post-dosing and are not included. Additional adverse event data for this study are described/displayed in section 10.1.1.19 of this review. PK study D1221c0004 event table is displayed in Appendix 10.1.2 of this document.

Table S4 **Number (%) of subjects with the most commonly reported adverse events, sorted by decreasing order of frequency, by treatment, safety population**

AE (preferred term) [a]	Zolmitriptan (N=200)		Placebo (N=184)		Total[b] (N=214)	
	n	(%)	n	(%)	n	(%)
Dysgeusia	13	(6.50)	5	(2.72)	14	(6.54)
Nasal discomfort	5	(2.50)	2	(1.09)	5	(2.34)
Dizziness	3	(1.50)	1	(0.54)	4	(1.87)
Nasal congestion	3	(1.50)	2	(1.09)	4	(1.87)
Pharyngolaryngeal pain	1	(0.50)	3	(1.63)	4	(1.87)
Nausea	3	(1.50)	0		3	(1.40)
Throat irritation	3	(1.50)	1	(0.54)	3	(1.40)
Somnolence	1	(0.50)	2	(1.09)	2	(0.93)

[a] Non-serious AEs outside of the 24-hour window are excluded from the table.
[b] Total may not be the sum of zolmitriptan and placebo column because the subjects may have contributed adverse events in both treatments.
AE, adverse event; N, Number (total population); n, number (subpopulation).

7.1.5.4 Identifying common and drug-related adverse events

Dysgeusia is a common, drug-related adverse event using the definition of occurring at the rate of 5% and 2x that of the placebo group.

7.1.6 Less Common Adverse Events

"Trimus" as a preferred term for an adverse event was reported in one adolescent and in one adult in the uncontrolled study D1221c0004. Both events are classified as "mild" (p.84/1047). This is a singular event in each population without a placebo group comparison.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In study D1221c00005, by protocol, laboratory assessments were at screening, pre-dosing of any treatment, and at visit 3, which occurred within two weeks of treating the 2nd attack (p.37/4494). Assessments included hematology, clinical chemistry (ALT, AST, ALP, and total bilirubin, creatinine, sodium, potassium, albumin, and glucose) and a urine pregnancy test for females of child-bearing potential.

Given the crossover design of the study, without a mid-point evaluation, the data are not comparative. Also, the timing of visit 3 may have been separated from visit 1 by days or months, which allows for other confounding factors that again cannot be definitively assessed without a placebo group comparison. For these reasons, I did not review mean change data. Also,

this is single dose exposure of a known active moiety. Based on the active moiety, I would not expect to see significant impact on lab values from a single dose of 5mg.

For study D1221c00004, laboratory assessments were collected at screening,-1 to 0 hours, and at 10 hours post-dosing. Limitations of these data are no placebo group and a small number of subjects. Urine pregnancy testing was performed as was a urine drug screen. Laboratory assessments also included clinical chemistry laboratories, hematology laboratories, and (at screening) a screen for infectious hepatitis.

7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 Analyses focused on measures of central tendency

Study D1221c00004 and D1221c00005 data were not reviewed-see 7.1.7.1

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

D1221c0005-Shifts from normal to abnormal with this design and timing of assessments cannot be conclusively interpreted (see 7.1.7.1 above) and were given a cursory review only. Tables 12.3.2.2 -12.3.2.5 and Tables 12.3.3.2 and 12.3.3.3 are listings of laboratory values (hematology and chemistry respectively-pages 4282-4356 and 4364-4400) with values out of reference ranges flagged as high (*H) or low (*L). No obvious clinically significant pattern was seen. There were no patterns for LFT increases.

The Sponsor states that no clinically important changes in hematology results or for clinical chemistry results occurred in this study.

D1221c00004- The study report states that no clinically significant changes from baseline occurred for any laboratory results. Two adolescents and one adult had chemistry values outside of the extended reference ranges. For the adolescents, the lab parameters are noted to be high before treatment. One adult had a high potassium on day 1 post treatment thought to possibly be due to hemolysis. Four urinalysis results were considered abnormal by the investigator; two in adult females (trace of blood post- treatment with continuing WBC and one with 3+ occult blood post-treatment) and two were in adolescents, one with no change from screening of 2+WBC and one male with trace proteinuria at 8-10 hours, not noted at screening.

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

In study D1221c0004, there was one event of hyperkalemia post-treatment in an adult that was considered an adverse event that was potentially treatment related or possibly caused by sample hemolysis. The listing 11.3.7.2.2 in the study report of abnormal chemistry values did not list any adolescents with post-treatment high creatinine or bilirubin values and the adolescent with a high glucose (6.55 mmol/L) does not appear to be flagged as treatment emergent although a pre-treatment value is lower (3.05 mmol/L).

7.1.8 Vital Signs

Single use dosing of this product may have the potential to impact vital signs at or near Tmax specifically. Data collection method in study D1221c0005 did not capture Tmax (vital sign data were collected at screening and visit 3). In study D1221c00004, vital signs (blood pressure, pulse, temperature, and respiratory rate) were collected at screening. Vital signs were collected on the day of treatment before dosing and, for blood pressure and respiratory rate, 30 minutes before dosing, and at 1, 2, 4, 6, and 8-10 hours post dose.

For both studies, mean data were looked at in a cursory way as the interpretations are not conclusive due to collection times or lack of placebo comparison.

7.1.8.1.1 Marked outliers and dropouts for vital sign abnormalities/Mean changes

The Sponsor states that no clinically important changes in vital signs occurred in the study D1221C0005.

In study D1221c00004, mean changes appeared to be small and not likely of clinical significance. At some time-points, mean rates were in opposite directions in adolescents and adults (DBP at 4, 6, and 8-10 hours post-dose) and mean SBP changes at 6 hours post-dose were larger in adolescents than in adults (2.7 mm Hg v 0.5 mm Hg). One adult had a decrease in SBP of -24 with a result of 86. Mean respiratory rates were increased at 6 hours post dose and at 8-10 hours post dose by 0.7 and 1.1 breaths per minute respectively in adolescents as compared to 0 and 0.9 breaths per minute in adults.

7.1.9 Electrocardiograms (ECGs)

I include a brief description of the EKGs from study D1221c0004 as well as those of D1221c00005 for completion. Given EKG acquisition, a conservative approach would be to assume all adverse changes are related to zolmitriptan exposure. The timings of the collection of EKGs were not adequate to have captured Tmax of either parent or metabolite in either study.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In study D1221c00005, EKGs were collected at screening and visit 3 (final visit after treating 2 attacks or 12 weeks after visit 1 or withdrawal). Given the crossover design and the lack of collection at each period (optimally at Cmax), the collection of EKGs at end of study does not provide placebo controlled data for comparative purposes.

Table 49 Categorical shift in ECG results, safety population

		ECG result at Visit 3					
		Normal		Missing		Abnormal	
Baseline ECG result	Number assessed	n	(%)	n	(%)	n	(%)
Zolmitriptan/Placebo							
Normal	109	99	(90.83)	7	(6.42)	3	(2.75)
Abnormal	5	1	(20.00)	1	(20.00)	3	(60.00)
Placebo/Zolmitriptan							
Normal	94	86	(91.49)	5	(5.32)	3	(3.19)
Abnormal	6	5	(83.33)	0		1	(16.67)

ECG, electrocardiogram; n, number (subpopulation).
Data derived from Table 11.3.2.1 in Section 11.

The sponsor did not describe the abnormalities in the study report. The EKG dataset was reviewed for these abnormalities. There were 23 EKGs called abnormal in the dataset. 13 of these were from screening and 10 were from visit 3. 3/10 visit 3 abnormalities were present on visit 1 EKG. The remaining abnormalities were either "sinus bradycardia" or "ectopic supraventricular rhythm". T wave changes were noted in two subjects, one went from sinus bradycardia with an inverted T wave to sinus bradycardia with a flat T wave and one went to flat T wave only at visit 3. The lowest heart rate of the bradycardias was 47bpm in a subject with baseline of 62. Two subjects had "ectopic supraventricular rhythm" at screening.

The sponsor states that no clinically important changes in individual ECGs occurred in the study.

In study D1221c0004, EKGs were collected at screening, -1 to 0 hours, and at 10 hours post-dosing. These EKG likely missed Tmax and there is no placebo group in the study. The study report notes that no EKG events were considered adverse events. The listing of abnormal EKGs in the study report indicates all the abnormal EKG readings (six) were in adolescents. All except one reading were abnormal either at screening or hours -1 to 0 on day 1. A 14 year old male, had abnormalities noted to just qualify for LVH on day one prior to treatment and flat, biphasic T waves on day 1 at -1 to 0 hour. Post treatment, he had sinus bradycardia and flat, biphasic T waves. At an unscheduled visit, he still had a sinus bradycardia.

7.1.9.2 Additional analyses and explorations

Pre-study and end of study nasopharyngeal exams were conducted in both study D1221c00005 and in study D1221c0004. In study D1221c00005, the end of study exam was at visit 3, after treating two migraine attacks or 12 weeks after visit 1. In study D1221c0004, the last exam was also at visit 3, 24-hour follow-up.

In the study report for study D1221c00005, the Sponsor's description of the nasopharyngeal exams is by treatment sequence and is minimal. The dataset NOSETHR.xpt was used. No exam

finding at visit 3 was considered clinically significant. There were 22 subjects noted to have changes since the 1st exam using the variable CHANGE. Most descriptors of the specific areas (nasal mucosa, septum, etc) described mild or slight changes. One person was noted to have a tonsillar infection diagnosed and one a sinusitis (red, edematous nasal mucosa with no visualization of the turbinates due to edema)

No abnormal exam findings were noted in study D1221C0004 (Appendix 12.2.4.5). Naso-pharyngeal adverse events occurred in three adolescents (4 events-cough and streptococcal pharyngitis in one subject, rhinorrhea, and burning sensation) and six adults (7 events-3 pharyngolaryngeal pain, 2 rhinorrhea, and one pharyngeal hypoesthesia). The events were considered mild.

7.1.10 Withdrawal and Abuse Potential

Not assessed in these single dose studies.

7.1.11 Human Reproduction and Pregnancy Data

No pregnancies were noted in the study reports for studies D1221c00005 or D1221c00004.

7.1.12 Overdose Experience

None reported in the two studies referenced above.

7.1.13 Postmarketing Experience

One PSUR was submitted with the application and a second PSUR was submitted during the review cycle as part of routine submissions made.

7.1.13.1 PSUR with the sNDA

This PSUR covers the period from March 7, 2006-March 6, 2007 and includes Zomig, Zomig Rapimelt, and Zomig Nasal Spray. Safety information is received from worldwide sources by Clinical Drug Safety, AstraZeneca.

As of this PSUR, Zomig was approved in 90 countries and ZNS was approved in either 2.5 mg and/or 5 mg in 14 countries while 5mg was approved in another 8 countries. The 2.5 mg ZNS appears to be marketed only in Sweden and Switzerland while the 5 mg ZNS is marketed in 13 countries including the U.S.

The PSUR states that no actions were taken by regulatory authority or marketing authorization for safety reasons.

Clinical Trial Exposure:

There were 53 subjects exposed to Zomig in six clinical studies during the reporting period. A table displaying the studies and a summary as per the PSUR may be found in Appendix 10.2 of this review. Overall, the PSUR summaries of these are that no new safety issues were identified.

The Company reports reviewing respiratory tract infections specifically as these were reported at a higher frequency in the group treated with Zomig in clinical trials. The PSUR states that all of these events were non-serious and in general, infectious etiology was not supported. The Company suspects a misclassification by coding diagnosis as Zomig is known to give pain and sensation of pain, tightness, and pressure in the throat and chest.

Volunteers receiving 50 mg single oral dose of zolmitriptan experienced sedation (p.84/350). This information is in the overdose section of the label. Proposed changes to this are wording changes from "volunteers" to "clinical study subjects".

Newly Analyzed Clinical Studies during the Reporting Period:
Studies D1221C00005, Study 311CUS/012 (open, randomized study to compare stratified care versus standard care for acute migraine), and Study 311CUS00022 (multi-center, randomized, placebo-controlled, double-blind study to evaluate early efficacy and tolerability of zolmitriptan in the acute treatment of adults with migraine) were analyzed or the study reports finalized in this PSUR time period. The Company states that no new safety issues were identified for these studies.

Published Studies:
A study authored by Cittadini E et al 2006 (Neurology 2006) described a study performed using ZNS 5 mg and 10 mg doses in adults with cluster headache. There were 68 evaluable patients out of 92. The PSUR notes that no SAES were reported in the study.

Post marketing:
Post-marketing patient exposure is based on the assumptions that 18 migraine attacks are treated per year and that 5mg Zomig was used per attack and 90 mg per patient year. Total milligrams of Zomig (all formulations) sold during the reporting period March 2006 through February 2007 were used in the market experience estimate. Based on sales figures, about (b) (4) patients had been exposed for the reporting period with a crude estimate of cumulative exposure of (b) (4) patients to Zomig.

Adverse event coding used the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1 at the Preferred Term (PT) level in summary tabulations and both Preferred Terms and Lowest Level Terms (LLT) in the line listings. "Listedness" is assigned to the PT level. For purposes of the PSUR text, an "unlisted" adverse reaction is an adverse reaction not consistent with the AZ core data sheet.

129 adverse event reports representing 252 adverse events met criteria for inclusion in the principal line listings of the safety update report. 169 of the adverse events were spontaneous reports, 74 were from regulatory authorities, and nine were from the literature. There were 87 serious unlisted events and 38 serious listed events.

The PSUR states that serotonin syndrome was evaluated and discussed at a safety review meeting. One adverse event of serotonin syndrome was suspected in the clinical trial database. From the Clintrace spontaneous safety database, there were six identified spontaneous adverse event reports with serotonin syndrome (associated with SSRIs and with other drugs) and five additional reports where the serotonin syndrome could not be excluded by the Company's medical review. The Company states the number of reports is small relative to the exposure to Zomig of (b) (4) in clinical trials and (b) (4) in patients on the market. The Company reports that none were assessed as life-threatening and there were no outcomes of death. Based on the literature that there is an association between serotonergic drugs and the potential for a life-threatening or fatal risk, a core label change was decided (labeling for combined use of a triptan and SSRI/SNRI).

Death: During this reporting period, the PSUR states that there was one case report with a fatal outcome reported. The case report was received from a pharmacist of a road traffic accident in a male who died. The subject was on multiple medications including clonazepam and zolmitriptan. Blood levels for zolmitriptan are reported as negative. The reporting pharmacist suspected all drugs the subject was taking. Autopsy results were not available.

Drug Interactions: The PSUR states that interaction with inhibitors of the P450 isoenzyme CYP1A2 such as fluvoxamine, sertraline, and the quinolone antibiotics cannot be excluded.

Pregnancy: In the reporting period, there were 20 reports on females known to have been exposed to zolmitriptan during pregnancy. At the time of the PSUR, the outcomes were unknown for 16 of these pregnancies.

Outcome	
Healthy baby	26 y.o. female , 33 weeks pregnant experienced premature contractions 2 hours after use of zolmitriptan
Induced abortion	Fetus with renal tubular atrophy-mother on candesartan also for 1st six weeks of pregnancy
Baby recovered post surgery	Pulmonary malformation, congenital arterial malformation-37 y.o. mother also took desloratidinie daily during the first 10 weeks
Bradycardia/respiratory distress in one day old	29 y.o. mother used ethinylestradiol and received buprenorphine up to month before delivery. Baby developed pneumothorax and pneumomediastinum
Vaginal bleeding	Non serious report-34 year old pregnant in February 2006 treated with zolmitriptan until April 1, 2006

Literature: There were two cases from the literature of serious, unlisted events; hypertensive encephalopathy, serotonin syndrome and renal infarction.

AZ uses the following frequency categories and states these are in consistent with current recommendations by the Council for International Organizations of Medical Sciences (CIOMS 1999); Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare

(≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Conclusion of the Company:

- The PSUR states that the following events are being kept under "close surveillance": cerebrovascular accident, hypertensive crisis, malignant hypertension, medication overuse headache, drug-induced headache, chronic daily headache, rebound headache, and non-coronary vasospasm. Serotonin syndrome and renal infarction will be added to the list.
- The Company is removing the following adverse events from the list of surveillance: influenza, influenza-like illness, nasopharyngitis, pharyngitis, rhinitis, and sinusitis since such events have not been reported spontaneously in the reporting period.

7.1.13.2 PSUR May 2008

This PSUR for ZOMIG™, ZOMIG RAPIMELT™ and ZOMIG NASAL SPRAY™ (zolmitriptan) summarizes the safety information received and evaluated by Patient Safety, AstraZeneca from worldwide sources from 07 March 2007 to 06 March 2008.

This PSUR states that the previous PSUR for zolmitriptan, dated 24 April 2007, concluded that cerebrovascular accident, hypertensive crisis, malignant hypertension, medication overuse headache, drug induced headache, chronic daily headache, rebound headache and non-coronary vasospasm required continuous close monitoring and that serotonin syndrome and renal infarct should be added to the list of close safety surveillance. The PSUR states that these topics have been reviewed in detail and subsequent to this review, the Sponsor concluded that the safety information in the current Core Data Sheet accurately described the known safety profile for zolmitriptan.

No *AstraZeneca sponsored* clinical studies with zolmitriptan are reported as conducted during the PSUR period.

Newly Analyzed clinical studies:

Study D1220C00002 and D1220C00004 were open, crossover bioequivalence studies comparing 0.5 mg (study 002) and 2.5 mg (study D1220C00004) doses of zolmitriptan when administered to healthy volunteers as the commercial device and the device used during clinical development. The Sponsor reports that no safety concerns were raised in the studies and that there were no deaths, SAEs, or discontinuations due to an adverse event.

Zolmitriptan has been approved in 93 countries for the acute treatment of migraine with/without aura and is available in two tablet formulations and an intranasal spray. The total world patient exposure, from market experience, is estimated to be about (b) (4) patients during this reporting period with the cumulative exposure estimated at (b) (4) patients. The method of estimating exposure is based on the same assumptions as noted for the earlier PSUR.

The Sponsor states that no actions have been taken by Regulatory Authority or Marketing Authorization Holder for safety reasons although the Sponsor notes that confusion and

convulsions were added to the topics to be kept under close surveillance during the PSUR period at the request of the Swedish Medical Products Agency.

The Core Data Sheet was not revised during the PSUR period.

The PSUR states that no case reports with a fatal outcome were received during the reporting period of the PSUR.

112 cases reports, associated with 216 adverse events, met the Sponsor's criteria for inclusion in the principal line listings of this PSUR. The PSUR notes that Table 2 includes non-serious events.

Table 1 Overview of case reports by reporting source

	Number of case reports	Number of adverse events
Spontaneous	87	174
Regulatory authority	20	33
Literature	4	8
Clinical studies	1	1

Table 2 Overview of adverse events by seriousness and listedness

Type of adverse event	Serious unlisted	Serious listed	Non-serious unlisted	Non-serious listed	Total
Number of adverse events	70	18	94	100	282

In the **literature**: 4 serious case reports. Two of these involved headache. One subject was using 15mg zolmitriptan daily for two months and was hospitalized secondary to this use/abuse and the 2nd patient experienced malaise and loss of consciousness 5 minutes post zolmitriptan use. (There was a case report from a consumer with physician follow-up that included the events of loss of consciousness. She was weaned off zolmitriptan and experienced rebound headaches. Zolmitriptan reportedly had been taken in excessive amounts.)

- there was one report of acute renal failure in a 17 year-old with concurrent acute lymphocytic leukemia after using methotrexate and oral zolmitriptan. *{Reviewer note: A quick check of AERS DataMart was performed looking for cases of methotrexate interaction with zolmitriptan. Two cases were found and both appear to be this case of the 17 year old.}*.
- Renal injury in a 26 year old female who underwent kidney transplant and was on immunosuppressant therapy (tacrolimus, mycophenolate mofetil, and prednisone). Follow-up visits between 2002 and 2005 were unremarkable in terms of stable creatinine values about 100 umol/l. She was also on oral contraceptives. During summer 2005, she had worsening migraines and was prescribed zolmitriptan, which she used 3-4 x/month. Her creatinine increased to 120 in October 2005. She increased her zolmitriptan due to

increase in headaches. In March 2006, her creatinine was higher and she had proteinuria. Renal biopsy was performed. Zolmitriptan and tacrolimus were stopped as both were suspected to be involved in the decline of her renal function. Her creatinine decreased and was back to 100 umol/l. Tacrolimus is reportedly described to give rise to vasoconstriction with secondary nephrotoxicity. The PSUR notes that it cannot be ruled out that zolmitriptan could have increased this risk.

Cumulatively, there are singular or a few cases of serious, unlisted events; hyperprolactinemia, optic neuritis, relapsing pancreatitis, Stevens-Johnson Syndrome, pulmonary fibrosis (history of dexfenfluramine),anasarca, mediastinal fibrosis, hypotension (+2 this reporting period, total 8/8) respiratory failure, relapsing pancreatitis, hematochezia (1 in reporting period, total 2/2), rhabdomyolysis, osteonecrosis, cytolytic hepatitis, drug-induced hepatitis under overdose (p.122/270), drug ineffective (2/2 reporting period, total 6/6), acute pulmonary edema, and QT prolongation. Additionally, there are several cases (2) each of retroperitoneal fibrosis, thrombocytopenic purpura, agranulocytosis, hypertensive crisis (+ one malignant hypertension), Raynaud's phenomenon, and retinal vein thrombosis. pharyngeal edema (3) or swollen tongue (4). Given the estimated exposure of **(b) (4)** , these reports seem unlikely to be above background.

Cerebrovascular accident - 5 serious cases in this reporting period (4 ischemic and 1 hemorrhagic). Two involved arterial dissection (dissection of a vertebral artery) and the bleed was suspected to be a cryptic arteriovenous malformation. There was another arterial dissection (left vertebral) which was received in the "Vascular Disorder" SOC (p. 19/270).

Selected Cumulative Preferred Term or HLG* term (or contains Preferred Term)	**Adverse Events/Case Reports**
Death	6/6
Anxiety Disorders/Symptoms	14/11
CNS vascular	73/63
Cardiac arrhythmias Including v fib (2)	21/20
Aneurysms and artery dissections	54/51
Dyspnea or exertional dyspnea	20/20
Spontaneous abortion	14/14
Drug interaction	20/20
Overdose of some type	14/14
Pulmonary embolism	8/8
Pulmonary hypertension	2.2 with 1 this reporting period
Seizure as HLGT	19/19

Data from Table 3 of the PSUR, Cumulative Tabulation of Serious Unlisted Adverse Events/Case Reports
HLG=High Level Group

Drug Interactions;

Five cases were received with four meeting inclusion in the PSUR. Of these, three were considered serious, unlisted events and one was considered non-serious. The PSUR indicates that in two of the case reports, the interaction is between zolmitriptan and a pharmaceutical described in the Core Data Sheet (fluvoxamine in one and an ergot containing compound in the other). The third case is of a 17 year old with lymphocytic leukemia using methotrexate. [Other cases -drug interaction vertigo and circulatory collapse (onset 2 days post treatment of zolmitriptan) and drug interaction with loss of consciousness (concurrent fluvoxamine and history of dyspnea, anxiety-reported considered this an enhanced effect).]

Overdose: Nine cases were received in the reporting period. The PSUR states that all reports were reviewed and that there was no new significant information on overdose when considering the cumulative experience.

There was a case report of overdose received from a physician through a sales representative in which the patient experienced hepatitis (2007CG01626). This patient was a 56 year old female (56 kg and 160 cm with history of depressive syndrome) on no concomitant medications with the Zomig-ZMT. She took about 20 tablets of Zomig-ZMT from October 10 to October 17. She experienced asthenia, abdominal pain, and vomiting on October 17. Liver function testing showed AST up to 117, ALT up to 202, GGT up to 375 and ALP up to 360 (units for all IU/L). Zolmitriptan was withdrawn. Liver work-up reportedly then improved. The physician considered this drug-induced hepatitis secondary to Zomig-ZMT overdose. *Reviewer's note: Although there are missing details, as presented, this case sounds as though the role of zolmitriptan cannot be ruled out. The Company note is that in this case, the hepatitis could be related to zolmitriptan overdose, however important information is missing concerning complete etiological investigations, making causality assessment impossible.*

Pregnancy: 19 cases were reported in the reporting period. As of the time of the PSUR, outcome was not known for 12 of these. Three reported "healthy baby". One report was of hypospadias in a neonate whose mother reportedly was exposed to several drugs during pregnancy. One report was of a voluntary abortion at 8 weeks due to concerns the pregnant female had of malformation. The language used is "fear" of malformation. One female experienced pregnancy-induced hypertension and premature labor. She is stated to have had a history of preeclampsia and multiple pregnancies. One female experienced a deep vein thrombosis at the time of delivery. One case report concerned a 15 month old child of a mother who had been exposed to several triptans during early pregnancy. The child was diagnosed with petit mal epilepsy. One case was of a female who experienced post-partum myocardial infarction.

The Company concludes that there was no new significant information on pregnancy outcomes or lactation when taking the cumulative experience into consideration.

Children and Adolescents:
There were six case reports regarding children ages 0-11 years and six regarding adolescents 12-17 years old, including consumer reports. The Sponsor displays listings in Tables 5 and 6, section 9.10.1 of the PSUR. Two of the six in children 0-11 years were considered serious;

hypospadias and petit mal epilepsy. The four events considered non-serious were 1) epistaxis, 2) choking sensation, malaise, palpitations, 3) overdose, mydriasis, depressed level of consciousness, drug ineffective, and 4) chest pain, parosmia. Two of the six adolescents ages 12-17 experienced events considered serious; drug interaction, renal failure acute and suicide attempt, altered state of consciousness. The events considered non-serious are 1) visual disturbance, 2) nausea, vomiting, 3) drug interaction, headache, and 4) rhinalgia, pharyngolaryngeal pain, chest pain.

Literature: The PSUR states there were five published studies during the PSUR that addressed safety issues with 3/5 addressing triptans as a group.
1) Population-based, observational study from 1994-2001 of migraine and the risk of stroke, TIA, and death in the UK. The authors reportedly concluded that it is not possible to fully separate the effect of migraine from a potential impact of triptans on the stroke risk (Becker C et al 2007).
2) Population-based follow-up from 1994 to 2001 migraine and risk of newly diagnosed asthma in the UK. Reportedly, the authors conclude that the risk of developing asthma was "not materially" changed for patients with a general practitioner-recorded migraine diagnosis regardless of triptan use (Becker C et al 2008-early online publication).
3) Prevalence of concomitant use of a triptan and SSRI or SNRI using the U.S. National Ambulatory Medical Care Survey for years 2003 and 2D1221C0004. It is reported that 1.3% of patients, an annualized mean of 694,276, were prescribed a triptan plus either a SSRI or SNRI (Sclar DA et al 2008).
4) meta-analysis of 24 randomized controlled trials of 15,408 patients with acute migraine attacks. It is reported that the authors conclude that zolmitriptan 5 mg tablet use was associated with similar proportions of patients experiencing adverse events as sumatriptan 50 and 100 mg. Zolmitriptan 2.5 mg had a higher risk of adverse events than naratriptan 2.5 mg and rizatriptan 10 mg but lower risk than eletriptan 80 mg. Higher doses of zolmitriptan were associated with increased numbers of patients experiencing adverse events (Chen LC et al 2008).
5) Multicenter, double-blind, placebo-controlled 3-period crossover study using ZNS 5 mg and 10 mg for cluster headache. 25% of the 5mg ZNS group and 33% of the 10 mg ZNS group experienced adverse events compared to 16% of the placebo group. The PSUR states no serious adverse events were reported and adverse events were mild, non-specific, and typical of triptan sensations reported in other clinical trials of triptans. (Rapoport AM et al 2007).

(b) (4)

[redacted]

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PSUR conclusion as per the PSUR:
The following safety topics will continue to be kept under close surveillance: cerebrovascular accident, confusion, convulsions, hypertensive crisis, malignant hypertension, medication

overuse headache, drug induced headache, chronic daily headache, rebound headache, noncoronary vasospasm, renal infarct and serotonin syndrome will be kept under close surveillance. During this PSUR period, the Swedish Medical Products Agency requested both confusion and convulsions to be kept under close surveillance.

Reviewer based on both PSURS: I recommend the Sponsor search for possible drug-induced hepatitis cases and that the Division consider asking the Sponsor to provide background rates for cumulative cases of SOC by PT for events and compare the cumulative exposure to the background in subsequent PSUR or Periodic Adverse Drug Experience Reports (for rare, serious events). I recommend consideration of modification of language in the label regarding possible drug interactions with CYP1A2 as discussed in section 1.3.5 of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In this submission, the Sponsor posits that the overall safety information provided by the open-label long term study with the zolmitriptan oral formulation in the adolescent population is valid for the nasal spray (clinover.pdf page 19/29). The components of this argument are that extrapolation across the nasal spray and tablet formulations is justified since there are only small differences in absorption after oral and intranasal application and that, based on what is known of the adult safety profile of ZNS, other than local adverse events, the safety profile of the tablet formulation is not different than that of the nasal spray. I was unable to locate detailed support for this position in this application.

The Sponsor noted that absorption is faster intranasally than orally with about 40% of the Cmax achieved within 15 minutes of intranasal dosing, that plasma concentrations are sustained for about 4-6 hours after dosing, and that since first-pass metabolism in the liver is avoided with the nasal spray, there is a delay in the appearance of the active metabolite 183C91 relative to zolmitriptan.

With this application, the Sponsor submitted three study reports, D1221c00005, D1221c0004, and 311CUS/00005 (the adolescent tablet pivotal study). I include exposure information for the tablet from study (review of the study) 311CUS/00005 in this section. Otherwise, as the data are not new to this application, this study is described in Appendix 10.1.3.

7.2.1.1 Study type and design/patient enumeration

In study D1221c00005, 248 subjects were in the randomized population. 171 subjects were in the randomized and treated with randomized treatment group (104 had efficacy results for two migraine attacks and 67 subjects treated and had efficacy results for one attack). There were 275

total migraine attacks. The protocol defined the safety data analysis set as all patients who are given study treatment (p.836/4494). 214 were analyzed for safety.

In study D1221c0004, 15 adults and 15 adolescents (12-17 years) with a history of migraine used a single dose of zolmitriptan 5mg NS.

In study 311CUS/00005, 850 subjects enrolled in phase 1 and 696 took a study medication. In phase 2, 680 subjects entered and 603 were included in the safety population. 151 completed phase 2 of the study (>326 days by the Sponsor). 75% discontinued phase 2 (n=452 with110 due to early study termination and classified as "other" for reason of discontinuation, 8.3% due to AEs/concurrent illness (n=50), and 9% (n=54) due to ineffectiveness of the study medication. (Tables displaying these data may be found in Appendix 10.1.3.2 of this review.)

7.2.1.2 Demographics

Demographic information is presented for the controlled studies. In study D1221c00005, the average age was 14 years, about 57% of subjects were female, and about 80% of subjects were Caucasian. In study 311CUS/0005 (tablet study for NDA 20768), the mean age of all subjects treated was 14.2 years and the majority were female (59%).

7.2.1.3 Extent of exposure (dose/duration)

In study D1221c00005, a total of 275 migraine attacks were treated. 114 subjects were analyzed for safety in the ZP sequence and 100 in the PZ sequence. This was a single dose of ZNS trial.

TOTAL ATTACKS TREATED (USING 2ND OR 3RD DEVICE)	146	75.6	132	72.1	278	73.9

Excerpted from Table 11.2.1.2 of the study report for D1221C0D1221C00005

311cus/0005- The following is the status of exposure for the tablet formulation as per Dr. Prohaska's review of the pediatric supplement for NDA 20768 (p13/30). " Despite the early termination of this trial the Sponsor reports that 319 subjects with exposures up to 180 days treated a total of 1555 attacks and 239 patients with exposures "between 181 to 360 days" treated a total of 4690 attacks. Forty-two subjects had exposure times greater than 1 year and treated a total of 989 attacks. The study report does not clearly state how many subjects received at least 6 months of treatment (180 days) and how many received at least 1 year of treatment (360 days) during phase II of the study. This information was requested from the Sponsor during this review. In response the Sponsor reports that during phase 2 of this study, 281 subjects took Zomig 5 mg (highest planned marketed dose) for at least 6 months and treated 3408 attacks (approximately 2 attacks/month) and 42 patients took Zomig 5 mg for at least 1 year (360 days) and treated 989 attacks (approximately 2 migraines/month). However 151 subjects took Zomig tablet 5 mg for at least 326 days and treated approximately 2 migraines per month. Overall the amount of long-term exposure is considerable although it is slightly short of the requirements we generally expect for migraine studies. In the long term phase of the study 68.4% of subjects took between 0 to 20 tablets of zolmitriptan and 22.7% of patients took between 21 to 40 tablets. The remainders of subjects took between 41to 80 tablets of zolmitriptan."

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The adolescent supplement to sNDA 20768 is discussed above.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is not sufficient to support efficacy.

The overall clinical experience is not sufficient to support safety (with respect to approvability) of ZNS in terms of numbers of subjects and data collection (specifically EKG and, to a lesser degree VS), at Tmax of active metabolite and parent and to cover the faster absorption of the intranasal formulation. See section 7.2.4.

7.2.4 Assessment of Quality and Completeness of Data

Neither D1221c00004 of D1221c00005 can be expected to provide long term data as they were single dose studies. The safety data provided by these studies are limited in interpretability.

- D1221c00004 was an open-label study without a placebo group and EKG measures during dosing likely did not capture Tmax of either the parent or of the active metabolite. Also, the study was small with only 15 subjects in each age group (adolescent and adult) dosed.
- D1221c00005 provided the possibility of a single dose of ZNS in each treatment sequence in a cross-over design. The assessments were at the beginning and end of the study making controlled data comparison not possible (and missed Tmax).

7.2.5 Additional Submissions, Including Safety Update

Periodic Safety Update Reports were submitted and are discussed under the post-marketing section of this review, heading 7.1.13, and in Appendix 10.2.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See comments in sections 7.1.5.4 and 7.2.2 above.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

One new efficacy study was submitted and one new PK study. Due to differing designs (double-blind, placebo-controlled v open), the safety data are not pooled.

7.4.1.1 Explorations for dose dependency for adverse findings

There was no dose finding capacity in these studies. Study D1221c00005 and D1221c0004 are single dose studies of 5 mg ZNS.

7.4.1.2 Explorations for time dependency for adverse findings

The Sponsor described events within 24 hours of dosing for study D1221c00005 for non-serious adverse events and throughout the study for serious adverse events. In study D1221c0004, adverse events were collected from the time of placebo nasal spray administration through 24 hours after zolmitriptan administration with serious adverse events collected from the time of acquiring informed consent/assent through the time of the follow-up phone call one week later.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Not applicable as the data are not interpretable. If considered interpretable, the data are not positive.

8.2 Drug-Drug Interactions

No new information was obtained from the clinical studies submitted with this supplement.

As noted in section 1.3.5 and review of the PSURs, the PSUR included with the initial submission of this NDA supplement states that interaction with inhibitors of the P450 isoenzyme CYP1A2 such as fluvoxamine, sertraline, and the quinolone antibiotics cannot be excluded. Section 4.5 of the Company's Core Data Sheet (CDS) describes that following cimetidine, the half-life of zolmitriptan was increased by 44% and the AUC by 48% and those of the active metabolite were doubled. Based on the overall interaction profile, an interaction with P450 CYP1A2 cannot be excluded. The CDS recommends dosage reduction with compounds of this type, such as fluvoxamine and the quinolone antibiotics.

Current U.S. labeling contraindicates use within 24-hours of treatment with another 5-HT1 agonist or ergotamine and has a precaution/warning for combined use with SSRIs or SNRIs, which would capture fluvoxamine (a SSRI). There is no direct language regarding a possible link to CYP1A2 mediated metabolism, and ciprofloxin, a prescribed antibiotic that is an inhibitor of the CYP1A2 path, is not mentioned in current U.S. labeling.

8.3 Special Populations

See pediatric section below.

8.4 Pediatrics

I recommend Pediatric Use section of the label contain language noting that a trial was conducted to evaluate efficacy in 12-17 year olds with migraine and that the trial design was problematic and efficacy was not established. If the pediatric safety data from 311CUS/0005 is referenced in this label, the trial should be noted to have not established efficacy (to prevent/minimize encouragement of off-label use). Also, I recommend the language discuss the limitations of the safety data from the ZNS trial and probably briefly describe the safety findings seen with the tablet formulation. Specific labeling recommendations will be made to the Division in a document with the proposed label.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

Literature utilized in the review are referenced during the review and/or in the Reference section after the appendices.

8.7 Postmarketing Risk Management Plan

(b) (4)

No recommendations at this time.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

See the Executive Summary of this document.

9.2 Recommendation on Regulatory Action

Please see section 1.1 of this document.

9.3 Recommendation on Postmarketing Actions

Please see sections 1.1 and 1.2 of this document.

9.3.1 Risk Management Activity

Not applicable.

9.3.2 Required Phase 4 Commitments

I recommend that PREA not be considered fulfilled by the study D1221C00005 based on the lack of ability to definitively interpret the study. Please see section 1.1 for details.

9.3.3 Other Phase 4 Requests

None related to this NDA submission at this time.

9.4 Labeling Review

Dr. Bastings performed most of the labeling review. Written labeling recommendations were made to Dr. Bastings.

9.5 Comments to Applicant

The comments below are my draft comments/ideas for consideration in the letter.

We do not believe your study is definitively interpretable. However, for the sake of argument, if the study were interpretable, the results of first attack data are not statistically positive by our internal review with three different analyses. (These analyses and results are described below after the text of the comments). WCS analysis is also negative, although FDA agrees this likely is a conservative analysis. As this study is not conclusively interpretable, FDA does not believe you have met the PREA requirement. You will need to conduct an additional study in the pediatric population. Due to changes in the thinking of migraine treatment since you originally started pediatric studies, such a study may need to dose children down to six years of age.

As was true before the submission of this NDA, FDA urges you to consider a parallel group design (not cross-over). Any placebo enrichment should be done pre-randomization. FDA encourages you to study more than one dose and evaluate recurrence at 24 hours. You will need to have a 1-hour endpoint with a co-primary of sustained headache relief at 2 hours in those who meet the one hour response. Additionally, you may need to perform a safety study that allows for collection of EKG and vital sign data at Tmax of both the parent and active metabolite and that includes a placebo group.

In future PSUR submissions, please provide background rates for events listed in the cumulative, unlisted serious event table and provide a comparison to the rates seen of events in this table.

We note one serious and unlisted case of hepatitis with overdose in the PSUR submitted in May, (2007CG01626). Please advise of the total number of cases of hepatitis in post-marketing for which there were no concomitant medications, if such exist. Please provide use data for children ages 6-18 years.

FDA analyses of first attack data:

- Analysis 1 was performed based on the ART patient population using LOCF. All 208 treated patients were included. Subjects without assessment post 2nd device carried forward their assessment value of placebo challenge, which could be imputed. 62/100 (62%) subjects who took placebo were responders at one hour and 77/108 (71%) who were treated with zolmitriptan were responders. The logistic regression test yielded a p-value of 0.1538.
- Analysis 2 was a LOCF analysis that only carried forward values after the 2nd device. A total of 142 subjects were included. Of these, five subjects did not take 2nd device but had assessments post 2nd device. A total of 31/61 (51%) of the placebo-treated subjects and 52/81 (64%) of zolmitriptan-treated subjected were responders at one hour. The p-value was 0.1254 from the logistic regression model.
- Analysis 3 was an analysis on observed cases (OC). A total of 131 subjects who had assessed value at 1 hour after 2nd dose were included. Of these, 28 (50%) of the 56 subjects treated with placebo and 49 (65%) of 75 subjects treated with zolmitriptan were responders at one hour. The p-value was 0.0866 from the test.

Table 2 Analysis of 1-hour headache response (Source: Reviewer's analysis)

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

10 APPENDICES

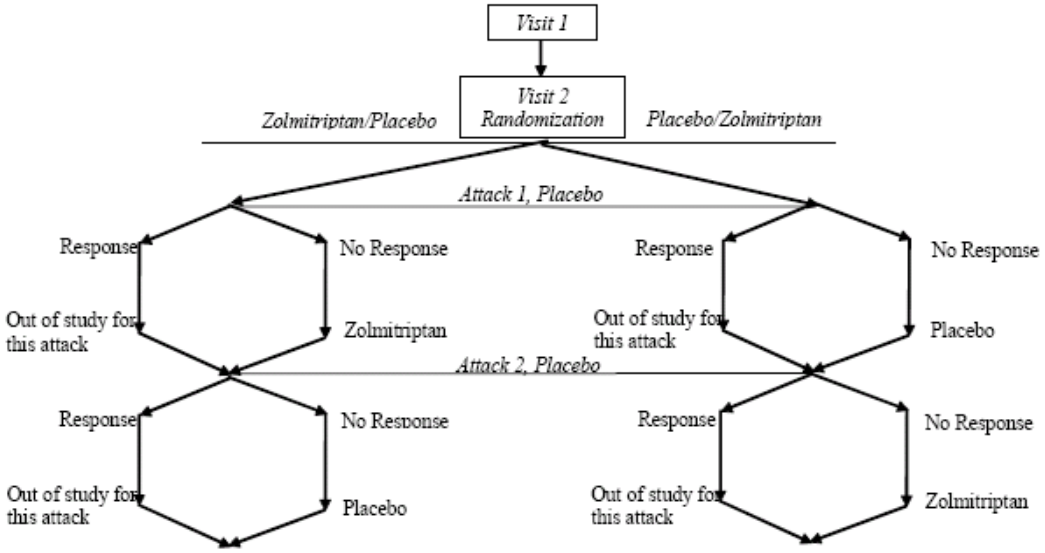
10.1 Review of Individual Study Reports

10.1.1 D1221c00005

"A Multicenter, Double-blind, Randomized, Placebo-controlled, 2-way Crossover Study with a Single-blind, Placebo-challenge to Evaluate the Efficacy of Zolmitriptan 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents" 1st enrolled: 9-13-03, Last subject enrolled: 7-6-04

10.1.1.1 Study Design

Figure 1 Study flow chart (double-diamond design)



10.1.1.2 Inclusion Criteria

1. Adolescents aged 12-17 years at the time of screening. Patients were not to turn 18 within 12 weeks after randomization.
2. An established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by IHS or IHS-R criteria
3. Parent or legal guardian able to provide written informed consent and patient able to provide written assent
4. A minimum of 2 migraines, considered to be moderately/severely disabling, per month on average during the school year
5. A history of usual migraine duration of >2-hours untreated for the 3 months prior to screening
6. Has a body weight . 35 kg. Body Mass Index (BMI) cannot exceed 95th percentile
7. Have the ability to differentiate between migraine and non-migraine headaches
8. Females of childbearing potential use a reliable method of contraception. Reliable methods of contraception include double-barrier methods (eg, condom and diaphragm, condom and foam, condom and sponge) and intrauterine devices.
9. Absence of clinically significant abnormalities indicated from the medical history, physical examination, clinical chemistry, hematology, and urine drug screen results
10. Clearly understands and is likely to comply with all study procedures and scheduled visits
11. Can use a PDA device
12. The investigator believes participation in the study will not be harmful to the patient.

10.1.1.3 Exclusion Criteria

1. Any medical condition that may put the patient at increased risk with exposure to zolmitriptan or that may interfere with the safety or efficacy assessments (in the opinion of the investigator).

2. A history of basilar, ophthalmoplegic or hemiplegic migraine headache or any potentially serious neurological condition that is associated with headache.
3. Had an unacceptable adverse experience following previous use of any 5-HT1B/1D agonist drug (in the opinion of the investigator).
4. Evidence of ischemic heart disease, arrhythmia (eg atrial fibrillation or flutter, frequent premature ventricular contractions, atrioventricular block), accessory conduction pathway disorder (eg, Wolff-Parkinson-White syndrome) as determined by central cardiologist using predetermined and agreed upon pediatric standards
5. History, symptoms, or significant risk factors for ischemic heart (eg, silent ischemia, angina, myocardial infarction) or other cardiovascular disease, including coronary vasospasm, cardiac accessory conduction pathways or arrhythmias
6. Clinically significant abnormalities indicated from the medical history, physical exam, clinical chemistry, hematology, urine drug screen, and nasopharyngeal exam
7. Had a diagnosis or suspicion of drug induced or chronic daily headaches within 1 year
8. Has 14 or more non-migraine headache days each month for 3 months before the screening visit.
9. Has uncontrolled hypertension defined as: systolic or diastolic blood pressure that exceeds the 95th percentile for age and height. (See Appendix C for normative table)
10. Has used monoamine oxidase inhibitor-A (MAO-A), methysergide, methylergonovine or cimetidine in the 2 weeks before randomization.
11. Has any recent history of abuse (in the previous year) of alcohol or other drugs including drugs for the acute treatment of headache
12. Is a female who is pregnant or breast-feeding
13. Has severe hepatic impairment or any serious condition which in the opinion of the investigator, would present a risk to the patient participating in the study.
14. Has a clinically relevant abnormality on nasopharyngeal examination as determined by the investigator
15. Is currently participating or has participated in another clinical study within 7 days prior to screening for this study
16. Had previous enrollment or randomization of treatment in this study
17. Has a positive urine test for drug abuse

10.1.1.4 Study Drug administration

1. Patients to treat headache within 30 minutes of headache pain reaching moderate or severe
2. Patients to be completely symptom free from any previous headache
3. Patients to treat the migraine headache with only the study treatment. Escape medications, as determined by the protocol and the investigator, could be taken 2 hours after taking study treatment (device #2) and could include a 3rd dose of study treatment (device #3), non-steroidal anti-inflammatory drugs (NSAIDS), anti-emetics, analgesics, or sedatives.
4. Before taking study treatment patients were not to have treated this headache with any other medication or received any ergotamine derivative or triptan in the 24-hour period before treatment with study treatment.
5. After taking study treatments, patients were not to sleep for 2-hours, use escape medication before 2 hours after treatment (see above for use of escape medication), or use an ergotamine derivative or non-study triptan for at least 24-hours.
6. Patients could continue any medication being taken at the time of entry into the study (other than medication referred to above for the acute treatment of migraine), including medication normally taken for migraine prophylaxis or medication normally taken to control a long standing condition, provided it was for a condition that was stable, and in the investigator's opinion, not adversely affected by participation in the study.

10.1.1.5 Primary Objective

The primary objective was to evaluate the efficacy of zolmitriptan 5mg nasal spray as compared to placebo for the acute treatment of migraine headache in adolescent patients 12-17 years of age.

10.1.1.6 Primary endpoint

The primary endpoint, as per the final protocol, was the 1-hour headache response rate based on the ITT population. The primary endpoint was changed (see discussion below).

10.1.1.7 Analysis Planned

In the final protocol dated 8-6-03, the primary endpoint was the 1-hour headache response rate based on the ITT population. The ITT population included all patients if at least 1 migraine headache was treated with study treatment and both baseline and post-baseline 4-point pain intensity data are available. Only patients with efficacy data for both attacks were to be subject to statistical comparisons between placebo and zolmitriptan. Separate summaries were to be produced for patients with efficacy data for both attack and those with data from only one attack,

The primary variable of 1-hour headache response was analyzed by the Generalized Estimating Equations (GEE) using the Alternating Logistic Regression (ALR). The statistical model was to include the factors for treatment, period, center (or region), and baseline headache intensity. The results were to be presented as an odds ratio for the treatment effect and a 95% CI.

10.1.1.8 Analysis Conducted

As noted, the primary endpoint was changed subsequent to interactions with the Sponsor during which FDA expressed concern over issues of post-randomization exclusion and 2-hour sustained effects. The final SAP dated March 7, 2005 reflected changes made by the Sponsor as per FDA. This SAP indicates that there were two primary outcome variables, 1-hour headache response rate and 2-hour sustained headache response after randomized treatment use a worst case imputation for the placed responders for the "FDA mandated" All Randomized-Treated (ART) population. The Sponsor intended other analyses using an ITT population. The ITT population was defined at the patient level. To be in the ITT population a patient had to treat at least one moderate or severe migraine with randomized medication and provide at least 1 baseline and post-randomized treatment efficacy data for the 4 point intensity scale.

The primary analysis in the final SAP of March 2005 was to be the logistic regression analysis using the 1st period data. The factors in the model were treatment and region. The secondary efficacy endpoint used the GEE model using Alternating Logistic Regression. Since there were only two treatment groups for the primary comparisons and there was a requirement for both variables to obtain significance, no multiplicity adjustment was performed.

Headache response at 1 hour was defined as a Yes if there was an improvement in migraine headache intensity from severe or moderate to mild or none. The two primary efficacy variables were evaluated in the FDA-requested ART population and other efficacy variables were evaluated in the ITT population as originally described in the protocol. The ART population included all subjects who were randomized and treated. This set of subjects included individuals only if they treated with either the 1st, 2nd, or 3rd device. The ITT population included subjects who treated at least 1 moderate or severe migraine headache with randomized medication (2nd or 3rd device) and who provided at least 1 baseline and post-randomized treatment efficacy data for the 4-point intensity scale for a minimum of 1 migraine headache. The efficacy data that is used to define the ITT population includes visit, date and time of trial treatment, and migraine headache intensity at baseline and at any time point.

Two-hour sustained headache response was defined as Yes if there was a headache response at 1 hour and this lasted through two hours without the subject using rescue medication or experiencing the return of moderate or severe pain.

The primary analysis for the co-primary endpoints was the logistic regression analysis using 1st attack data only. The factors in the models were treatment and region (Middle, South, or West). There were only two treatment groups for the primary comparisons and both variables were required to obtain significance, therefore, no multiplicity adjustment on the p-value was needed. Nominal p-values were reported for all the secondary analyses. No adjustments were made to the reported p-values.

10.1.1.9 Sponsor's Arguments regarding design and statistics

The Sponsor states that although there is no formal way to completely prove the non-existence of carry-over effect in a 2-way cross-over design, it was unlikely as the appropriate time separation between the two attack (at least 24 hours) and the clinical experience with zolmitriptan indicating an effect of < 1 day. A test for carry-over was performed by testing the treatment by period interaction, which the Sponsor states was not significant (0.762).

The Sponsor states that the GEE with alternating logistic regressions (references Carey VC et al, 1993) for 2-way cross-over design is an appropriate analysis method if there is no differential carry-over effect and no missing data or missing data are completely at random (MCAR). The Sponsor states that evaluation of the post-randomization exclusion provided support for the validity of the MCAR assumption since 73% of all missing data among the treated attacks are due to placebo challenge responses and notes the censoring process was due to design and was independent of the randomized treatment. The Sponsor states an additional evaluation of the effect of missing data pattern on the primary endpoint of 1-hour headache response was performed to further test the MCAR assumption and that it showed no effect of missing data pattern (p=0.334) or treatment by missing data pattern interaction (p=0.581) in the models. To further examine whether by design, bias and inflation of Type I error might be introduced by removal of early placebo challenge responders and to examine the adequacy of the GEE-ALR analysis based on the ITT population, a simulation was conducted under the null-hypothesis based on the this trial design, similar randomized patient sample, similar observed placebo

challenge response rates (20%) and similar observed placebo response at 1-hour post randomized treatment (40%). Reportedly, Type I error rates were preserved at the 5% region and estimated odds ratios were very close to 1. The Sponsor states these results indicate that there was no inflation of Type I error rates and no systematic bias introduced by the GEE-ALR analysis based on the ITT population.

10.1.1.10 Demographics, General Disposition, and Study Populations

The following information is based on the Sponsor's presentation in the study report.

In table S1 duplicated below, the safety population is noted to be 114 in the zolmitriptan/placebo (ZP) sequence and 100 in the placebo/zolmitriptan (PZ) sequence. Figure 3 in the study report (p.76/4494) and not reproduced in this review indicates that 16 subjects were excluded from the safety population in the ZP sequence and 19 in the PZ sequence due to being withdrawn before the first dose. Also, two subjects switched the sequence of taking study drug. Major protocol violations led to the exclusion of 24 ITT subjects in the ZP sequence and 20 ITT subjects in the PZ sequence leaving 83 in the per protocol population (PP) for the ZP sequence and 72 in the PP population for the PZ sequence.

Overall, 57% of the study subjects were female and 80% were Caucasian. The mean age was 14 years with 61% from 12-14 years of age. In both treatment sequences, 10% were Black, 9% were Hispanic, and <1% were Asian. The mean number of migraine attacks per month was 4.6. The Sponsor's tables of the migraine history for the all randomized population (Table 11.1.4. 1and 2) indicates that over 55% of the subjects had a history of migraines lasting >8 hours, 61% to 66% had a history of migraine without aura, and most experienced nausea, photophobia, and phonophobia with their migraines (see table displaying selected data from Table 11.1.4.1 and 11.1.4.2 below).

Table S1 Subject population and disposition (ITT and ART populations)

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

Table S1 Subject population and disposition (ITT and ART populations)

		Zolmitriptan/Placebo		Placebo/Zolmitriptan		Total	
	Hispanic	11	(12.1)	5	(6.3)	16	(9.4)
	Asian	0		1	(1.3)	1	(0.6)
Baseline characteristics (ITT)							
Average number of attacks/month							
Mean (SD)		4.6	(2.6)	4.6	(2.8)	4.6	(2.7)
Minimum, maximum		2.0, 12.0		2.0, 16.0		2.0, 16.0	

[a] Subjects who completed the study treated at least 1 headache and completed visits 1.1, 1.2, and 3.
[b] Two subjects (0002005 and 0006006) switched the sequence of taking the study drug.
ART, all randomized; ART, all randomized treated; ITT, intention to treat; N, number (total population); n, number (subpopulation); PP, per-protocol; SD, standard deviation.

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TABLE 11.1.1.1 AGE OF SUBJECTS AT TRIAL ENTRY
ALL RANDOMIZED

Parameter	Class	DOSE ZOLMITRIPTAN-PLACEBO (N=128)	DOSE PLACEBO-ZOLMITRIPTAN (N=120)	Total (N=248)
AGE GROUP	12 - 14 YEARS	82 (64.1%)	73 (60.8%)	155 (62.5%)
	15 - 17 YEARS	46 (35.9%)	47 (39.2%)	93 (37.5%)
AGE	N	128	120	248
	MEAN	14.1	14.1	14.1
	STD	1.6	1.5	1.5
	MEDIAN	14.0	14.0	14.0
	MIN	12.0	12.0	12.0
	MAX	17.0	17.0	17.0

Migraine history all randomized

	ZP sequence N=128	**PZ sequence** N=120
Age of onset of migraine attacks	9.6 ±3.2	9.9 ± 3
Average # of migraine/month at school	4.5 ±2.7	4.5 ±2.8
Average # of non-migraine days/month	4 ±4	3.6 ±4.1
Migraine with aura	18 (14.1%)	21 (17.5%)
Migraine without aura	85 (66.4%)	73 (60.8%)
Both with and without aura	25 (19.5%)	26 (21.7%)
Duration > 2 hours to 4 hr	11 (8.6%)	8 (6.7%)
Duration >4-6 hours	23 (18%)	24 (20%)
Duration >6-8 hours	20 (15.6%)	15 (12.5%)
Duration >8 hours	74 (57.8%)	73 (60.8%)
Associated with nausea	104 (81.3%)	101 (84.2%)
Associated with photophobia	122 (95.3%)	117 (97.5%)
Associated with phonophobia	117 (91.4%)	107 (89.2%)
Associated with vomiting	51 (39.8%)	60 (50%)

Data from Sponsor's tables 11.1.4.1 and 11.1.4.2 of the study report p. 192-193/4494.

10.1.1.11 Concomitant Medications

The study report indicates that the use of cimetidine and MAO-A inhibitors was not permitted. The dose of any SSRI or migraine prophylactic agent must have been stabilized within 2 months prior to randomization. No triptan, ergotamine or ergotamine containing compound was to have been used within 24 hours before, concurrently, or after study treatment. Opiates were not to be used within 24 hours before study treatment.

10.1.1.12 Protocol Violations

The following were considered major protocol violations as per the Define file. It is noted that major deviations 5 and6 seem to be the same: 1) TREATED HEADACHE (1ST DEVICE) AFTER 50 MIN. OF HEADACHE PAIN REACHING MODERATE OR SEVERE INTENSITY 2) USED TRIAL TREATMENT LESS THAN 24 HOURS AFTER A PREVIOUS MIGRAINE 3) USED ESCAPE MEDICATION WITHIN 2 HOURS OF TAKING RANDOMIZED MEDICATION (2nd device) 4) USED OPIATES, ERGOT-AMINE DERIVATIVES, TRIPTANS WITHIN 24 HOURS OF RANDOMIZED TREATMENT(2ND DEVICE) 5) SUBJECT SLEPT WITHIN 2 HOURS OF RANDOMIZED TREATMENT(2ND DEVICE) 6) SUBJECT SLEPT WITHIN 2 HOURS OF RANDOMIZED TREATMENT(2ND DEVICE) *{Reviewer note-this seems to be the same as #5)* 7) SUBJECT HAD PREVIOUS ENROLLMENT OR RANDOMIZATION AND WERE TREATED WITH STUDY MEDICATION.

10.1.1.13 Efficacy Results

10.1.1.13.1 Number of Migraine Attacks Treated by Sequence-All Randomized

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TABLE 11.2.1.2 NUMBER OF MIGRAINE ATTACKS TREATED BY TREATMENT
ALL RANDOMIZED

	ZOLMITRIPTAN		PLACEBO		TOTAL	
	N=193		N=183		N=376	
	n	%	n	%	n	%
TREATED WITH 1ST DEVICE ATTACK 1	108	56.0	100	54.6	208	55.3
TREATED WITH 1ST DEVICE ATTACK 2	83	43.0	78	42.6	161	42.8
TOTAL ATTACKS TREATED WITH 1ST DEVICE	191	99.0	178	97.3	369	98.1
TREATED WITH 2ND DEVICE ATTACK 1	80	41.5	63	34.4	143	38.0
TREATED WITH 2ND DEVICE ATTACK 2	62	32.1	56	30.6	118	31.4
TOTAL ATTACKS TREATED WITH 2ND DEVICE	142	73.6	119	65.0	261	69.4
TREATED WITH 3RD DEVICE ATTACK 1	37	19.2	45	24.6	82	21.8
TREATED WITH 3RD DEVICE ATTACK 2	24	12.4	32	17.5	56	14.9
TOTAL ATTACKS TREATED WITH 3RD DEVICE	61	31.6	77	42.1	138	36.7

(Continued)

	ZOLMITRIPTAN		PLACEBO		TOTAL	
	N=193		N=183		N=376	
	n	%	n	%	n	%
TREATED WITH 2ND OR 3RD DEVICE ATTACK 1	83	43.0	72	39.3	155	41.2
TREATED WITH 2ND OR 3RD DEVICE ATTACK 2	63	32.6	60	32.8	123	32.7
TOTAL ATTACKS TREATED WITH 2ND OR 3RD DEVICE	146	75.6	132	72.1	278	73.9
TREATED ONLY ONE ATTACK (USING 2ND OR 3RD DEVICE)	48	24.9	34	18.6	82	21.8
TREATED BOTH ATTACKS (USING 2ND OR 3RD DEVICE)	49	25.4	49	26.8	98	26.1
TOTAL ATTACKS TREATED (USING 2ND OR 3RD DEVICE)	146	75.6	132	72.1	278	73.9

10.1.1.13.2 Summary of the enrichment process (results of the placebo challenge)

For the all randomized group, Table 15 of the study report (not displayed) indicates that 107 of 112 subjects treated a 1st attack in the ZP group with 23 responding to placebo and 97/102 subjects treated a 1st attack in the PZ group with 29 responding to placebo. Five subjects in the ZP group were missing because they treated the 2nd attack and five were missing in PZ group.

74 subjects in the ZP group, with 14 responding to placebo, and 81 subjects in the PZ group, with 15 responding to placebo, treated a 2nd attack. 38 subjects in the ZP group were missing. 28/38 were missing because they treated only 1st attack. 21 subjects in the PZ group were missing with 17 missing because they treated only 1st attack.

Table 11.2.2.2 is reproduced from the submission and displays the responders by treatment group.

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TABLE 11.2.2.2 NUMBER OF PLACEBO RESPONDERS AND NONRESPONDERS BY TREATMENT
ALL RANDOMIZED

	ZOLMITRIPTAN		PLACEBO		TOTAL	
	N=193		N=183		N=376	
	n	%	n	%	n	%
PLACEBO RESPONDER FOR ONLY ONE ATTACK	26	13.5	31	16.9	57	15.2
PLACEBO RESPONDER FOR BOTH ATTACKS	12	6.2	12	6.6	24	6.4
PLACEBO NONRESPONDER FOR BOTH ATTACKS	98	50.8	98	53.6	196	52.1

Table 16 Summary of subjects who reported placebo challenge (enriched enrollment) response for both attacks, ART population

ART population	Zolmitriptan/Placebo (N=112)	Placebo/Zolmitriptan (N=102)
Placebo responded for both attacks	6	6

Placebo responded in 1 attack and only treated 1 attack	6	6
Placebo responded in 1 attack and missing post baseline efficacy information	5	5
Nonresponder and missing post baseline efficacy information	1	3
Missing efficacy for both attacks	3	2
ITT population	91	80

[a] Data derived from Table 11.2.20.5 in Section 11.

10.1.1.13.3 As per Sponsor's primary analysis (ITT population)

The Sponsor states that based on the ITT population, zolmitriptan was statistically significantly superior to placebo for headache response at 1 hour for both attacks (p=0.013). Using the Sponsor's ITT data as displayed in the table below, ½ of the time-points are statistically positive and favor zolmitriptan and ½ are not statistically significantly different (45-minutes, 1.5 hours, 2-hour with p values of 0.066, 0.060, and 0.061). Based on the Sponsor's ITT groups, the differences in the percentages of responders in the placebo group versus that in the zolmitriptan group ranges from 11.2% (at 2-hours, 65.5% v 54.3% to 15.6% at 30 minutes, 43.2% v 27.6%).

Table S2 Headache response rate for both attacks at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, and 2 hours post dosing by treatment

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

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

10.1.1.13.4 Per attack

The Sponsor provided descriptive data per attack in Table 24 (below) and a sensitivity analysis of the headache response rate results (Table 25 below). The Sponsor states that the within attack data did not reach statistical significance because the study was powered for two attacks.

Table 24 **Headache response rate for each attack at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, and 2 hours post dosing by treatment sequence**

	Zolmitriptan/Placebo ITT (N=91), PP (N=83)			Placebo/Zolmitriptan ITT (N=80), PP (N=72)		
Attack		**Headache response**			**Headache response**	
Timepoint Population	**Number assessed**	**n**	**(%)**	**Number assessed**	**n**	**(%)**
First attack						
At 15 min						
ITT	82	36	(43.9)	65	18	(27.7)
PP	75	33	(44.0)	60	16	(26.7)
At 30 min						
ITT	82	40	(48.8)	65	21	(32.3)
PP	75	37	(49.3)	60	18	(30.0)
At 45 min						
ITT	82	43	(52.4)	65	26	(40.0)
PP	75	39	(52.0)	60	23	(38.3)
At 1 hour						
ITT[a]	**82**	**52**	**(63.4)**	**65**	**31**	**(47.7)**
PP	75	47	(62.7)	60	28	(46.7)
At 1.5 hours						
ITT	82	54	(65.9)	65	35	(53.8)
PP	75	49	(65.3)	60	32	(53.3)
At 2 hours						
ITT	82	59	(72.0)	65	42	(64.6)
PP	75	53	(70.7)	60	39	(65.0)

Table 24 **Headache response rate for each attack at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, and 2 hours post dosing by treatment sequence**

	Zolmitriptan/Placebo ITT (N=91), PP (N=83)			Placebo/Zolmitriptan ITT (N=80), PP (N=72)		
Attack		**Headache response**			**Headache response**	
Timepoint Population	**Number assessed**	**n**	**(%)**	**Number assessed**	**n**	**(%)**
Second attack						
At 15 min						
ITT	62	11	(17.7)	66	19	(28.8)
PP	60	11	(18.3)	59	18	(30.5)
At 30 min						
ITT	62	14	(22.6)	66	24	(36.4)
PP	60	14	(23.3)	59	23	(39.0)
At 45 min						
ITT	62	19	(30.6)	66	26	(39.4)
PP	60	18	(30.0)	59	25	(42.4)
At 1 hour						
ITT	**62**	**24**	**(38.7)**	**66**	**34**	**(51.5)**
PP	60	24	(40.0)	59	30	(50.8)
At 1.5 hours						
ITT	62	27	(43.5)	66	35	(53.0)
PP	60	27	(45.0)	59	33	(55.9)
At 2 hours						
ITT	62	27	(43.5)	66	38	(57.6)
PP	60	27	(45.0)	59	35	(59.3)

[a] Originally intended primary endpoint.
ITT, intention to treat; N, number (total population); n, number (subpopulation); PP, per-protocol.
Data derived from Tables 11.2.4.1.1 and 11.2.5.1 in Section 11.

Table 25 Logistic regression of headache response rates at each time point for each attack separately, ITT population

	Statistical comparison (logistic regression) of zolmitriptan vs placebo		
Time point	Odds ratio	95% confidence interval (L,U)	p-value
First attack			
15 min	1.841	(0.892, 3.801)	0.099
30 min	1.903	(0.939, 3.859)	0.074
45 min	1.523	(0.772, 3.008)	0.225
1 hour[a]	**1.773**	**(0.901, 3.489)**	**0.098**
1.5 hour	1.535	(0.777, 3.032)	0.217
2 hour	1.241	(0.601, 2.565)	0.559
Second attack			
15 min	2.078	(0.873, 4.950)	0.098
30 min	2.350	(1.034, 5.340)	0.041
45 min	1.669	(0.778, 3.581)	0.188
1 hour[a]	**1.966**	**(0.937, 4.126)**	**0.074**
1.5 hour	1.793	(0.845, 3.804)	0.128
2 hour	2.292	(1.058, 4.964)	0.035

[a] Originally intended primary endpoint.
ITT, intention to treat; (L,U), Lower and upper 95% confidence limits of odds ratio of rates for subjects treated with zolmitriptan versus subjects treated with placebo.
Data derived from Table 11.2.4.6.2 in Section 11.

10.1.1.13.5 ART

For the ART population, the results of the analyses of the co-primary endpoints did not show statistical separation between zolmitriptan and placebo for response rate at 1-hour although placebo was slightly superior (p=0.051) or for 2-hour sustained headache response (p=0.236) using 1st attack data.

Table 21 Headache response rate at 1 hour post dosing for the 1st attack, worst-case scenario and ART population, by treatment

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

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

Table 22 Two-hour sustained headache response rate for the 1st attack, worst-case scenario, ART population, by treatment

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

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

10.1.1.13.6 Associated Symptoms

The Sponsor's submission included a presentation of the ITT population for the associated migraine symptoms of photophobia, phonophobia, and nausea at various time points (Table 34) using both attacks combined. For nausea, there were no statistically significant differences between zolmitriptan and placebo at any time point. For phonophobia and for photophobia, zolmitriptan showed statistical superiority at some time points, not others.

Table 34 Proportion of subjects reporting associated migraine symptoms for both attacks, by treatment, ITT population

	Zolmitriptan (N=162)			Placebo (N=148)			Statistical comparison (GEE analyses) of zolmitriptan vs placebo		
		Proportion reporting			Proportion reporting				
Symptom Timepoint	Number assessed	n	(%)	Number assessed	n	(%)	Odds ratio	95% confidence interval (L,U)	p-value
Nausea									
At 15 min	148	43	(29.1)	127	41	(32.3)	0.863	(0.556, 1.339)	0.511
At 30 min	148	43	(29.1)	127	43	(33.9)	0.801	(0.508, 1.262)	0.338
At 45 min	148	39	(26.4)	127	38	(29.9)	0.888	(0.554, 1.423)	0.621
At 1 hour	148	33	(22.3)	127	36	(28.3)	0.715	(0.438, 1.167)	0.179
At 1.5 hours	148	30	(20.3)	127	36	(28.3)	0.625	(0.381, 1.025)	0.062
At 2 hours	148	30	(20.3)	127	37	(29.1)	0.621	(0.367, 1.051)	0.076
Phonophobia									
At 15 min	148	77	(52.0)	127	75	(59.1)	0.748	(0.489, 1.143)	0.179
At 30 min	148	66	(44.6)	127	74	(58.3)	0.557	(0.358, 0.867)	0.010
At 45 min	148	63	(42.6)	127	66	(52.0)	0.700	(0.442, 1.108)	0.128
At 1 hour	148	55	(37.2)	127	58	(45.7)	0.709	(0.455, 1.104)	0.128
At 1.5 hours	148	49	(33.1)	127	58	(45.7)	0.578	(0.366, 0.914)	0.019
At 2 hours	148	47	(31.8)	127	52	(40.9)	0.671	(0.431, 1.044)	0.077

Table 34 **Proportion of subjects reporting associated migraine symptoms for both attacks, by treatment, ITT population**

	Zolmitriptan (N=162)			Placebo (N=148)			Statistical comparison (GEE analyses) of zolmitriptan vs placebo		
		Proportion reporting			Proportion reporting				
Symptom Timepoint	Number assessed	n	(%)	Number assessed	n	(%)	Odds ratio	95% confidence interval (L,U)	p-value
Photophobia									
At 15 min	148	98	(66.2)	127	91	(71.7)	0.754	(0.485, 1.174)	0.212
At 30 min	148	83	(56.1)	127	86	(67.7)	0.594	(0.379, 0.930)	0.023
At 45 min	148	82	(55.4)	127	81	(63.8)	0.699	(0.447, 1.091)	0.115
At 1 hour	148	69	(46.6)	127	73	(57.5)	0.641	(0.405, 1.012)	0.056
At 1.5 hours	148	61	(41.2)	127	74	(58.3)	0.490	(0.304, 0.790)	0.003
At 2 hours	148	55	(37.2)	127	62	(48.8)	0.617	(0.388, 0.981)	0.041

GEE, generalized estimated equations; ITT, intention to treat; (L,U), Lower and upper 95% confidence limits of odds ratio of rates for subjects treated with zolmitriptan versus subjects treated with placebo; N, number (total population); n, number (subpopulation); vs, versus.
Data derived from Tables 11.2.15.2, 11.2.15.5, 11.2.16.2, 11.2.16.5, 11.2.17.2, and 11.2.17.5 in Section 11.

10.1.1.14 Protocol Deviations

I used the DEVIATE.xpt dataset (variable MAJDEV=1) and Table 12.1.13.3 to quality check the major protocol violations. Using Table 12.1.13.3, there were 43 subjects with 54 deviations. By my count, there were 16 subjects in the dataset who had 20 of the major deviation of treating the headache with the 1st device >50 minutes out of moderate-severe pain.

Table 11 **Number (%) of subjects with major protocol violations and deviations, ITT population**

Protocol violation/deviation	Number (%) of subjects[a]			
	Zolmitriptan/Placebo (N=91)		Placebo/Zolmitriptan (N=80)	
	n	(%)	n	(%)
Violated entry criteria (see Sections 5.3.1 and 5.3.2)				
Total number of subjects with violations	0		1	(1.25)
Has positive urine test for drug abuse	0		1	(1.25)
Other important deviations from the protocol				
Total number of subjects with deviations	20	(21.98)	15	(18.75)
Subjects treated headache (1st device) after 50 minutes of headache pain reaching moderate or severe intensity	7	(7.69)	4	(5.00)
Subject used escape medication within 2 hours of taking randomized medication (2nd device)	3	(3.30)	5	(6.25)
Subject slept within 2 hours of randomized treatment (2nd device)	9	(9.89)	7	(8.75)
Subject used opiates, ergotamine derivatives, triptans ($5HT_{1B/1D}$ agonist), or rescue medication within 24 hours before randomized treatment (2nd device)	2	(2.20)	2	(2.50)
Subject took a concomitant medication or	2	(2.20)	0	

10.1.1.15 Escape Medication Use

Subjects were permitted to take an approved escape medication beginning 2 hours after taking the initial dose of study medication for each attack (after the 2-hour assessments were made). The escape medication used must have had approval of the investigator before study enrollment. Escape medications included nonsteroidal anti-inflammatory drugs (NSAIDs), anti-emetics, analgesics, sedatives, or opiates. Triptan, ergotamine, or ergotamine-containing medications were prohibited within 24 hours of any dose of study medication. The dates and use of the 3rd dose of study medication were captured in the PDA diaries or on the symptom/medication log.

The Sponsor presented this by ITT population only. Table 40 from the study report is duplicated below.

Table 40 Incidence of use of escape medication, for both attacks, by treatment, ITT population

	Zolmitriptan (N=162)		Placebo (N=148)		Statistical comparison (GEE analyses) of zolmitriptan vs placebo[c]		
Medication classification[a]	n	(%)	n	(%)	Odds ratio	95% confidence interval (L,U)	p-value
No escape medication	100	61.73	74	50.00			
3rd device medication	38	23.46	48	32.43			
Any escape medication[b]	62	38.27	74	50.00	0.602	(0.400, 0.905)	0.015

[a] Counts represent all remedications with either 3rd device of trial medication or escape medication within 24 hours after the 2nd device of trial treatment. Therefore, a subject could have been counted in more than 1 category.
[b] Including 3rd device.
[c] GEE analyses was not available for the no escape medication or the 3rd device medication.
GEE, generalized estimated equations; ITT, intention to treat; (L,U), Lower and upper 95% confidence limits of odds ratio of rates for subjects treated with zolmitriptan versus subjects treated with placebo; N, number (total population); n, number (subpopulation).
Data derived from Tables 11.2.13.2 and 11.2.13.3 in Section 11.

10.1.1.16 Concomitant medication

Given the other issues with this study, I did not verify any of the Sponsor's information that follows in this section as it will not change the decision process. The study report states that 72.8% and 81% in the ZP and PZ sequence respectively reported at least 1 concomitant medication. The Sponsor states that the types of medications reported appeared similar between the two groups with the most frequently reported medications other therapeutic products (30.7% and 31.0%, respectively), proprionic acid derivatives (20.2% and 23.0%), anilides (18.4% and 12.0%), non-selective monoamine reuptake inhibitors (14.9% and 14.0%), other antiepileptics (10.5% and 6.0%), and centrally acting sympathomimetics (5.3% and 9.0%).

10.1.1.17 Recurrence at 2 hours

Incidence of recurrence (FDA requested) was based on a subset of the ITT population for those that had a headache response at 1 hour. It appears that neither the PDA diary nor the CRF captured recurrence at 24 hours. The Sponsor presented these data several ways. The OC ITT data are displayed below.

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TABLE 11.2.12.4 RECURRENCE RATES BY TREATMENT - OC
INTENT-TO-TREAT POPULATION

	ZOLMITRIPTAN			PLACEBO			TOTAL		
	N=162			N=148			N=310		
	NO. RESPONDERS	RECURRENCE RATE		NO. RESPONDERS	RECURRENCE RATE		NO. RESPONDERS	RECURRENCE RATE	
	Sum	N	%	Sum	N	%	Sum	N	%
RECURRENCE									
YES	81	25	30.9	52	21	40.4	133	46	34.6
NO	81	56	69.1	52	31	59.6	133	87	65.4
MISSING		81			96			177	

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TABLE 11.2.12.3 RECURRENCE RATES FOR EACH MIGRAINE ATTACK BY TREATMENT SEQUENCE - OC
INTENT-TO-TREAT POPULATION

		ZOLMITRIPTAN-PLACEBO			PLACEBO-ZOLMITRIPTAN			TOTAL		
		N=91			N=80			N=171		
		NO. RESPONDERS	RECURRENCE RATE		NO. RESPONDERS	RECURRENCE RATE		NO. RESPONDERS	RECURRENCE RATE	
		Sum	N	%	Sum	N	%	Sum	N	%
MIGRAINE ATTACK	RECURRENCE									
1	YES	49	18	36.7	28	13	46.4	77	31	40.3
	NO	49	31	63.3	28	15	53.6	77	46	59.7
	MISSING		41			52			93	
2	YES	24	8	33.3	32	7	21.9	56	15	26.8
	NO	24	16	66.7	32	25	78.1	56	41	73.2
	MISSING		44			40			84	
TOTAL	YES	73	26	35.6	60	20	33.3	133	46	34.6
	NO	73	47	64.4	60	40	66.7	133	87	65.4
	MISSING		95			92			177	

10.1.1.18 Safety Assessments Overview

Visit 1/Screening: written informed consent, inclusion and exclusion criteria, medical and migraine history, current medication, 12-lead EKG, chemistry and hematology labs, urine drug screen and urine pregnancy testing, physical exam including nasal/throat exam, and blood pressure and vital signs were performed/collected/reviewed.
Visit 2a: 3-7 days after visit 1- Randomization, drug dispensing, dosing instructions, PDA training and distribution, AE reporting (non-serious AEs that occurred within 24 hours of study drug treatment were recorded. SAEs were recorded from time of informed consent signing through study completion)
Visit 2b-telephone call at 8 weeks-dosing instructions and adverse event reporting as noted at visit 2a.
Visit 3-final visit after treating 2 attacks or 12 weeks after visit 1: Current medication reviewed, 12-lead EKG, chemistry and hematology labs, and blood pressure and vital signs. A brief physical exam was to be performed to include nose and throat.
Adverse event definition: the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, regardless of presumed causally to the product. This could have been symptoms signs or the abnormal results of an investigation. An adverse event could have occurred at any time, even if no study treatment had been administered, however, adverse events

were collected for 24 hours post dosing *(Reviewer's note : some events appear to have been collected outside this window, as indicated in the AE section below)*. Serious adverse events were recorded throughout the trial and within 7 days after the last dose of trial treatment or until the termination visit, which ever occurred last.

Patients received a symptom log to record any additional medications taken and unusual experiences that may occur during the study. At the final visit, investigators were to review the logs to determine if any events were to be considered adverse events and then captured on the CRF. (p 827/4494). Pregnancy was not an adverse event unless it was thought that the product interfered with the effectiveness of contraception.

10.1.1.19 Adverse Events

The Sponsor's table is below (from clinover.pdf) and indicates that 18.5% of the zolmitriptan-treated patients and 10.3% of the placebo-treated patients experienced at least one adverse event. The study report states that when subjects who had adverse events during the designated time window were summarized by gender, females were more likely to report adverse events than males (22.32% versus 9.09%, respectively, in the zolmitriptan group and 13.46% versus 6.25% in the placebo group).

Table 8 Number (%) of patients with an adverse event by treatment, safety population (study D1221C00005)

	Number (%) of subjects with an AE[a]					
	Zolmitriptan (N=200)		Placebo (N=184)		Total[b] (N=214)	
Category of AE	n	(%)	n	(%)	n	(%)
No. of patients with at least 1 AE	37	(18.50)	19	(10.33)	44	(20.56)
No. of patients with at least 1 AE within 24 hours [c]	33	(16.50)	19	(10.33)	40	(18.69)
No of patients with drug-related AEs	32	(16.00)	17	(9.24)	40	(18.69)
No of patients with drug -related AEs within 24 hours	29	(14.50)	17	(9.24)	37	(17.29)
SAE	0		0		0	
Discontinuations of study treatment due to AEs	0		0		0	

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.
[b] Total may not be the sum of zolmitriptan and placebo column because the subjects may have contributed adverse events in both treatments in this cross-over study.
[c] Adverse events within a 24-hour window following the last device taken for the attack.
AE, adverse event; N, Number (total population); n, number (subpopulation); SAE, serious AE.

As a quality control check, I explored the adverse event dataset. There are 81 adverse events in the dataset ADE.xpt (all corresponding subjects are coded as in the safety population) experienced by 56 subjects. Six are coded as not in the 24-hour window (all zolmitriptan) and 75 as in this window (total 81). The six events coded as not in the 24 hour window are, as per Lower Level Term (LLT) "bad taste", "upset stomach", "tiredness", "feeling of warmth", "exasperation of severe migraine" was PT, LLT is "migraine", and "nasal discomfort". 42 events are coded as mild, 29 as moderate, and 10 as severe.

From the dataset, 54 of the events (37 subjects) were in the zolmitriptan use group and 27 events (19 subjects) were in the placebo use group. In the zolmitriptan group, by event, 25 were

classified as mild, 21 as moderate, and 8 as severe. In the placebo group, by event, 17 were classified as mild, 8 were classified as moderate, and 2 were classified as severe.

Lower Level Term	Zolmitriptan Events	Placebo Events
DIZZINESS/DIZZY/DIZZINESS UPON STANDING	2	2
NASAL BURNING/STINGING	**5**	**4**
NASAL CONGESTION/STUFFINESS/DISCOMFORT	4	2
SORE NOSE	2	0
TASTE BITTER/ALTERATION/DISTURBANCE	4	2 + AFTER TASTE
NAUSEA/UPSET STOMACH	4	1
THROAT BURNING SENSATION OF/BURNING IN THROAT	5	2
BAD TASTE	**12**	**2**
SORE THROAT	1	**3**
Singular events included	Difficulty breathing (moderate), migraine (severe), lightheadedness (moderate), pains in legs,	Altered visual depth perception, blurred vision, chills, hyperactive, numbness of head

Reviewer table made from dataset data ADE.xpt.

The sponsor's table displaying data in the 24 hour period may be found in the ISS (section 7.1.5.3).

10.1.1.20 EKG

EKGs were collected at screening and visit 3 (final visit after treating 2 attacks or 12 weeks after visit 1 or withdrawal). Given the crossover design and the lack of collection at each period (optimally at Cmax), the collection of EKGs at end of study does not provide placebo controlled data for comparative purposes. The Sponsor's shift table is displayed below.

Table 49 Categorical shift in ECG results, safety population

		ECG result at Visit 3					
		Normal		Missing		Abnormal	
Baseline ECG result	Number assessed	n	(%)	n	(%)	n	(%)
Zolmitriptan/Placebo							
Normal	109	99	(90.83)	7	(6.42)	3	(2.75)
Abnormal	5	1	(20.00)	1	(20.00)	3	(60.00)
Placebo/Zolmitriptan							
Normal	94	86	(91.49)	5	(5.32)	3	(3.19)
Abnormal	6	5	(83.33)	0		1	(16.67)

ECG, electrocardiogram; n, number (subpopulation).
Data derived from Table 11.3.2.1 in Section 11.

The Sponsor stated that no clinically significant changes in individual EKGs occurred in the study, however, the study report did not describe the specific abnormalities noted on the EKGs. I sent a request for such information to the Sponsor on 2/25/08. The Sponsor's response of 4/03/08 was a table from the study report, Table 12.3.6, that listed by subject per treatment sequence the EKG assessment (normal or abnormal), but did not describe the abnormality when such was noted. Therefore, I used the dataset ECG.xpt to obtain these data.

Using the EKG dataset (ECG.xpt), 19 patients had EKGs read as abnormal with 23 abnormal readings. 13 of these readings were at screening and 10 were at visit 3. Three patients appear to have had the same abnormality at visits 1 and 3 (-subject 0003-023, 0006-011,and 0010-031) and another one patient's EKG was noted abnormal at visit 1 with no rhythm explanation and T wave inversion and abnormal at visit 3 with "sinus bradycardia" and flat T wave (patient 0017-002). Three patients with visit 1 EKGs read as normal had a rhythm "ectopic supraventricular rhythm" at visit 3 (0007-005, 0011-006, and 0017-009). One visit 3 abnormality not noted at visit 1 was T wave flat (0019-0004). The remaining visit 3 abnormalities were noted as sinus bradycardia.

10.1.1.21 Laboratory

Hematology labs, chemistry labs (AST/ALT, ALP, total bilirubin, creatinine, sodium, potassium, albumin, and glucose), and pregnancy testing for females of childbearing potential were collected at screening (visit 1) and visit 3.

Please see the ISS section of this review.

10.1.1.22 Vital Signs

Vital signs (respiratory rate, temperature, and seated blood pressure with corresponding peripheral pulse) were to be measured at screening and at trial completion/withdrawal

(Visit 3). The Sponsor states that changes in vital signs were not considered clinically relevant. Looking at the safety population (n=214) in the dataset VITALS.xpt and not separating visit 1 from visit 3 (given the design of the study, this distinction would not be very useful), the minimum and maximum seated heart rates were 46 and 119 bpm respectively, minimum and maximum seated systolic blood pressures were 80 and 140mm Hg respectively, and the minimum and maximum seated diastolic blood pressures were 46 and 93mmHg respectively.

10.1.1.23 Physical Exam

A complete physical examination and medical history were performed at Visit 1. Additionally, a brief physical examination, including nose and throat examination was performed at Visit 3 or time of withdrawal from the study. This included nasal examination using a nasal speculum and otoscope and a throat examination. The study report (p. 132/4494) states there was no evidence of treatment-related adverse changes on physical examination. Nasopharnygeal exam findings are discussed under headings 7.1.5 and 7.1.9.2 of this document.

10.1.2 D1221c0004

10.1.2.1 Title

"Open Label, Nonrandomized Comparison of the Pharmacokinetics of a Single 5.0-mg Dose of Zolmitriptan in Adult and Adolescent Migraineurs when Given as a Nasal Spray Between Migraine Attacks"

This was a phase 1 study to compare the PK of zolmitriptan 5 mg NS in adolescent and adult migraineurs between migraine attacks. 15 male and female adults ≥ 18 years of age and 15 male and female adolescents ages 12 to 17 years of age with a history of migraine were entered into the study. There were 12 evaluable subjects in each age group. The majority were Caucasian.

10.1.2.2 Safety assessments:

- Physical exam including nasopharyngeal exam was performed at screening, and -1 to 0 hours before zolmitriptan, and at 24 hour follow-up.
- Vital signs were collected at screening, within 30 minutes before dosing and 1, 2, 4, 6, 10, and 24 hours post-dosing. Temperature was taken on Visit 2 before medication, 2 hours post dosing and final at 8-10 hours.
- EKG, clinical labs, and urine dipsticks were collected at screening, -1 to 0 hours, and at 10 hours post-dosing.
- Drug and pregnancy screening (for females of childbearing potential)-at screening and visit 2 (-1 to 0 hours before zolmitriptan). Pregnancy results were to be obtained before study medication was given.
- Adverse events were collected from the time of placebo nasal spray administration through 24 hours after zolmitriptan administration. Serious adverse events were collected

after informed consent/assent was obtained and through the follow-up phone call at 1 week later.

10.1.2.3 Safety Results:

Exposure: 30 subjects each received a single 5 mg intranasal dose of zolmitriptan.
SAEs-there were no fatal SAEs. There was one SAE of hyper-anticoagulation in an adult (subject 002-0205). This was in an adult subject. After 4 attempts at IV placement, an IV line was established was 8:15 in the morning. At 2 pm, the subject complained of swelling at the attempted and established IV sites. The line was removed but the subject continued to bleed despite compression. The subject was taken to the ER and treated with compression and protamine. The subject had elevated PT and APTT levels (high of >249 with reference range 20.6-38). She also developed a severe headache. She held for observation and discharged the next morning. APTT levels were normal at discharge. The syringe used to flush the heparin lock was analyzed. The concentration of heparin was 16000IU/mL.
AEs leading to discontinuation: none are reported
Common adverse events: 93% of adolescents (14 subjects with 32 events) and 87% of adults (13 subjects with 31 events) experienced an adverse event. The most commonly reported adverse events occurring in both groups were dysgeusia (80% adolescents, 60% adults) followed by headache (20% each). Two adverse events were reported as severe (coagulation time prolonged and headache) and one event was reported as moderate (headache).

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Table 11.3.2.3 Summary of Adverse Events by Descending Incidence - Dosed Subjects

	Adolescents (N=15)		Adults (N=15)	
Preferred Term	N	%	N	%
DYSGEUSIA	12	80.0	9	60.0
HEADACHE	3	20.0	3	20.0
DIZZINESS	2	13.3	2	13.3
RHINORRHOEA	1	6.7	2	13.3
TRISMUS	1	6.7	1	6.7
VOMITING NOS	1	6.7	0	0.0
FATIGUE	1	6.7	0	0.0
OEDEMA PERIPHERAL	1	6.7	0	0.0
TENDERNESS NOS	1	6.7	0	0.0
PHARYNGITIS STREPTOCOCCAL	1	6.7	0	0.0
BODY TEMPERATURE INCREASED	1	6.7	0	0.0
BURNING SENSATION NOS	1	6.7	0	0.0
HYPOAESTHESIA	1	6.7	0	0.0
COUGH	1	6.7	0	0.0
CONTUSION	1	6.7	0	0.0
PAIN OF SKIN	1	6.7	0	0.0
PHARYNGOLARYNGEAL PAIN	0	0.0	3	20.0
DRY MOUTH	0	0.0	2	13.3
HYPOAESTHESIA ORAL	0	0.0	1	6.7
INFUSION SITE ERYTHEMA	0	0.0	1	6.7
COAGULATION TIME NOS PROLONGED	0	0.0	1	6.7
PAIN IN JAW	0	0.0	1	6.7
TRIGEMINAL NEURALGIA	0	0.0	1	6.7
PHARYNGEAL HYPOAESTHESIA	0	0.0	1	6.7
THROAT IRRITATION	0	0.0	1	6.7

Nasopharyngeal AEs: Nasopharyngeal adverse events occurred in 3 adolescents and 6 adults. The study report indicates that most adverse events were considered mild.

Table 11.3.2.6 Summary of Treatment Related Nasopharyngeal Adverse Events by Preferred Term - Dosed Subjects

Preferred Term	Adolescent N=15		Adult N=15	
	N	%	N	%
BURNING SENSATION NOS	1	6.7	0	0
PHARYNGEAL HYPOAESTHESIA	0	0	1	6.7
PHARYNGOLARYNGEAL PAIN	0	0	3	20.0
RHINORRHOEA	1	6.7	2	13.3
THROAT IRRITATION	0	0	1	6.7

10.1.2.3.1 Other Safety Assessments:

Clinical laboratory, urinalyses, and EKG assessments were collected. There is no placebo group and the study is small, so interpretation is quite limited. Vital signs were collected at various time-points during the day of dosing.

Clinical labs and Urinalyses: One adult subject (1-17) with a low screening hemoglobin of 109 also had a low hemoglobin (100 G/L with normal from 120 to 156 G/L) on day 1 before the end of treatment. Two adolescent subjects and one adult subject had chemistry results outside of the extended reference ranges. For the adolescents, the same lab parameters were abnormal before treatment. One adolescent (2-213) had an unscheduled visit at which hematocrit, WBC count, platelets, and neutrophils, particle concentration were all lower than the low end of the reference range. The listing of this did not indicate this as treatment emergent (Table 11.3.7.2.1). The adult had a high potassium result on day 1 post-treatment (7.1 mmol/L with normal 3.5-5.3 mmol/L) which was thought to possibly be due to hemolysis while collecting the blood sample.

There were four **urinalysis** results considered abnormal by the investigator. Two were in adult females (trace of occult blood post treatment with continuing 3+WBC and one with 3+ occult blood post treatment) and two were in adolescents (one female with screening and post- dose 2+WBC sediment and one male with trace proteinuria at 8-10 hours).

There were some lab parameters with higher maximum post- treatment values than those at screening (for example, total bilirubin, creatinine, and glucose). In the adolescents, these were within the extended references ranges for total bilirubin and slightly above it for glucose (118 mg/dL maximum with extended reference range high of 110 for up to age 12 years and 115 for up to age 49 years) and creatinine (1.2 mg/dL maximum with extended reference range of 1 in 3-12 year olds and 1.4 in subjects ≥ 13 years). Listing 11.3.7.2.2 (Listing of Abnormal Clinical Chemistry Results in SI units) did not list any adolescents with post-treatment high creatinine values. There was one adolescent (1-107) with a high glucose (6.55 mmol/L with high of RR at 6.4mmol/L) at an unscheduled visit. As I read the flag in this listing, it is not noted to be treatment emergent although her day 1 (-1 to 0 hour) glucose was 3.05mmol/L.

Vital Signs: As per the Listing of abnormal vital signs, (Table 11.3.8.4.1), one adult had a decrease in SBP of -24 with a result of 86.

Mean respiratory rates were increased at 6 hours post dose and at 8-10 hours post dose by 0.7 and 1.1 breaths per minute respectively in adolescents as compared to 0 and 0.9 breaths per minute in adults. Mean systolic blood pressures also changes a bit more than adults at both 6 hours post-dose (2.7 mm Hg versus 0.5 mm Hg respectively). Mean changes in diastolic blood pressure were negative in adolescents at 4, 6, and 8-10 hours post dose (-1.5, -2, and -0.9 mm Hg) when compared to adults at the same time-points (+2, +1.1, and +.09 mm Hg).

EKG: EKGs were centrally read by a designated cardiologist at (b) (4). Criteria for what constituted normal or abnormal EKG readings were not specifically stated in the protocol. EKG assessments were not at peak PK times (Cmax).

86.7% of the adolescent EKGs and 100% of the adult EKGs were read as normal at screening/baseline. All adult EKGs were considered normal. About 67% of day 1 (-1 to 0 hour) EKGs in adolescents were considered normal and 33% abnormal. At 8-10 hours post dose, about 7% of EKGs in adolescents were "unavailable", 80% were normal, about 7% (n=1) were abnormal, and 7% (n=1) were missing. The Sponsor's table describing these abnormalities is below. No EKG results were reported as adverse events.

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Table 11.3.8.4.2 Listing of Abnormal Electrocardiogram Results

Center/ Subject	Age Group	Age/Gender/ Race-Ethnicity*	Trial Day	Abnormality#
0001/0107	Adolescent	17/F/C	Day 1 (-1 to 0 hour)	NCS
0001/0112	Adolescent	14/M/C	Screening	SIN V4 and R in V5; just qualifies for LVH. PI felt ECG was normal.
			Day 1 (-1 to 0 hour)	Flat biphasic T waves
			Day 1 (8 to 10 hours post d	Sinus bradycardia; Flat biphasic T waves
			Unscheduled Visit	Sinus Bradycardia
0002/0201	Adolescent	12/M/C	Day 1 (-1 to 0 hour)	J point + ST elevation not completely typical for early repolarization
0002/0202	Adolescent	14/M/C	Day 1 (-1 to 0 hour)	Sinus bradycardia
0002/0208	Adolescent	15/F/C	Day 1 (-1 to 0 hour)	Sinus bradycardia
0002/0213	Adolescent	15/F/C	Screening	NCS - investigator feels this is a variant of normal

10.1.3 311CUS 0005

Much of this information is from Dr. K. Prohaska's review of NDA 20768, the pediatric supplement of Zomig tablets. It is included here to provide safety and exposure data.

10.1.3.1 Title

'A Multicenter, Double-blind, Placebo-controlled, Randomized Study and Open-label, Long-term, Tolerability Study with Zolmitriptan (Zomig™) for the Acute Treatment of Migraine Headaches in Adolescent Patients'

This was a 2-phase, multicenter, outpatient safety and efficacy study of oral zolmitriptan in the acute treatment of migraine headache in adolescent patients. In Phase I of the study, patients

were randomized to either 2.5 mg, 5.0 mg, or 10.0 mg zolmitriptan, or placebo for a single treatment. In the Phase II, open-label portion of the study, patients treated multiple migraine headaches over a 12-month period with 5.0 mg zolmitriptan tablet formulation. A second 5.0 mg tablet was allowed in Phase II, if necessary, between 2 hours and 24 hours after the 1st dose of study treatment. Phase II of the study was stopped early due to lack of efficacy in phase 1. Subjects and disposition: 850 subjects enrolled in phase I and 696 subjects took study medication. 80 to 82% of each drug group completed phase I. No placebo or 5mg Zomig subjects withdrew 2nd to an adverse event. 1.9% of the 10mg zolmitriptan group and 1% of the 2.5 mg zolmitriptan group withdrew 2nd to an adverse event. In phase II, a total of 680 subjects entered and 603 took study medication and 151 completed the study (>326 days as defined by the Sponsor).

10.1.3.2 Disposition:

Table 6 Summary of patient disposition - all randomized patients (Phase I)

Reasons for withdrawal	Treatment group number (%) of patients					
	Zolmitriptan 10.0 mg N=214	Zolmitriptan 5.0 mg N=212	Zolmitriptan 2.5 mg N=210	All zolmitriptan N=636	Placebo N=214	All treatments N=850
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed patients (Phase I)*	176 (82.2)	172 (81.1)	168 (80.0)	516 (81.1)	174 (81.3)	690 (81.2)
Lost to follow-up	7 (3.3)	9 (4.3)	13 (6.2)	29 (4.6)	14 (6.5)	43 (5.1)
Adverse event/concurrent illness	4 (1.9)	0	2 (1.0)	6 (0.9)	0	6 (0.7)
Protocol noncompliance	10 (4.7)	12 (5.7)	10 (4.8)	32 (5.0)	11 (5.1)	43 (5.1)
Informed consent withdrawn	5 (2.3)	4 (1.9)	2 (1.0)	11 (1.7)	1 (0.5)	12 (1.4)
Other	12 (5.6)	15 (7.1)	15 (7.1)	42 (6.6)	14 (6.5)	56 (6.6)

* Patients for Phase I were considered completed if they treated 1 migraine headache according to the protocol rules within a 12 week period from their randomization date.
N Total number of patients; n number of patients in category.
Data derived from Table T9.2.1, Section 11.1.

Table 7 Summary of patient disposition (Phase II) – safety population

Reasons for withdrawal	Zolmitriptan 5.0 mg (N=603)
	Number (%) of patients in category
Completed patients (Phase II)[a]	151 (25.0)
Discontinuations	452 (75.0)
Lost to follow-up	47 (7.8)
Adverse event/concurrent illness	50 (8.3)
Protocol noncompliance	81 (13.4)
Informed consent withdrawn	44 (7.3)
Other[b]	176 (29.2)
Patient feels medication ineffective	54 (9.0)

[a] Completed patients were defined as any patient who completed >326 days of treatment calculated from the time the first dose of study treatment to the date of withdrawal.
[b] Approximately 110 (60.0%) of the patients in the withdrawal category classified as "Other" were patients terminated as a result of the AstraZeneca decision to discontinue Phase II of the study.
N Total number of patients in safety population.
Data derived from Table T10.2, Section 11.1.

10.1.3.3 Adverse events:

There were no deaths in either phase of the study. **During phase I, one serious adverse event** occurred in one 5mg zolmitriptan patient in phase I . This was a prolonged migraine headache in a 14 year old male who had treated a migraine on 3-18-01 in the evening and was hospitalized on (b) (4) with a diagnosis of prolonged migraine headache. He was also diagnosed with acute labyrinthitis on (b) (4) . He was treated for his migraine, recovered, and discharged on (b) (4) . Dr. Prohaska's review includes a table of adverse events leading to discontinuation in phase I. This table is reproduced below.

Table 10 Adverse Events resulting in Discontinuation, Phase 1

Patient ID	Treatment	Event
0017/0152	Zomig 10 mg	Paresthesia, lymphadenopathy, tightness
0026/0438	Zomig 10 mg	Pain, conjunctivitis, heaviness, tightness
0038/2127	Zomig 2.5 mg	Headache
0041/2041	Zomig 10 mg	Vasodilation (flushed head)
0048/1697	Zomig 10 mg	Dyspnea, stiffness, tightness
0251/2463	Zomig 2.5 mg	Abnormal MRI (no details provided)*

*subject did not use study medication.

In phase II, ten patients experienced **serious adverse events**. Dr. Prohaska notes that he reviewed the narratives and agrees with the investigator's assessment that no serious adverse events were considered study medication related. The table below is reproduced from Dr. Prohaska's review and displays these serious adverse events.

Table 11 Serious AE, Phase 2

Patient ID	Event
0001/0301	Intractable migraine
0001/1405	Intractable migraine
0008/0085	Diabetes mellitus
0013/0250	Abdominal pain
0020/0140	Tonsilar Abscess
0041/0762	Ulcerative Colitis
0651/2302	Malaise*
0011/0323	Increased Migraine
0026/0032	Injury with multiple spinal fractures
0036/0702	Migraine

*Occurred within 24 hours of treatment

Adverse event related withdrawals included migraine/headache, paresthesia, tightness, nausea, asthenia, pharyngitis, and dizziness.

Common Adverse Events: In **phase I,** more zolmitriptan patients (45% , 27%, 32.2% for the 10 mg, 5 mg, and 2.5 mg zolmitriptan group respectively) experienced at least one adverse event than did placebo patients (15.3%). The most common adverse events across all zolmitriptan groups were tightness (6.7%), dizziness (6.1%), nausea (5.5%), and paresthesia (4.2%) versus 1.1%, 2.3%, 1.1%, and 0% for these events, respectively, in the placebo group.

In **phase 2**, about 58% (351) of patients in the safety population reported at least one adverse events with 279 (46.3%) reporting at least one adverse event within the 24-hour time window at the patient level. At the attack level, the most common adverse events reported in phase 2 were tightness (3.7%), paresthesia (2.8%), nausea (2%), dizziness (1.6%), and pain (1.2%). At the patient level, dizziness (14.5%), nausea (14.3%), tightness (12%), and paresthesia (9.5%), pharyngitis (8%), pain (7.3%), and asthenia (6.3%) were common adverse events.

LABS/Vital Signs/EKG/PREGNANCY: Dr. Prohaska's review states that there were no clinically significant changes in mean laboratory values or shifts from baseline and no clinically significant changes in mean vital signs from baseline to visit 3. Dr. Prohaska reported that none of the abnormal EKGs were considered adverse events. There were three pregnancies during the trial. All three reportedly went to term and resulted in healthy newborns. Additionally, there was a serious adverse of event of blighted ovum leading to withdrawal in a patient who reportedly did not receive study treatment.

10.1.3.4 EXPOSURE:

Long term exposure, as per Dr. Prohaska's review, was somewhat short of the 300 subjects for six months and 100 for one year. Exposure was 281 subjects using Zomig 5 mg tablets for at least 180 days treating 3408 attacks (about 2 per month) and 42 subjects took Zomig 5mg tablets for at least 360 days treating 989 attacks (about 2 per month). 151 subjects took Zomig 5mg tablets for at least 326 days and treated about 2 attacks per month.

10.2 PSUR

10.2.1 PSUR with the initial sNDA

10.2.1.1 Clinical Study exposure

Trial	Study type	Continent	# pts recruited to date	Ongoing y/n	Summary
D1221C00005	MC, DB, PC, 2-way CO Efficacy/Safety	North America	248	n	No SAE No DC 2nd AE
311CUS/0012	O,R,MC migraine disability status	North America	2864	n	6 SAEs in Z pts; 2 considered related; chest pain and asthma-caused dc
311CUS/0022	MC, R, PC,DB early efficacy and tolerability 5mg ZNS in adults acute treatment	North America	2122	n	5SAEs in Z group and 3 in P group 6 DC 2nd to AE Events not described in the PSUR "no new safety issues"
D1221C00002	O, R, 2-period CO BE 0.5mg clinical v comm. Device ZNS	Sweden	46 healthy vol	n	"no new safety issues identified" No SAE
D1221C0004	O, NR, 2-period, CO BE 2.5 mg clinical v commercial device	Sweden	46 healthy vol	n	"no new safety issues identified" No SAE
US IIT Nasal Cluster Study	DB, PC, CO,ZNS 5 and 10mg acute cluster	US	53	n	No SAE reported-results in progress

Data extracted from Table D in PSUR, MC=multicenter, R=randomized, NR=nonrandomized, PC=placebo-controlled, O=open, CO=crossover, DB=double-blind

10.3 Zomig Tablet PK Data

Table 20 Mean PK Parameters for zolmitriptan and ranges by age and gender

	Adolescents	Adults
Mean Cmax (SE)	9.66(0.87) ng/ml	8.54(0.60) ng/ml
Range Cmax	3.7 to 20.3 ng/ml	3.7 to 12.9 ng/ml
Mean Cmax-Male	7.31 (1.36) ng/ml	7.57 (1.12) ng/ml
Mean Cmax-Female	11.11 (0.95) ng/ml	9.08 (0.69) ng/ml
Mean AUC (SE)	51.4(4.0) ng/ml	46.4(4.1) ng/ml
Range AUC	16.9 to 83.3 ng.h/ml	20.7 to 66.3 ng.hr/ml
Mean AUC-Male	37.0 (6.1) ng.h/ml	41.9 (9.0) ng.h/ml
Mean AUC-Female	60.3 (3.4) ng.h/ml	48.6 (4.4) ng.h/ml
Mean t½ (SE)	3.01 (0.16) h	3.75 (0.22) h
Range t½	2.22 to 5.35 h	2.21 to 5.92 h

Source: Adapted from sponsor table 4, study report 0009, page 29.

Table 19 PK parameters of zolmitriptan; ratio of geometric means[a] for adolescents

Parameter	Adolescents (geometric mean)[a]	Adults (geometric mean)[a]	Ratio of geometric means[b]	90% CI for ratio[b]
C_{max} (ng/mL)	8.9	8.2	1.09	0.89 to 1.33
AUC (ng.h/mL)	47.8	42.7	1.12	0.89 to 1.40
$t_{1/2}$ (h)	3.01	3.75	-0.74	-1.18 to -0.30

[a] Mean for $t_{1/2}$.
[b] Difference of means for $t_{1/2}$.
CI Confidence interval.
C_{max} Maximum plasma concentration.
AUC Area under the curve.
$t_{1/2}$ Half–life.

Source: Sponsor table 4, study report 0009, page 33.

Table 21 PK parameters of 183C91; ratio of geometric means[a] for adolescents

Parameter	Adolescents (geometric mean)[a]	Adults (geometric mean)[a]	Ratio of geometric means[b]	90% CI for ratio[b]
C_{max} (ng/mL)	4.9	3.5	1.39	1.17 to 1.65
AUC (ng.h/mL)	28.2	20.8	1.36	1.15 to 1.60
$t_{1/2}$ (h)	3.01	3.05	-0.04	-0.55 to 0.47

[a] Mean for $t_{1/2}$.
[b] Difference of means for $t_{1/2}$.
CI Confidence interval.
C_{max} Maximum plasma concentration.
AUC Area under the curve.
$t_{1/2}$ Half–life.

Source: Sponsor table 8, study report 0009 page 35.

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