

## CLINICAL REVIEW

Application Type	NDA 505(b)(1) sNDA PMR 948-1
Application Number(s)	21450/S-008
Priority or Standard	Standard
Submit Date(s)	August 14, 2014
Received Date(s)	August 14, 2014
PDUFA Goal Date	June 14, 2015
Division / Office	Division of Neurology Products
Reviewer Name(s)	Suhail Kasim, MD MPH
Review Completion Date	May 22, 2015
Established Name	Zolmitriptan Nasal Spray
(Proposed) Trade Name	ZOMIG
Therapeutic Class	Triptan agonist
Applicant	AstraZeneca LP
Formulation(s)	Intranasal spray
Dosing Regimen	Zolmitriptan 5 mg; 2.5 mg
Indication(s)	Acute migraine
Intended Population(s)	Adolescents 12-17 years old

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Approval action is recommended for NDA 21450/S-008 ZOMIG nasal spray 5 mg and 2.5 mg doses for the indication, acute treatment of migraine with or without aura in adolescent migraineurs 12-17 years old. The sponsor has complied with the terms of PREA commitment PMR 948-1, as noted in the agreed upon FDA issued deferral extension letter sent to AstraZeneca on June 4, 2013 and the efficacy data from study D1220C00001 support this approval.

### 1.2 Risk Benefit Assessment

ZOMIG (zolmitriptan) nasal spray, marketed in the United States for adult migraineurs since September 30, 2003, has a well characterized safety profile. No new or unexpected adverse events were identified in the course of the development program of ZOMIG nasal spray in the adolescent patients with acute migraine. The overall risk to benefit ratio of ZOMIG nasal spray in adolescent migraineurs 12 to 17 years of age is therapeutically acceptable.


### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine postmarketing surveillance is appropriate.

### 1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric studies in 6-11 y/o patients was deferred/delayed (PMR-2) until additional safety and effectiveness data were available in adolescents, which is the efficacy supplement under review NDA 21450/S-008 in response to PMR-1.

The draft guidance to assist sponsors in the clinical development of drugs for the acute treatment of migraine recommends evaluation of pediatric patients 6-17 years<sup>3</sup>. (b) (4)



(b) (4)  
However, the literature suggests that there are between 4-11% pediatric patients in age group 6-11 years based on epidemiological estimates using varied diagnostic criteria. Even if DNP considered the lower estimate of 4%, there should be at least over 50,000 pediatric patients in age group 6-11 years and therefore a study is possible albeit that pediatric study in patients 6-11 years might take longer than expected to complete.

In an attempt to further assess the use of ZOMIG nasal spray in pediatric patients since the approval of triptans for acute migraine treatment for <17 year old patients, DNP requested information for Drug Utilization data from OSE/DEPI-II for the period 2011-2014. Drug Utilization data is available from 2008-2011 (previous PAC review for Zomig). The results of the drug use data appeared that there was declining zolmitriptan use in the 6-11 y/o population (22% over the last 4-years), which may be due to approved product rizatriptan availability and the healthcare providers experience using sumatriptan. However, the drug use data informed that there are at least >30,000 6-11 y/o children prescribed triptans, and there were approximately 5,500 6-11 y/o children who received a nasal spray prescription (sumatriptan and zolmitriptan) in the past 4 years suggesting there is steady nasal spray use in the age group. This additional information provide sufficient information to request studies in 6-11 y/o pediatric patients since a clinical study in the age group appears practicable. The information was discussed with the Pediatric Review Committee (PeRC), a committee established under FDAAA to carry out activities related to BPCA and PREA (b) (4)

### **Proposed PMR's**

Conduct a controlled efficacy study in children ages  $\geq 6$  years to 11 years with migraine that includes sparse PK samples throughout the efficacy trial. Conduct a long-term open-label safety study in pediatric patients with migraine ages  $\geq 6$  years to 11 years. The long-term safety study must provide a descriptive analysis of safety data in at least (b) (4) pediatric patients exposed for at least 6 months, (b) (4) treating on average at least one migraine attack per month, at doses evaluated in the efficacy study.

Conduct a juvenile rat toxicology study to identify the unexpected serious risk of adverse effects of zolmitriptan on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of sumatriptan/naproxen on growth, reproductive development, and neurological and neurobehavioral development.

The sponsor should submit timelines for the above-mentioned studies.



Final Protocol Submission:  
Study Completion:  
Final Report Submission:

## 2 Introduction and Regulatory Background

ZOMIG nasal spray was indicated for the acute treatment of migraine in adults in 2003. Pediatric exclusivity for the active moiety was granted in adolescents using the tablet formulation (NDA 20768). In compliance with initial Pediatric Research Equity Act (PREA) obligations for ZOMIG nasal spray, AstraZeneca submitted supplemental NDA 21450/S-005 on December 14, 2007, followed by submissions of additional information through September 15, 2008 that included PK study, (D1221C0004) and an efficacy and safety study (D1221C00005).

On October 14 2008, following review of sNDA 21450/S-005

(b) (4)

(b) (4)

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(b) (4)

I refer the reader to clinical review of NDA 21450/S-005 by Dr. Teresa A. Podruchny for further submission related regulatory activity, in addition to the clinical review of NDA 20768 (sequence 12, dated December 10, 2003 by Dr. Prohaska), the reviews of submission PB 000 to NDA 21450/PU 37 IND 53848, signed December 10 2002, and the 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 the

(b) (4)

For the reasons stated above, AstraZeneca did not fulfil the PREA obligation for NDA 21450.

(b) (4)

that efficacy was not established.

The current ZOMIG Nasal Spray label states the following regarding the safety in children:

(b) (4)

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(b) (4)

(b) (4)

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(b) (4)

In accordance with the PREA 21 CFR 314.55, AstraZeneca Pharmaceuticals LP (hereafter referred to as AstraZeneca) submitted a supplemental New Drug Application (sNDA) for NDA 21450/S-008, ZOMIG nasal spray (zolmitriptan) to address PREA commitment PMR 948-1, as noted in the agreed upon FDA issued deferral extension letter sent to AstraZeneca on June 4, 2013.

*PMR 948-1: Deferred pediatric study under PREA for the acute treatment of migraine in pediatric patients ages 12 to 17 years. Final report due September 30, 2014.*

(b) (4) the pediatric sNDA applicant, provided a letter authorizing AstraZeneca as the US agent, which is enclosed in module 1.4.1 of the eCTD submission.

AstraZeneca intends that the results from the submitted adolescent pediatric (Study D1220C00001) will permit expanding the indication for ZOMIG nasal spray to treat acute migraine in adolescents aged 12-17 with safety information from studies D1220C00001 and D1221C00005 supporting its use in adolescents aged 12-17 years.

As stated in the October 14, 2008 Agency communication, a determination as to whether or not a study in 6 to 11 year olds (PMR 984-2) is practicable would be made following review of additional safety and effectiveness data in pediatric patients aged 12 to 17 years. Please see details in section 1.4 of this review.

*PMR 948-2: Deferred pediatric study under PREA for the acute treatment of migraine in pediatric patients ages 6 to 11 years. Upon review of additional safety and effectiveness data in pediatric patients ages 12 to 17 years, we will make a determination as to whether or not pediatric studies are practicable for this age range.*

## **2.1 Product Information**

ZOMIG nasal spray is a 5-hydroxytryptamine (5-HT; also known as serotonin) 1B/1D receptor agonist, or triptan, approved in the United States on September 30, 2003 as an anti-migraine agent indicated for the acute treatment of migraine with or without aura in adults. ZOMIG nasal spray contains (b) (4) zolmitriptan and the unit delivers a dose of either 2.5 mg or 5 mg. The 2.5 mg (b) (4) doses were approved for use in adults on September 23, 2009 fulfilling phase-4 post-marketing commitment.

Zolmitriptan oral tablet formulation is additionally available that was approved in 1997, and as orally disintegrating tablet (ZOMIG-ZMT) approved in 2001. The tablet formulations exist in 2.5 mg or 5 mg of zolmitriptan per tablet.

## **2.2 Currently Available Treatments for Proposed Indication**

Almotriptan malate (approved 2009), rizatriptan benzoate (approved 2011), and treximet (approved 2015) are indicated for acute (abortive) treatment of migraines in adolescents 12 – 17 years old. Rizatriptan is additionally approved for use in children 6-11 y/o for the treatment of acute migraine. The referenced review summarizes products that may be used by healthcare providers in the treatment of pediatric patients with migraine<sup>1</sup>.

## **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 Safety Issues With Consideration to Related Drugs (Triptans)**

Zolmitriptan is a chemical analog of the class of products - 'triptans', developed for their potent cranial vasoconstrictor properties. Triptans are selective 5-HT<sub>1B/1D</sub> receptor agonists and mediate their vasoconstrictor activity via 5-HT<sub>1B</sub> receptors expressed on vascular smooth muscle.

While triptans are generally recognized as safe and effective, there have been class concerns raised as large numbers of patients were exposed to triptans, that their vasoconstrictor mechanism of action also conferred a risk of serious cardiovascular adverse events, some fatal. Consistent with their common pharmacology, sumatriptan, zolmitriptan, rizatriptan, eletriptan and naratriptan induced comparable dose-dependent contraction of isolated human coronary arteries. Because triptans are known to cause coronary vasospasm, they are contraindicated in patients with known coronary artery disease (CAD). It is strongly recommended that 'triptans' are not prescribed to patients with risk factors for undiagnosed CAD (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, male over 40 years of age) without first undergoing a thorough cardiovascular evaluation. It is recommended that the first dose of a triptan should be given in a physician's office, and preferably followed by an electrocardiogram (ECG).

The current label recommends patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described

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<sup>1</sup> O'Brien HL, Kabbouche MA, Hershey AD. Treating pediatric migraine: an expert opinion. *Expert Opin Pharmacother*. 2012 May;13(7):959-66

above, undergo periodic interval cardiovascular evaluation as they continue to use the drug.

Cerebrovascular events and fatalities (cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events) have also been described, but this relationship is confounded by the presence of these complications in the migraine population in general. Other (non-coronary artery) vasospasm-type events are known with triptan use including peripheral vascular and colonic ischemia and (rarely) transient and permanent blindness. Migraine patients are already at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). The incidence of all of these disorders remains low, when the widespread use of triptans is considered.

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

The Division of Pharmacovigilance (DPV) summarized pediatric (ages 0-21 years) post-marketing adverse event reports (from September 2003 – March 2011) associated with the use of zolmitriptan nasal spray in July 2011 for the BPCA review of pediatric reports of serious unlabeled adverse events with ALL zolmitriptan formulations. The reviewed pediatric adverse events were similar for all marketed triptan products and consistent with events reported in older populations (DARRTS document reference ID: 2977211).

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

FDA requested that AstraZeneca design and conduct an *additional study of zolmitriptan in adolescents (ages 12 to 17 years), in addition to a new commitment for a deferred pediatric study in children ages 6 to 11*. The conduct of the pediatric study in children ages 6 to 11 years old was to be deferred and to be contingent on final study results from the adolescents study. Please refer to details in section 2 of this review regarding PMR 948-1 and PMR 948-2.

### **Renewed PREA Commitment - SPA Protocol D1220C00001**

AstraZeneca engaged in discussions with the Division of Neurology Products for ZOMIG nasal spray pediatric study development in adolescents since June 2009 and reached Special Protocol Assessment (SPA) agreement with DNP on the study design and analysis plan for study protocol D1220C00001, submitted on September 23, 2010. However, there were subsequent SPA protocol amendments which were considered acceptable changes that did not affect the previously agreed upon Special Protocol Assessment agreement. AstraZeneca submitted the final agreed upon protocol in September 2012. Please refer to the recent publication by Sun et al<sup>2</sup> that discussed

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<sup>2</sup> Sun H, Bastings E, Temeck J, Smith PB, Men A, Tandon V, Murphy D, and Rodriguez W, 2013, A Systematic Analysis and Historic Perspectives of Triptan Trials in Adolescents, *JAMA Pediatr.*, 167(3):243-49.

some of the challenges inherent in conducting trials in a pediatric migraine population, and possible reasons for failed pediatric studies conducted previously.

SPA agreement Protocol D1220C00001, entitled “A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel-Group Study to Evaluate the Efficacy of Zolmitriptan 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents”, was conducted to fulfill a Pediatric Research Equity Act (PREA) postmarketing commitment previously issued on October 14, 2008 (PMR 948-1).

## **2.6 Other Relevant Background Information**

### **Deferral Extension Granted (PMR-1 & PMR-2) - SPA Protocol D1220C00001**

AstraZeneca requested deferral extension for SPA protocol study D1220C00001 (submitted on December 19, 2012) for this previously agreed upon SPA protocol in order to fulfill PREA obligation for ZOMIG nasal spray (PMR 948-1; PMR 948-2). AstraZeneca submitted deferral extension request via eCTD submission, sequence number 0027. <\\CDSESUB1\EVSPROD\NDA021450\021450.enx>.

PeRC granted AstraZeneca request for deferral extension due to their patient recruitment challenges, and the delays caused due to the SPA negotiations following formal FDA reviews and discussions. Originally, the final study report for study D1220C00001 was due on October 14, 2011 based on initially agreed upon commitments specified in the approval letter for NDA 21450/S-005 October 14, 2008. However, PeRC granted AstraZeneca extension for the submission of the final Study Report for Study D1221C00001 to the renewed timeline of September 30, 2014. AstraZeneca’s reasons for requesting extension for study report submission is in Section 5.2 of this review discussed with the protocol amendments sub-section.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The overall quality of the submission was acceptable. The NDA was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well-organized, easy to navigate, and complete.

### **3.2 Compliance with Good Clinical Practices**

The sponsor affirms that ethics committees or institutional review boards approved all studies in the clinical development program. The studies were in compliance with Good Clinical Practice (GCP) standards according to the ICH guidelines and the Declaration of Helsinki. Written informed consent was obtained for all subjects prior to any study related procedure.

### **3.3 Financial Disclosures**

The sponsor provided required information regarding financial disclosure and there was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of this trial. Form FDA 3454 provided information for the clinical studies with no financial interests to disclose related to the sponsor of the covered study. Since there were no principal investigators participating who had financial interests to disclose (royalty), proprietary (patent), and equity (stock holder) interests of concern, Form FDA 3455 was not included. Please see additional Clinical Investigator final disclosure document completed for NDA 21450, sequence 0040. EDR location <\\CDSESUB1\EVSPROD\NDA021450\021450.enx>; Module 1.3.4.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

N/A

### **4.2 Clinical Microbiology**

N/A

### **4.3 Preclinical Pharmacology/Toxicology**

N/A

#### 4.4 Clinical Pharmacology

##### 4.4.1 Mechanism of Action

No new data was submitted.

##### 4.4.2 Pharmacodynamics

No new data was submitted.

##### 4.4.3 Pharmacokinetics

The pharmacokinetic profile of ZOMIG nasal spray 5 mg was evaluated during NDA 21450/S-005 review of study D1221C00004 (Table 2) including 15 adults and 15 adolescents (12-17) with a history of migraine. Briefly, I recapture the discussions from the clinical reviews for that submission. “The 5-mg dose was selected on the basis of efficacy and tolerability demonstrated for the approved oral tablet formulation in adults. Both zolmitriptan and its major active metabolite, 183C91, were studied. For zolmitriptan, systemic exposure measures ( $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$ ) following a single intranasal dose of 5-mg zolmitriptan were similar in adolescents and in adults.

Adolescents had 8-13% lower AUCs and 3% lower  $C_{max}$  compared to that seen in adults. The clearance in adolescents was 15% higher than adults, corresponding to the slightly lower exposure. The median  $T_{max}$  was similar at about 2.0 hours in both adults and adolescents and  $t_{1/2}$  was slightly shorter at 3.0 hours in adolescents compared with 3.8 hours in adults. For active metabolite 183C91, systemic exposure was slightly higher in adolescents than in adults based on geometric mean ratios (adolescents had approximately 27- 32% higher AUCs and 17% higher  $C_{max}$  compared to adults). The difference was not considered clinically significant.

Considering the similarity of exposure between zolmitriptan oral and nasal spray, and between adults and adolescents, it was considered that further pharmacokinetic or pharmacodynamic data was not required for the adolescent population.”

**Table 1: NDA 21450 AUC and  $C_{max}$  for ZOMIG 5 mg in Adolescents and Adults**

Parameter	Gender	N	Adolescent		Adult		Ratio (Adolescent/Adult)
			95% CI	Geometric means ratio (lower, upper limit)	95% CI	Geometric means ratio (lower, upper limit)	90% CI
AUC (hr*ng/mL)	All	15	40.9 (30.0, 55.6)		15	46.9 (34.5, 63.9)	0.87 (0.61, 1.25)
$C_{max}$ (ng/mL)	All	15	6.2 (4.7, 8.2)		15	6.4 (4.9, 8.5)	0.97 (0.70, 1.34)
$t_{max}$ (hours)	All	15	2.0 (0.3, 4.0)		15	2.0 (1.0, 4.0)	NC

Ref: eCTD seq 0040; Module 2.5; Sponsor’s Table 2. Source: NDA 21-450/S-005, Module 2.7.2; Study D1221C00004

## **5 Sources of Clinical Data**

All documents and datasets reviewed for this NDA submission are in electronic format. The path to this information in the CDER Electronic Document Room is:  
<\\CDSESUB1\EVSPROD\NDA021450\021450.enx>



**5.1 Tables of Studies/Clinical Trials**

<b>Table 2: NDA 21450/S-008 Overview of Clinical Studies</b>						
<b>Study Number</b>	<b>Study Objectives</b>	<b>Study Design</b>	<b>Study Population</b>	<b>N Total Enrolled and Dosed</b>	<b>Test Product(s); Dosage Regimen</b>	<b>Site location (number of centers)</b>
<b>Pharmacology</b>						
<b>D1221C00004</b>	Compare the PK of single dose of ZOMIG nasal spray 5 mg in between migraine attacks	Open-label, single-dose, parallel-group clinical pharmacology study	Adolescent (12-17) and Adult (18-65) migraineurs	15/ group	A single dose of ZOMIG nasal spray 5 mg	2 centers in the US
<b>Efficacy and Safety</b>						
<b>D1220C00001</b>	Pain Free* 2-hrs after dosing	Rand, DB, PBO, parallel-group study with single-blind run-in period (enriched enrollment)	Adolescent patients (12-17) with migraine headache	N=798 (12-17) Placebo (n=296) ZOMIG 0.5 mg (n=115) ZOMIG 2.5 mg (n=99) ZOMIG 5 mg (n=288)	A single dose of ZOMIG 0.5, 2.5, or 5 mg or placebo in a nasal spray device administered double-blind for treatment of 1 moderate or severe migraine headache during a 10-week study period	153 centers (total) in the US, Latin America, and Europe
<b>D1221C00005</b>	Headache response** rate 1-hour after dosing	Rand, DB, PBO, two-way crossover study with a single-blind, placebo challenge that excluded early placebo responders after randomization. (b) (4)	Adolescent patients (12-17) with migraine headache	N=248 ZOMIG /placebo (n=128) OR placebo/ Zomig (n=120)	A single dose of ZOMIG 5 mg AND a single dose of placebo in nasal spray devices administered double-blind for treatment of 2 moderate or severe migraine headaches during a 12-week study period	17 centers in the US
Ref: eCTD seq 0040; Module 5.2; Sponsor's Table 1. TABULAR LISTING OF ALL CLINICAL STUDIES						
*Headache Pain Free was defined as patients with a baseline headache pain score of moderate (2) or severe (3) improving to none (0) **Headache Relief/response was defined as patients with a baseline headache pain score of moderate (2) or severe (3) improving to either mild (1) or none (0)						

## **5.2 Review Strategy**

The clinical program for ZOMIG nasal spray includes one pharmacokinetic study (D1221C00004) and (b) (4) and safety studies (D1220C00001 and D1221C00005) that have been conducted in adolescents aged 12 to 17 years with ZOMIG nasal spray (Table 2). The efficacy review will focus on data from Study D1220C00001.

During pre-sNDA written response communication on April 10, 2014, it was considered acceptable to provide the evaluation of the safety of ZOMIG nasal spray based upon the data from 2 studies (D1220C00001 and D1221C00005), and adverse event (AE) pooled safety data from these 2 studies. Data from studies D1221C00005 and D1221C00004 have been previously reviewed (NDA 21450/S-005). One previous ZOMIG tablet study (Study 311CUS/0005, New Drug Application [NDA] 21-450/S-005) included information for the evaluation of the long-term safety of ZOMIG in adolescents.

The clinical evaluation of ZOMIG nasal spray for the acute treatment of migraine in pediatric patients aged 6 to 11 years was deferred pending FDA review of the efficacy and safety data from Study D1220C00001. Please see PerRC discussions included in section 1.4 of this review.

Dr. Tristan Massie, Ph.D. Division of Biometrics performed the statistical analysis for this submission. Applicable portions of Dr. Massie's efficacy review have been referenced and incorporated in this review.

## **5.3 Discussion of Individual Studies/Clinical Trials**

### **5.3.1 Protocol D1220C00001**

#### **Title**

A Randomized, Double-blind, Placebo-controlled, Multicenter, 4-Armed Parallel-Group Single-Attack Study to Evaluate the Efficacy of Zolmitriptan 0.5 mg, 2.5 mg and 5 mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents 12-17 years.

#### **Study Sites**

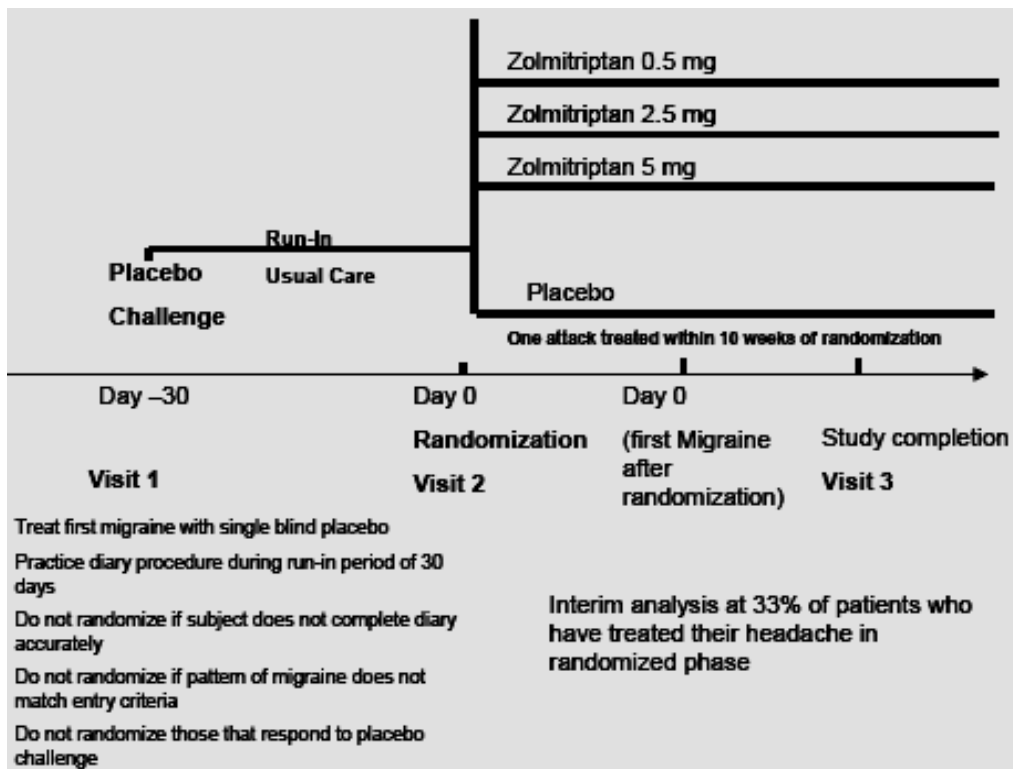
153 centers (total) in the US, Latin America, and Europe

#### **Objectives**

To evaluate the efficacy and safety of zolmitriptan nasal spray 0.5 mg, 2.5 mg, and 5 mg as compared to placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17).

### Design and Methodology

D1220C00001 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that included a single-attack, single-dose placebo-challenge, during the single-blind *run-in period* followed by treatment of a double-blinded single-attack period with one dose of zolmitriptan nasal spray 0.5 mg, 2.5 mg, 5 mg or matching placebo during the *treatment period*.



At 2 hours after treating with single-blind placebo, if the patient's migraine headache had not responded (i.e., the pain had not reduced to mild or none), the patient could use approved rescue medication(s). For any subsequent migraine episodes, the patient used their usual acute migraine medication. During this run-in period, patients were asked to complete a diary of symptoms. Visit 2 (randomization) occurred at the end of the 30-day run-in period. At this visit, patients were randomized to treatment only if they failed to respond to the placebo challenge (i.e., they maintained a moderate or severe headache pain intensity at 2 hours), completed their paper diary correctly, and had the protocol-specified untreated headache duration. Patients not treating a migraine headache with blinded placebo during the 30-day run-in period were considered screen failures.

Following treatment of one migraine attack within 10 weeks of randomization (**Visit 2**), the subject returned for **Visit 3** within 2 weeks of treatment with study drug. This

included the final follow up visit. There was an **interim visit** 4 weeks from Visit 2, if there was no treatment of a migraine headache or attack with study drug. To ensure that the sample size was sufficient to test the primary hypothesis, an interim sample-size re-estimation analysis was included. The sponsor included the interim futility analysis to prevent patients from receiving ZOMIG doses unlikely to demonstrate significant benefit.

#### Specific characteristics

The study design includes enrichment procedures to limit the participation of placebo-responders and randomize a population less likely to have a placebo response. Patients had to have an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura with a typical untreated migraine headache attack of *3-hour headache duration* or more. The study included treatment of a single migraine headache attack with 1 dose of *single-blind placebo challenge* during the 30 day run-in period. If the patient met all conditions for randomization, including a failed response to a single-blind placebo conducted in a run-in phase, a subsequent single migraine headache attack was treated with 1 blinded dose of either ZOMIG nasal spray 5 mg, 2.5 mg, or matching placebo.

#### Sponsors rationale and key features of D1220C00001 study design:

- Parallel-group, single-attack design. Rationale: design requires only one device available for the patients, which eliminates the chance of device mix-up.
- The study population will be enriched by requiring patients with a history of at least 3-hour headache duration, by randomizing patients who failed-response to a single-blind placebo challenge, and by excluding subjects who did not require treatment of migraine headache during the 30-day run-in period.
- Primary endpoint, pain free at 2 hours. Rationale: IHS guideline-recommended primary endpoint; this endpoint showed large separation between zolmitriptan and placebo in Study D1221C00005 and is considered the most likely to differentiate the treatments.

#### **Dose**

A *single acute moderate to severe migraine episode* was treated with **1 dose** of ZOMIG nasal spray either 0.5 mg, 2.5 mg, 5 mg or matching placebo in a blinded manner. Each nasal spray applicator contained one dose of 100 µL volume, the active treatment containing ZOMIG at the strength of 5, 25, or 50 mg/mL.

When a headache pain reached moderate or severe intensity and the patient could complete the diary as instructed, patients were to treat the migraine headache by administering a single spray with the single-blind placebo treatment into 1 nostril.

#### Reviewer comments

*During the SPA meeting in June 2009, the Division recommended that the sponsor should investigate the full dosing range and include a 2.5 mg and a 0.5 mg arm in the*

*pediatric study, in order to identify the lowest effective dose (if any). The Division also recommended exploring higher doses as well, unless safety reasons preclude that.*

*AstraZeneca stated that since 0.5, 2.5 and 5 mg represent the full range of doses that have been shown to be effective in adults they proposed to test the 3 doses which cover the widest possible dose range. No rationale was provided for higher doses. However, it is very likely there may be a flat response with higher doses and that may not require evaluation. Study D1221C0004 evaluated the pharmacokinetics of nasally administered zolmitriptan in adolescents. Please see section 4.4.3 of this review.*

### **Duration**

Enrolled patients were required to treat one migraine attack within 10 weeks of randomization and to *return to the study site within 2 weeks of treating a migraine* with study drug. Subjects will have approximately 14 weeks to complete the study, which consists of a 30-day run-in period followed by 10 weeks to complete treatment. If there was no treatment with study drug within 4 weeks of randomization, subjects were to return to the study site for the interim visit to review the study dosing instructions.

<b>Inclusion Criteria</b>	<b>Rationale</b>
Adolescents aged 12 to 17 years at the time of screening. Patients must not be enrolled if they will turn 18 years of age within 12 weeks after randomization.	Consistent with FDA guidelines for adolescents. Patients must not “age out” of eligibility during the randomization period.
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.	IHS-R is the most robust diagnostic tool, incorporating the expanded symptoms complex for pediatric and adolescent migraine. If a patient satisfies IHS, then by definition he/she will satisfy IHS-R.
A minimum of 2 migraines, considered to be moderately/severely disabling, per month on average during the school year.	To maximize chance of a migraine occurring during the study period.
A history of usual migraine duration of >3-hours untreated (by history) for the 3 months prior to screening.	Primary endpoint is pain free at 2 hours. This ensures migraine of appropriate duration.
A history of migraine attacks occurring at intervals >24 hours apart, confirmed by medical history.	
(b) (4)	(b) (4)
Have the ability to differentiate between migraine and non-migraine headaches.	To ensure ability to participate in the protocol.

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Inclusion Criteria	Rationale
<p>Women should be on a stable method of birth control for a minimum of 3 months prior to study entry. 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.</p>	<p>GCP/SOP/Safety.</p>
Exclusion criteria	Rationale
<p>A history of basilar, ophthalmoplegic or hemiplegic migraine headache, or any potentially serious neurological condition that is associated with headache.</p>	<p>Patient safety and diagnostic precision.</p>
<p>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.</p>	<p>Patient safety consistent with label.</p>
<p>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, arrhythmias, cerebrovascular syndromes (eg., stroke), or peripheral vascular disease.</p>	<p>Safety, consistent with label.</p>
<p>Clinically significant abnormalities indicated from the medical history, physical exam, clinical chemistry, hematology, urine drug screen.</p>	<p>Safety.</p>
<p>Had a diagnosis or suspicion of drug induced or chronic daily headaches within 1 year.</p>	<p>Diagnostic precision.</p>
<p>Has 14 or more non-migraine headache days each month for 3 months before the screening visit.</p>	<p>Diagnostic precision. Frequent multiple headaches may lead to a non-migraine being treated in the study.</p>
<p>Has uncontrolled hypertension defined as systolic or diastolic blood pressure that exceeds the 95th percentile for age and height.</p>	<p>Safety.</p>

Exclusion criteria	Rationale
Has used MAO-A inhibitor, methysergide, methylergonovine or cimetidine in the 2 weeks before randomization, or a SSRI 4 weeks before randomization; if the patient had been on stable dose of SSRI for 8 weeks (2 months) prior to randomization, they could be included in the study.	Decrease risk of AEs and consistent with label. Cimetidine use may increase plasma exposure of zolmitriptan nasal spray.
Has any recent history of abuse (in the previous year) of alcohol or other drugs including drugs for the acute treatment of headache.	Current substance abuse will confound ability to assess efficacy of drug.
Is a female who is pregnant or breast-feeding.	GCP/SOP.
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.	Safety, will increase plasma exposure.
Has a clinically relevant abnormality on nasopharyngeal examination as determined by the investigator; nasopharyngeal examination was a standard physical examination to rule out gross abnormalities of the nasopharynx and did not imply specialist examination prior to enrolling a patient.	Will impair administration and absorption of study medicine.
Has a positive urine test for drug abuse	Safety, diagnostic precision.
Responded to the placebo challenge during the run-in period (ie, migraine headache intensity was mild or none at 2 hours after the placebo challenge).	

5-HT<sub>1B/1D</sub> Serotonin <sub>1B/1D</sub>; AE Adverse event; GCP Good Clinical Practice; MAO-A Monoamine oxidase inhibitor-A; SOP Standard operating procedure; URI Upper respiratory infection.

**Restrictions during study conduct:**

This applies during the placebo challenge and treatment period.

- Headache must be treated within 30 minutes of onset of moderate to severe headache pain.
- Subject must be symptom-free between headache episode intervals
- Rescue medication, as determined by the protocol and the investigator, may be taken 2-hours after study treatment
- After taking study drug, subject must not sleep for 2-hours.
- Also see concomitant medications

***Concomitant Medications***

See Inclusion and Exclusion criteria. Triptans and ergots may not be used 24 hours before, concurrently or after study treatment. The use of cimetidine and MAO-A

inhibitors are not permitted. The dose of any SSRIs or migraine prophylactic agent must be stabilized within 2 months prior to randomization. If the subject has been on stable dose of SSRI for 8 weeks (2 months) prior to randomization, they may be included in the study. Opiates should not be used 24 hours before study treatment.

***Rescue medication***

Rescue Medication approved by the sponsor is permitted at 2 hours post-study treatment. Triptans and ergots are not allowed as rescue medications. Allowable drugs include non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics, analgesics (eg, opioids), and sedatives. Rescue medications will not be provided by AstraZeneca.

***Subject Paper Diary***

Paper patient diaries were provided to patients to record the severity of the headache (mild, moderate, severe or none). Migraineurs were instructed to complete the diary for 24 hours after treating a migraine headache treated with study drug, as well as record any adverse events (AEs) and medications taken at any time. Patients were instructed to follow restrictions regarding use of other medications, including rescue medications, and were not permitted to sleep or nap for 2 hours after taking study drug.

**Interim Visit:** If there was no treatment of a migraine headache or attack with study drug within 4 weeks of randomization (Visit 2), subjects returned to the study site to review dosing instructions. Detailed instructions for use of the paper subject diary were reviewed. Adverse events that occurred since the last visit will be reported. The interim visit was captured in the eCRF and the visit date and confirmation that dosing and diary instructions have been provided were collected.



**Schedule of Assessments**

Study procedures	Visit 1 (-Days 30 to 0)		Visit 2 (30±3 days after Visit 1) Day 0 Randomization	Migraine attack, treatment, and patient's diary recording	Interim visit if no study treatment 4 weeks from randomization <sup>a</sup>	Visit 3 Final visit after treating 1 attack or within 10 weeks after Visit 2 or ET
	Screening	Run-in period and placebo challenge				
Signed informed consent and assent forms	X					
Inclusion/exclusion criteria	X		X			
Demography	X					
Medical & relevant surgical history	X					
Migraine headache history	X		X			
Medications, prior <sup>b</sup> and concomitant	X	X <sup>c</sup>	X	X <sup>c</sup>		X
Physical examination	X					X
Height	X					
Weight	X					
Urine test for drug abuse	X					
Urine pregnancy test	X		X			X
Dispense placebo nasal spray device	X					
Dispense study drug nasal spray device			X			

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Dose instructions	X		X		X	
Dispense patient diary	X		X			
Patient diary instructions	X		X		X	
Administer placebo nasal spray		X <sup>d</sup>				
Administer study drug nasal spray				X		
Patient enters diary data		X <sup>d</sup>		X		
Review and return of patient diaries, and record data on eCRF			X			X
Return placebo nasal spray device			X			
Return study drug nasal spray device						X
<b>Safety assessments</b>						
Vital signs (seated BP and pulse, oral body temperature)	X					X
12-lead ECG	X					X
Laboratory assessments (clinical chemistry, hematology, urinalysis)	X					X
AE reporting		X <sup>c</sup>	X	X <sup>c</sup>	X	X
<b>Rating scale</b>						
C-SSRS	X		X			X

BP blood pressure; C-SSRS Columbia-Suicide Severity Rating Scale; ET early termination.

<sup>a</sup> Patients returned for the interim visit to review study instructions. Visit date and confirmation that dosing and diary instructions were provided was documented on the eCRF. The nasal spray training device was not used at the interim visit.

<sup>b</sup> For 1 year (12 months). Subjects will receive instructions for placebo nasal spray and subject diaries in order to complete the placebo challenge portion of the study.

<sup>c</sup> Concomitant medications and AEs collected in patient diary.

<sup>d</sup> Patients received instructions for placebo nasal spray and patient diaries in order to complete the run-in and placebo challenge portion of the study

## ***Efficacy Endpoints and Analysis Method***

### **Primary Efficacy Endpoint**

- Pain-free at 2 hours post-treatment.
  - In the previous adolescent study, D1221C00005 there was no improvement at 1-hour and 2-hour, and did not differentiate active treatment from placebo on the primary endpoint. However, 2-hour pain free showed differentiation from placebo.

In the patient diary, patients assessed migraine pain severity and rated their pain intensity.

<b>Headache Severity Scale</b>	
Grade	Definition
0	None
1	Mild
2	Moderate
3	Severe

Percentage of subjects with Headache Pain-Free at 2 hours (120 minutes) after treatment with study drug, defined as a binary response variable (yes/no) derived from the headache intensities recorded in the patient diary. For each assessment time, pain-free status (= yes) is defined as a reduction in headache pain intensity from moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0] or mild [Grade 1] pain with no use of rescue medication prior to the assessment.

The migraine-associated symptoms of nausea, phonophobia, and photophobia were evaluated although these endpoints were not prospectively analyzed for efficacy.

### **Key Secondary Efficacy Endpoints**

These endpoints were not pre-specified for secondary analyses or multiplicity testing.

- Pain free at 15 minutes; and at 1, 2, 3, 4 hours and 24 hours post-treatment
- Headache response at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment.
- Sustained headache response at 2 hours subsequent to a 1 hour headache response
- Presence of associated symptoms of photophobia, phonophobia or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment
- Resolution of associated symptoms of photophobia, phonophobia or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment
- Incidence and time to use of rescue medication up to 24 hours post-treatment.
- Ability to perform normal activities at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment

- headache recurrence 2-24 hours post treatment
- bilateral headache (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment
- intensity increased by movement (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment

### Outcome Variables Description

- *Pain-free* is a reduction in headache pain intensity from severe or moderate at baseline to none at a specific assessment time. Pain-free is a binary response variable (yes or no).
- *Headache response* OR also referred to as *Headache pain relief* is defined as a reduction in migraine headache pain intensity from severe or moderate at time of initial treatment to mild or none at a specific assessment time. Headache response is a binary response variable (yes or no).
- *Sustained headache response* is defined as a reduction in migraine headache pain intensity from severe or moderate from 1 hour and maintained at 2 hours.
- *Time to use of rescue medication* starts with the dosing time of study drug and ends with the first use of rescue medication. If an event has not occurred by the final assessment point, the response is considered censored for the purpose of analysis.
- *Resolution of associated symptoms* of migraine is defined for those subjects who have associated symptoms at baseline who are then symptom free at the assessment timepoints. Associated symptoms of migraine are nausea, vomiting, photophobia, and phonophobia.
- *Headache recurrence* is defined for those subjects having no headache pain at 2 hours, but worsening of headache between 2 and 24 hours and/or requirement for rescue medication within 24 hours.

### **Safety Monitoring**

Safety monitoring has been summarized in previous sections. Incidence, nature and intensity of AEs; vital signs; physical examination changes; laboratory assessments (ie, chemistry, hematology and urinalysis); ECG; and incidences of suicidal behavior and suicidal ideation as measured by the Columbia Suicide Severity Rating Scale (C-SSRS). There was no safety monitoring committee established. Safety was monitored on an on-going basis. Adverse events (AEs) were coded by MedDRA preferred terms and coded using MedDRA version 16.1.

### **Analysis Plan**

The study design included enrichment procedures to limit the participation of placebo-responders and randomize a population less likely to have a placebo response: subjects were required to have a *history of 3-hour headache duration* and a failed response to a single-blind placebo challenge conducted in a run-in phase.

Eligible patients were assigned to receive ZOMIG 5, 2.5, or 0.5 mg, or matching placebo, in a 5:3:3:5 ratio. For the primary analysis of pain-free status at 2 hours, the SAP included a step-down approach to control for multiple statistical comparisons to maintaining the type I error at 5% for each of the 3 ZOMIG doses against placebo. Initially, ZOMIG 5 mg was compared with placebo. If ZOMIG 5 mg was significantly better than placebo at the 2-sided 5% level, then ZOMIG 2.5 mg was compared with placebo. If ZOMIG 2.5 mg was significantly better than placebo at the 2-sided 5% level, then ZOMIG 0.5 mg was compared with placebo. If any comparison between ZOMIG and placebo was not significant, then any lower doses of ZOMIG were not compared with placebo. All comparisons of secondary endpoints were tested at the 5% significance level without any multiplicity correction.

The primary efficacy variable is LOCF pain-free status at 2 hours on the FAS. Alternatively, if that was missing, the last non-missing post-baseline pain-free status was imputed. The Full Analysis Dataset (FAD) included all subjects who were randomized, received study drug, and recorded at least one post-treatment assessment of pain severity. The treatment group assignment in this population was designated according to the treatment received. The FAD served as the basis for the analysis of efficacy.

### **Sample Size**

A sufficient number of male and female adolescent patients, age 12 to 17 years with an established diagnosis of migraine, were planned to be screened to ensure that approximately 1000 patients (312 in the zolmitriptan 5 mg and placebo arms, 188 in the zolmitriptan 0.5 mg and 2.5 mg arms) were randomized into the study to obtain 800 evaluable patients (250, 150, 150, and 250 patients in the placebo, zolmitriptan 0.5 mg, zolmitriptan 2.5 mg, and zolmitriptan 5 mg treatment groups, respectively).

Based on the results of the blinded interim analyses for sample size re-estimation, the sample size assumptions were determined to be reasonable and no additional randomized patients were required. Additionally, because of an interim futility analysis, the 0.5 mg and 2.5 mg dose groups met the futility definition with patient allocation to these two doses discontinued and the total sample size adjusted to ensure 250 evaluable patients into the 5 mg and placebo groups. Enrollment was monitored during randomization to ensure balanced distribution between age groups 12-14 years and 15-17 years.

FDA/Sponsor SPA protocol recommendations

Prior to reaching SPA Agreement, AstraZeneca initially proposed a blinded interim sample size re-estimation analysis due to the considerably higher placebo rates reported in previous adolescent migraine studies. The blinded interim sample size re-estimation analysis was planned to occur after approximately one-third of the planned patients had treated a migraine headache with randomized treatment. During the interim analysis, the blinded overall 2-hour pain-free rate was estimated.

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

In addition, DNP asked for justification for the initially proposed estimated effect size of 0.15 for the primary efficacy endpoint (2-hour pain free response) between placebo and drug treated groups, which was the basis for the initial study power calculation. DNP referenced a review by S. Evers (*Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. Cephalalgia. 2008, 29, 436-444*), the maximum treatment difference or effect size for the endpoint 2-hour pain free response between placebo and drug treated groups in placebo-controlled parallel-group studies evaluating triptans was less than 11%. DNP recommended that the study be modified to have 80% power to demonstrate an active treatment vs. placebo difference of between seven and eleven percentage points for the proportion of patients with pain free at 2 hours (with a two-sided type I error rate of 0.05).

During the February 1, 2010 teleconference DNP was concerned that while study D1220C00001 results may demonstrate a 10% or more treatment difference, the study overall may fail to demonstrate statistically significant results for 10% or 11% treatment effect size for the primary efficacy endpoint pain-free at 2-hours. The sponsor rationale did not provide justification to estimate sample size with 80% power to detect treatment effect of 10%. The Division alternatively recommended option to estimate sample size with 80% power for different dose cohorts to detect treatment effect of 10%-11% at the highest dose, with option for including up to 15% treatment effect for the low and middle dose for the same study power. AstraZeneca resubmitted their statistical analysis including all assumptions planned with the interim blinded analysis factoring estimated screening failures.

In AstraZeneca's agreed upon SPA protocol (submitted on March 26, 2010), subjects were randomized to the different treatment arms with different probabilities. AstraZeneca estimated 800 evaluable patients to be randomized to placebo, 0.5 mg, 2.5 mg, and 5 mg in a ratio of 5:3:3:5. The Zomig 5 mg treatment arm was powered at 80% to be able to detect a true difference of 0.11 in 2-hour pain free rates between placebo and Zomig 5 mg (2-sided significance level 0.05) after it was agreed that the probability to show a treatment effect is greatest for Zomig 5 mg. To be able to perform

the study with a reasonable number of centers, the 0.5 mg and 2.5 mg Zomig arms were at a lower power, i.e., 67% power to detect a treatment difference of 0.11 versus placebo. The statistical assumptions of the design were to be evaluated after randomization of one third of the subjects, with a planned, blinded interim analysis specifically designed to increase sample size if needed.

### ***Protocol Amendments***

DNP originally determined that the design and planned analysis of SPA protocol (study D1220C00001) submitted on March 26, 2010 would adequately address the objectives necessary to support a regulatory submission.

However, for reasons stated below, AstraZeneca submitted SPA protocol amendment with questions (via eCTD submission, sequence number 0025) that were discussed via teleconference on August 30, 2012. The changes in the SPA protocol amendment were acceptable and agreed upon after conferring with PeRC following AstraZeneca's deferral extension request (see section 2.6 of this review).

AstraZeneca offered two reasons for the deferral request: (1) the delayed study start due to negotiations with DNP to secure agreement on study design and statistical analysis plan for Study D1220C00001, and (2) because of patient recruitment challenges. AstraZeneca stated that despite their considerable efforts to improve recruitment to Study D1220C00001, they were unable to achieve the originally anticipated rate.

### ***SPA protocol amendment justification***

AstraZeneca stated that despite their considerable efforts to improve recruitment to Study D1220C00001, they were unable to achieve the originally anticipated rate since AZ began screening subjects in September 2010. These efforts have included increasing the number of sites, changes to entry criteria, and use of a social media awareness campaign.

- **Recruitment Status SPA Protocol D1220C00001**

Study D1220C00001 began screening subjects since September 9, 2010. As of June 8, 2012,

<b>Parameter</b>	<b>Expected/Targeted</b>	<b>To Date</b>
Screened Subjects	2197	1048
Randomized	1000 (n=800 required)	463
Study Sites	150	108 actively recruiting

According to AstraZeneca recruitment had been considerably slower than the original predictions. The proportion of active sites recruiting at least 1 subject was more than 95%, therefore indicating the high level of commitment to the study, but also the

difficulty in recruiting the volume of subjects originally anticipated. The majority of sites were neurology centers or pediatric centers with neurological experience that, based on feasibility analyses, were expected to see a high volume of pediatric patients.

- Interventions Previously Attempted to Improve Recruitment

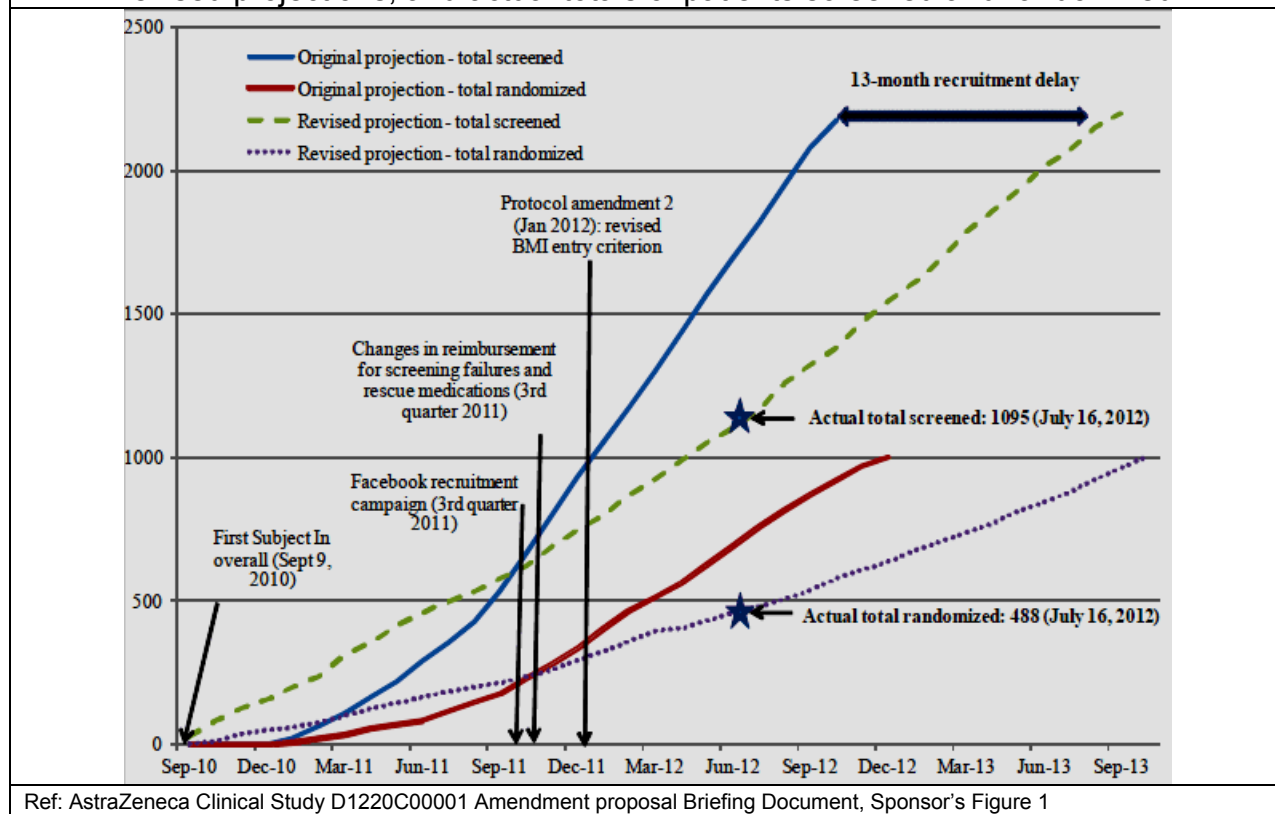
AstraZeneca made the following interventions to improve recruitment (Figure 1).

1. A Facebook social media campaign to address low awareness of the study was conducted in the USA, the region expected to provide the majority of subjects. It was directed at parents of adolescent migraineurs and generated over 20,000 unique respondents; however, the investigational sites reported that only 2 subjects were directly referred via this campaign.
2. Changes in the reimbursement structure to investigational sites for screen failures (in accordance with fair market principles), to compensate sites for the extra demand on personnel's time due to the high screening failure rate. In addition, in non-US countries, AstraZeneca began reimbursing sites for over-the-counter rescue medications used by subjects taking part in the placebo run-in. Both of these changes began implementation in 3rd quarter 2011.
3. Increasing the BMI limit for eligibility from <95th to ≤97th percentile for age (via protocol amendment 2, dated January 10, 2012). With this change, AstraZeneca rescreened 24 subjects, of whom 10 were randomized to study D1220C00001.

Despite these interventions by AstraZeneca, the recruitment rate did not increase significantly, where there was lack of upward deflection in the screening and randomization curves in Figure 1. The original estimated date for the last subject to complete was the 3rd quarter of 2012. The revised projections show last subject completion occurring in the 3rd quarter of 2013, with a **13-month delay**.



Figure 1: IND 53848 ZOMIG-Adolescents; Recruitment plans showing original and revised projections, and actual totals of patients screened and randomized



• Persistent Recruitment Issues Identified

Quintiles (the CRO running the study) provided the following feedback from the investigational sites on the key barriers to recruitment.

1. Low awareness of the study among parents of adolescent migraine patients
2. High screening failure rate, due in part to an inclusion criterion that limited the permissible Body Mass Index (BMI) to <95th percentile for age. The high screening failure rate created an increased burden for staff at the investigational sites.
3. Availability of other triptans for the acute treatment of migraine in adolescents in the USA. Rizatriptan and almotriptan are approved triptans for pediatric use. This may have reduced potential US subjects' interest in participating in a clinical trial with ZOMIG NS, especially as subjects entering Study D1220C00001 are required to have a failed placebo response during run-in.

*Protocol Amendments Proposed to Improve Recruitment to Study D1220C00001*

Feedback from the investigative sites indicated 3 inclusion criteria in the previous version of the SPA protocol that caused the highest rates of screening failure and were regarded the key barriers to recruitment. These were criteria 5, 6 and 7:

5. A medical history of usual untreated migraine duration of  $\geq 4$  hours for any 3-month period prior to screening (Visit 1)
6. A history of migraine attacks occurring at intervals of  $>24$  hours apart, which is confirmed during the run-in and placebo challenge period
7. A BMI of  $\leq 97$ th percentile for age

Criterion 6 was reported to have caused the highest rate of screening failure.

*DNP Position on Protocol Amendments to Improve Recruitment*

AstraZeneca proposed changes to these 3 inclusion criteria as was reflected in the revised/amended SPA protocol D1220C00001 in order to increase recruitment that would potentially accelerate completion of the study. In addition, AstraZeneca proposed an unblinded futility analysis (following the already completed prespecified blinded interim analysis) to identify and close any active treatment arms likely to be determined ineffective at the conclusion of the study. This would allow AstraZeneca to randomize future subjects only into effective treatment arms.

Division of Neurology Products agreed to the protocol amendment proposals, the futility analysis and the subsequent dropping of any dose arms shown to have a low likelihood of demonstrating significant improvement over placebo. DNP further agreed that they would be open to discussing options if the proposed measures (futility analysis and changes to inclusion criteria) failed to significantly improve enrolment rates and the study could not be completed by 3Q2013. On October 29, 2012, AZ communicated to the Agency that the results of the Interim Futility Analysis indicated that both the 0.5 mg and 2.5 mg dose groups met the futility definition and that patient recruitment will continue to the 5.0 mg dose. Following that communication, subject enrolment proceeded according to the agreed Protocol Amendment with eligible subjects allocated to treatment according to the revised randomization schedule.

After careful consideration of the above limitations and considering AstraZeneca exercised due diligence to keep FDA informed about these limitations in order to fulfill PREA obligations and facilitate completion of an adequately controlled study including meaningful pediatric labeling information, the request for extension of the pediatric deferral for completing pediatric study D1220C00001 appeared acceptable.

***Study Results - D1220C00001***

Please see section 6 of this review.

### 5.3.2 Protocol D1221C00005

Protocol D1221C00005 was previously reviewed by DNP. On October 14 2008, following review of sNDA 21450/S-005, FDA informed the sponsor

(b) (4)

Study D1221C00005 is included since the pooled safety database for ZOMIG nasal spray included the assessment of ZOMIG 5 mg dose versus placebo in adolescents, aged 12 - 17 years, who had an established diagnosis of migraine headache. Study D1221C00005 was a multicenter double-blind, randomized, placebo-controlled, 2-way crossover study with a single-blind placebo challenge excluded early placebo responders after randomization. Eligible patients had an established diagnosis of migraine headache, defined by the IHS and IHS-R criteria and they were randomized to 1 of 2 crossover sequences to treat 2 moderate or severe migraine headaches during a 12-week study period. I refer the reader to clinical review of NDA 21450/S-005 by Dr. Teresa A. Podruchny for further details.

## 6 Review of Efficacy

### **Efficacy Summary**

The results of SPA agreement study Protocol D1220C00001: "A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel-Group Study to Evaluate the Efficacy of Zolmitriptan 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents", suggest that ZOMIG nasal spray is effective, as compared to placebo, in adolescents with acute migraine with or without aura. The sponsor has adequately demonstrated statistically significant superiority of ZOMIG nasal spray 5 mg dose over placebo for the primary endpoint (headache pain-free). Even though ZOMIG 2.5 mg was declared futile and did not reach statistical significance for headache pain-free, there was nominally superior effect of ZOMIG nasal spray 2.5 mg dose over placebo for headache response (headache pain-relief) at 2 hours, and similar effects on the migraine associated symptoms compared to ZOMIG 5 mg. ZOMIG 0.5 mg lower dose did not demonstrate efficacy in comparison to placebo controls, showing almost no advantage post-dose for the endpoints. In addition, the results of study D1220C00001 fulfill the Pediatric Research Equity Act (PREA) postmarketing commitment issued on October 14, 2008 (PMR 948-1).

## **6.1 Indication**

The new information from the adolescent pediatric study D1220C00001 is supportive information for the expansion of the indication for ZOMIG (zolmitriptan) nasal spray for the acute treatment of migraine in adolescents aged 12-17.

### **6.1.1 Methods**

Phase 3 study D1220C00001 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that included a single-attack, single-dose placebo-challenge, single-blind *run-in period* followed by treatment of a single-attack with one dose of zolmitriptan nasal spray 0.5 mg, 2.5 mg, 5 mg or matching placebo during the *treatment period*.

Eligible patients entered a 30-day run-in period beginning at Visit 1 to establish whether the patient had a headache pattern of appropriate severity and duration to qualify for the study. Patients received single dose of single-blind placebo to treat a migraine headache of moderate or severe pain intensity during the run-in period. Patients were instructed to treat the first headache, which allowed for diary and dosing compliance, including accurate and timely completion of all diary assessments, and the ability to follow pre-treatment and post-treatment rules.

At 2 hours after treating with single-blind placebo, if the patient's migraine headache did not respond (i.e., the pain had not reduced to mild or none), the patient used approved rescue medication(s). For any subsequent migraine episodes, the patient used their usual acute migraine medication. During this run-in period, patients received instruction to complete a diary of symptoms.

Visit 2 (randomization) occurred at the end of the 30-day run-in period. At this visit, patients were randomized to treatment only if they failed to respond to the placebo challenge (i.e., they maintained a moderate or severe headache pain intensity at 2 hours), completed their diary correctly, and had the protocol-specified untreated headache duration. Patients not treating a migraine headache with blinded placebo during the 30-day run-in period were considered screen failures.

At Visit 2, eligible patients were randomized to treat a migraine headache with ZOMIG nasal spray 0.5, 2.5, 5 mg, or matching placebo spray. Paper patient diaries were provided to patients to record the severity of the headache (mild, moderate, severe or none). Patients were instructed to complete the diary for 24 hours after treating a migraine headache treated with study drug, as well as record any adverse events (AEs) and medications taken at any time. Patients were instructed to follow restrictions regarding use of other concomitant medications, including rescue medications, and instructed not to sleep or nap for 2 hours after taking study drug.

Patients had approximately 10 weeks to complete treatment. Those without a treated migraine within 4 weeks of randomization returned for an interim visit to review instructions. After treating a single migraine headache or 10 weeks after randomization (Visit 2) if no migraine headache was treated, patients returned to the study site for the final visit (Visit 3). At Visit 3, the nasal spray device was returned, patient diaries were returned and reviewed, and end-of-study assessments were performed.

### 6.1.2 Demographics

Overall, patients were 12 to 17 years of age (mean, 14 years) with similar percentages of patients in the 12 to 14 and 15 to 17 age groups. 93% patients were Caucasian (62% females and 38% males) similar to disease demographics represented in the adult migraineurs.

#### Baseline Migraine Severity

There was no difference in the baseline severity for the migraine headache treated in this study with moderate headache pain reported for 83% of subjects and severe for 17% of subjects.

Patients in age subgroups 12-14 and 15-17 reported a similar average number of migraines per month (4.0 for 12- to 14-year-old patients; 4.2 for 15- to 17-year-old patients). Most patients had a history of migraines lasting between 4 to 6 hours (42.4%) or greater than 8 hours (38.8%) in duration. Migraine associated symptoms history (Table 3), and these symptoms at baseline for subjects enrolled in study D1220C00001 are shown in Table 4.

Migraine Headache History	Zomig 5mg (%) (N=288)	Zomig 2.5mg (%) (N=99)	Zomig 0.5mg (%) (N=115)	Placebo (%) (N=296)
Vomiting	47%	46%	44%	50.7%
Nausea	85%	88%	85%	87.5%
Photophobia	87%	85%	84%	88.2%
Phonophobia	77%	79%	77%	82.4%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.1.5.4)

Migraine Associated Symptoms at Baseline	Zomig 5mg(%) (N=230)	Zomig 2.5mg(%) (N = 81)	Zomig 0.5mg(%) (N = 91)	Placebo(%) (N=253)
Vomiting	10%	14%	7%	11%
Nausea	56%	62%	51%	56%
Photophobia	77%	83%	79%	81%
Phonophobia	73%	75%	69%	76%
Ability to perform normal activities	21%	20%	20%	22%
Bilateral headache	57%	63%	52%	61%

<b>Migraine Associated Symptoms at Baseline</b>	<b>Zomig 5mg(%) (N=230)</b>	<b>Zomig 2.5mg(%) (N = 81)</b>	<b>Zomig 0.5mg(%) (N = 91)</b>	<b>Placebo(%) (N=253)</b>
Increase of migraine headache intensity increased by movement	88%	86%	92%	89%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.2.4)

Prior triptan use was recorded for 59/798 (7%) of study subjects. The most frequently used prior medications, at least 2% overall use, were:

ibuprofen	29.2%
acetaminophen	14.2%
acetylsalicylic acid+caffeine+acetaminophen	3.9%
diclofenac	3.6%
naproxen sodium	3.4%
naproxen	2.9%
caffeine+ acetaminophen	2.5%
sumatriptan	2.9%
rizatriptan	2.3%

<b>Prior Medications History</b>	<b>Zomig 5mg (%) (N=288)</b>	<b>Zomig 2.5mg (%) (N=99)</b>	<b>Zomig 0.5mg (%) (N=115)</b>	<b>Placebo (%) (N=296)</b>
ibuprofen	31%	25%	32%	27%
acetaminophen	14%	14%	15%	14%
sumatriptan	4%	1%	3%	3%
rizatriptan	1%	5%	0%	3%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.1.6.1)

### 6.1.3 Subject Disposition

N=1653 subjects were screened, and N=798 patients were randomized to the study: N=288 to ZOMIG 5 mg, N=99 to ZOMIG 2.5 mg, N=115 to ZOMIG 0.5 mg, and N=296 to placebo (Table 6). The difference in the number of patients in each treatment group is due to the combination of the 5:3:3:5 randomization schedules and the interim futility decision, which stopped randomization to the 2 lower ZOMIG dose treatment groups. 9.5% subjects discontinued from the study (N=20, 7% ZOMIG 5 mg; N=26, 9% placebo) for which the most common reason for study discontinuation was eligibility criteria not fulfilled (6.6%). No patients discontinued due to AEs.

**Table 6: NDA 21450/S-008 D1220C00001 Subject Disposition**

	Zomig 5mg n, (%)	Zomig 2.5mg n, (%)	Zomig 0.5mg n, (%)	Placebo n, (%)
Randomized	288 (100%)	99 (100%)	115 (100%)	296 (100%)
Patients who did not take study drug	57 (20%)	18 (18.2%)	23 (20%)	43 (14.5%)
Full Analysis Dataset (Took study drug)	231 (80%)	81 (82%)	92 (80%)	253 (85%)
Safety Dataset (Took study drug)	231 (80%)	81 (82%)	91 (80%)	253 (85%)
Discontinued study	20 (7%)	13 (13%)	17 (15%)	26 (9%)

Ref. NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.1.1.1)

Patients were not permitted to sleep within 2 hours after taking the study drug, which was a study restriction. This protocol violation was recorded for N=8/231 (3.5%) subjects in the ZOMIG 5 mg group, and N=4/253 (1.6%) subjects in the placebo group. Please see section 6.1.7 of the review for sensitivity analysis imputing values for these patients.

#### 6.1.4 Analysis of Primary Endpoint(s)

##### **Pain-free (no headache pain)**

I concur with the sponsors analysis that there was a statistically significant mean between-group treatment difference in the ZOMIG 5 mg group, where 29.7% subjects reported pain relief at 120 minutes versus the placebo group, 16.6% subjects (p<0.001). This information appears to be verified in Dr. Massie's review.

**Table 7: NDA 21450/S-008 Subjects (%) Pain-Free Primary Analysis D1220C00001**

Proportion of Subjects with Headache Pain-Free	Dose		p-value
	Zomig 5mg N=229	Placebo N=253	
2-Hours	68 (29.7%)	42 (16.6%)	<0.001

Ref. NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11).  
 Pain-free status (= yes) is defined as a reduction in headache pain intensity from severe (Grade 3) or moderate (Grade 2) pain to none (Grade 0) with no use of rescue medication prior to the assessment. FAD = full analysis dataset. The Last Observation Carried Forward (LOCF) imputation was used where the last non-missing post-baseline pain-free status carried forward. N=2 subjects in the ZOMIG 5mg dose randomized & treated group had missing post-treatment values. P-value was calculated by chi-square test (continuity-corrected).

##### **Test of Lower ZOMIG nasal spray doses**

As discussed previously (see section 5.3.1 discussed under sub-heading sample size) the study procedures included an unblinded sample size re-estimation and an interim futility analysis based on the results of which randomization was subsequently ceased to the low and middle doses (ZOMIG 0.5 and 2.5 mg). According to Dr. Massie's evaluation, there is no compelling reason to suspect that the interim futility analysis led to operational bias. Although Dr. Massie discusses that, there is still an issue with the validity of interpreting the middle dose and low dose results based on the final analysis since the middle dose was dropped (randomization ceased) at the interim but post-interim, placebo patients with no contemporaneous middle dose parallel are involved in the test. Dr. Massie's review discussed that placebo patients enrolled after the interim



analysis affect the test for the middle dose and they have no contemporaneous parallel in the middle dose cohort. Therefore, any trend in the placebo dose over time after the interim could potentially bias the test of the middle dose. Dr. Massie states the same is true for the lower dose, which was also dropped due to a futility determination made at the interim. The results for the middle dose using all available data would need an assumption that there was no temporal dependence of the characteristics of the placebo group after the interim analysis in order to be statistically valid. After considering the above, the high dose group continued in parallel with the placebo group, in a blinded design, and that there was another concurrent arm. Please see details of the discussion about interpreting information about the interim and futility analysis including several additional analyses performed in Dr. Massie’s review.

The sponsor declared ZOMIG 2.5 mg and 0.5 mg groups futile for the 2-hour primary endpoint during the interim futility analysis. ZOMIG was not significantly better than placebo for 2.5 mg ( $p < 0.071$ ); therefore, the 0.5 mg dose was not compared to placebo (Table 8).

**Table 8: NDA 21450/S-008 %Subjects Pain-Free D1220C00001**

	Zomig 5mg n, (%) N=231	Zomig 2.5mg n, (%) N=81	Zomig 0.5mg n, (%) N=91	Placebo n, (%) N=253
1-Hour	11.1%	9.9%	13.2%	8.3%
2-Hours	30.6%*	25.0%	22.2%	16.9%
3-Hours	44.8%	35.5%	31.4%	23.9%
4-Hours	55.6%	50.0%	35.2%	38.5%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.2.1.5); OC- Full Analysis Set; \* $p < 0.05$

ZOMIG 5 mg was superior to placebo at the 3- and 4-hour assessments ( $p < 0.001$  for both time points; data not shown). Despite being declared futile at the interim analysis for the 2-hour primary endpoint, ZOMIG 2.5 mg had nominal significance at 2 hours ( $p < 0.1$ ) and the 3-hour assessment ( $p = 0.032$ ), on pain free.

#### 6.1.5 Analysis of Secondary Endpoints(s)

##### **Headache Response (headache pain relief)**

Headache response was defined as a reduction in migraine headache pain intensity from severe or moderate at the time of initial treatment to mild or none at a specific assessment time. Headache response was a binary response variable (yes or no).

Although Headache Response was not prospectively analyzed and adjusted for multiplicity, there was nominally greater response at 120-minutes for all ZOMIG treatment groups when compared to placebo (Table 9).



	Zomig 5mg n, (%) N=231	Zomig 2.5mg n, (%) N=81	Zomig 0.5mg n, (%) N=91	Placebo n, (%) N=253
1-Hour	31.9%	34.6%	31.9%	25.8%
2-Hours	48.9%*	53.1%*	44.0%	38.7%
3-Hours	61.0%	67.1%	55.8%	25.8%
4-Hours	69.3%	71.6%	63.6%	57.1%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.2.2.3); \*p<0.05

### **Migraine Associated Symptoms**

FDA issued draft guidance to assist sponsors in the clinical development of drugs for the acute treatment of migraine, and it recommends that sponsors assess the migraine associated symptoms as secondary endpoints, not necessarily evaluating these endpoints as co-primary endpoints in the pediatric studies<sup>3</sup>.

Even though these endpoints were not prospectively analyzed for efficacy, comparisons between treatment groups for the proportion of subjects with each of the migraine symptoms at 120 minutes post dose is presented in Table 10. Please refer to Table 4 for the migraine associated symptoms at baseline and per history. Presence of an associated symptom is a binary response variable (yes/no) derived from the presence of associated symptoms recorded in the patient diary.

For the symptoms of nausea and vomiting, there were no significant reductions in the presence of symptoms for the ZOMIG doses at any time point. Nominally significant reductions were seen for photophobia and phonophobia after 2-hours for the ZOMIG 2.5 and 5 mg groups. ZOMIG 0.5 mg was not significantly better than placebo at any time point for either photophobia or phonophobia.

Migraine Associated Symptoms at 2-Hours post-treatment	Zomig 5mg (%)	Zomig 2.5mg n, (%)	Zomig 0.5mg n, (%)	Placebo n, (%)
No Nausea	72%	70%	69%	66%
No Photophobia	56%*	66%*	51%	44%
No Phonophobia	58%*	61%*	59%	48%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.2.4); OC- FAS; p<0.05

<sup>3</sup><http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM419465.pdf>

6.1.6 Other Endpoints

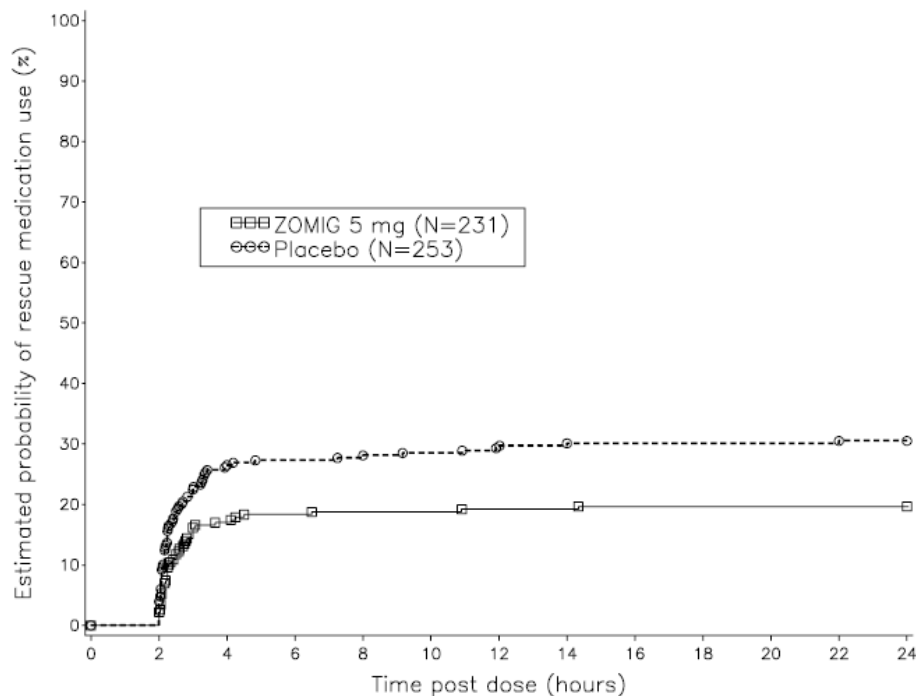
The following table summarizes additional endpoints evaluated during study D1220C00001.

<b>Table 11: NDA 21450/S-008 Secondary Endpoints D1220C00001</b>				
	<b>Zomig 5mg (%)</b>	<b>Zomig 2.5mg (%)</b>	<b>Zomig 0.5mg (%)</b>	<b>Placebo (%)</b>
Use of rescue medication up to 24 hours post treatment	20%	22%	24%	32%
Ability to perform normal activities at 2-hours post treatment	55%	67%	54%	48%
Ability to perform normal activities at 4-hours post treatment	71%	71%	62%	57%
Headache recurrence 2 to 24 hours post treatment	8% (5 of 62)	12% (2 of 17)	0%	10% (4 of 38)
Bilateral headache at 2-hours post treatment	51%	37%	46%	55%
Bilateral headache at 4-hours post treatment	49%	29%	38%	40%
Increase of migraine headache intensity increased by movement at 2-hours post treatment	52%	47%	59%	64%
Increase of migraine headache intensity increased by movement at 4-hours post treatment	35%	33%	47%	51%

Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.2.6.1, 11.2.7, 11.2.10); OC- FAS

- Approximately 20% of patients overall had the ability to perform normal activities at baseline (Table 4). Increases in the ability to perform normal activities were observed for all treatment groups across time with improvements in the ZOMIG treated groups compared to placebo from 2 to 24 hours post-treatment.
- Of those patients pain-free at 2 hours, approximately 10% of patients across all treatment groups had a recurrence of their headache between 2 and 24 hours after treatment.
- Subjects reported bilateral headache 2-hours post treatment similar to and unchanged from baseline rate of 50-60%.
- Almost 90% of patients reported having an increase in headache intensity by movement at baseline. Overall, there was reduction in the rates of migraine headache intensity by movement over time across all treatment groups.
- The use of rescue medication exhibited a dose-response pattern, with the percentage of patients using rescue medication in the placebo, ZOMIG 0.5, 2.5, and 5 mg groups being 31.6%, 24.2%, 22.2%, and 20.3% respectively (data not shown). The ZOMIG 5 mg group achieved nominal significance when compared to placebo (Figure 2). Using Cox proportional hazards regression analysis for time to first use of rescue medication (hazard ratio), patients in the ZOMIG 2.5 mg group were 58% (95% CI=0.33 to 1.00), and 59% for the ZOMIG 5 mg group (95% CI=0.40 to 0.85) less likely to use rescue medication as were patients in the placebo group.

Figure 2: NDA 21450/S-008 Rescue medication during first 24 hours post-treatment  
D1220C00001



Ref: Study D1220C00001 Amendment proposal Briefing Document, Sponsor's Figure 11.2.6.3  
Time to first use of rescue medication through 24 hours post treatment - Kaplan Meier curve - OC (Full Analysis Set)

### 6.1.7 Subpopulations

I concur with the sponsor's subgroup analyses based on demographic and baseline values. Similar results were observed for the age subgroups for the secondary efficacy variables of pain-free status and headache response (12- to 14-year-old and 15- to 17-year-old patients), and for each of the additional secondary efficacy variables shown in Table 10 and Table 11. These analyses are presented in study report Tables 11.2.1.11 and 11.2.2.7 (Module 5, Section 5.3.5.1) and in Module 2.5, Tables 8.1-8.8.

Several patients per group were reported to have slept within 2 hours after taking the study drug [N=4 (1.6%) placebo, N=1 (1.1%) 0.5 mg, N=2 (2.5%) 2.5 mg, and N=8 (3.5%) 5 mg for a total of 15 (2.3%)]. Dr. Massie's review comments that there were three ZOMIG 5 mg patients who slept within or at 2-hours and who were classified as responders. A sensitivity analysis imputing a value of not pain-free at 2 hours for these patients did not alter the significance of the primary endpoint result for ZOMIG 5 mg vs. placebo ( $p=0.0016$ ).

There appears to be no between subgroup treatment differences that varied by gender, race, or age subgroups. The results have been consistent with 'triptan' migraine

products in demonstrating that the treatment effect is nominally superior in a greater proportion of males and females across age groups and race who responded better to ZOMIG compared to the placebo response. The adolescent migraineurs appear to respond similarly to adults albeit the difference in headache bilateralism previously known as occurring in pediatric migraineurs. The results of study D1220C00001 show that there were proportionally similar older adolescents (>15 years of age) experiencing bilateral headache.

#### *6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations*

The proposed ZOMIG nasal spray labeling indicates use for acute migraine treatment in adults with a recommended starting dose of 2.5 mg or maximum single dose 5 mg not to exceed 10 mg in any 24 hour period.

Similarly, across the multiple endpoints in study D1220C00001, there was trend of increasing efficacy with ZOMIG 5 mg and 2.5 mg dose across multiple time points. Considering that, the ZOMIG 2.5 mg dose achieved similar effects of pain freedom and pain relief including the migraine associated symptoms, the availability of the lower dose may provide meaningful benefit as the starting dose in adolescent migraineurs. Although ZOMIG 0.5 mg dose showed nominal improvement over placebo for the migraine pain endpoints, there were no significant treatment differences on these endpoints or the associated symptoms.

#### *6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects*

Due to the short-term nature of this trial, no comment may be made upon persistence of therapeutic efficacy or tolerance effects of ZOMIG.

#### *6.1.10 Additional Efficacy Issues/Analyses*

No additional pre-specified efficacy issues or analyses were performed.

## **7 Review of Safety**

### **Safety Summary**

The safety of ZOMIG nasal spray in adolescent migraineurs discussion includes the product safety evaluation relating to systemic exposure, and local nasal cavity exposure conducted in studies D1220C00001 and D1221C00005. As agreed upon during the pre-sNDA written response communication (April 10, 2014), the safety evaluation includes the pooled adverse event (AE) safety data from these two clinical studies. The safety evaluations included assessment of AEs, clinical laboratory tests, vital signs measurements, electrocardiograms (ECGs), physical examinations (including

nasopharyngeal examinations), and suicidal risk (Columbia-Suicide Severity Rating Scale, for Study D1220C00001 only).

FDA previously discussed supportive data from the long-term portion of the ZOMIG tablet clinical study (Study 311CUS/0005) and data from study D1221C00004 in adolescents during submission of NDA 21450/S-005, and it was found acceptable without further requiring separate long-term safety data for ZOMIG nasal spray in adolescents. It does not appear the sponsor requires additional studies in order to fulfill the requirements of the ICH E1 for population exposure.

AE data from a controlled clinical trial of ZOMIG nasal spray in adult migraineurs (see Study 1 in the ZOMIG nasal spray label) are presented for comparison with AE data from Studies D1220C00001 and D1221C00005 (see section 7.4.1 of this review).

Adverse reactions observed in these studies were similar in nature and frequency to those reported in clinical trials of ZOMIG nasal spray in adults with no post marketing adverse events observed that need additional monitoring at this time and the safety profile of the tablet formulation is not different from that of the nasal spray.

## **7.1 Methods**

### *7.1.1 Studies/Clinical Trials Used to Evaluate Safety*

ZOMIG nasal spray for the treatment of acute migraine headache in adolescents aged 12 to 17 years was evaluated in four clinical studies (Table 2): One pharmacokinetic study (D1221C00004) and two efficacy and safety studies (D1220C00001 and D1221C00005). One previous ZOMIG tablet study (Study 311CUS/0005, NDA 21450/S-005) included the long-term safety evaluation in adolescents. Studies in children aged 6 to 11 years have not been conducted.

Information from the phase 3 study D1220C00001 for the doses studied (ZOMIG nasal spray 5 mg, 2.5 mg, 0.5 mg, and placebo comparator) is primarily included for evaluating safety information in the sNDA 21450/S-008 review (see section 5.3.1 and 5.3.2 of this review for study details). Please see section 6.1.4 about considering information for the lower ZOMIG doses in the absence of a placebo comparator after the interim and futility analysis. Pooled data from studies (D1220C00001 and D1221C00005) for ZOMIG nasal spray 5 mg are discussed in section 7.4.1 and Table 14.

### *7.1.2 Categorization of Adverse Events*

D1220C00001 adverse events (AEs) were coded to MedDRA dictionary 16.1 and study D1221C00005 was coded using MedDRA dictionary 7.1. However, since the studies were conducted at different times and to ensure coding consistency, the AEs across the

two studies were recoded using MedDRA dictionary version 16.1 for the pooled AE data. Coding included system organ class (SOC) and preferred term (PT). All verbatim descriptions and coded terms were listed. The submission module 2.7.4 Summary of Clinical Safety refers to Table 13 for PT mapping information.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooled safety analysis set for studies D1220C00001 and D1221C00005 included all patients who received randomized treatment and had post-treatment safety data, and AEs from both studies were coded to PT using MedDRA version 16.1. Study treatments across the two randomized controlled studies included ZOMIG 5 mg, 2.5 mg, 0.5 mg, and placebo, although study D1221C00005 included only patients treated with ZOMIG 5 mg (and placebo comparator in a cross-over design; see section 5.1.3).

Table 12 summarizes the treatment groups to which the subjects in each individual study were exposed. Combining exposures in studies D1220C00001 and D1221C00005, 550 adolescents (12 to 17 years inclusive) received single doses of ZOMIG nasal spray, and 70% of these subjects were exposed to ZOMIG 5 mg dose.

Study Number	Treatment Groups	Exposures
D1220C00001	ZOMIG 5 mg	231
	ZOMIG 2.5 mg	81
	ZOMIG 0.5 mg	92
	Placebo	253
D1221C00005	ZOMIG 5 mg	146
	Placebo	132

Ref: eCTD seq 0040; Module 2.7.4; Sponsor's Table 8

Adverse event data from the pooled studies is listed in section 7.4.1 of the review.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

N=550 subjects were exposed to a single dose of ZOMIG nasal spray in controlled studies D1220C00001 and D1221C00005, and additionally 15 adolescents (12 to 17 years of age inclusive) received single doses of ZOMIG 5 mg nasal spray in a PK study, which is not included in this safety evaluation (NDA 21450/S-005, Study D1221C00004) (Table 12).

Module 2.7.4, Table 4 of the sponsor's submission Summary of Clinical Safety presented the demographics discussion for studies D1220C00001 and D1221C00005. Demographic characteristics of adolescents in these studies were generally similar.

The mean age of patients in each study was 14 to 15 years, with nearly equal proportions of 12- to 14-year-old patients and 15- to 17-year-old patients in Study D1220C00001 and a higher proportion of 12- to 14-year-old patients (62.5%) in Study D1221C00005. Approximately 60% of the adolescents were female, and most adolescents were white. The majority of patients across all treatment groups (70% to 82%) treated their migraine within 30 minutes of onset.

The long-term pediatric safety experience for zolmitriptan oral formulation in the adolescent population is relevant for the nasal spray formulation. The open label portion of the adolescent ZOMIG oral tablet study 311CUS/0005 supports repeat use safety evaluation in this age group, which was discussed and the information found adequate during the review of NDA 21450/S-005. The extrapolation across the nasal spray and tablet formulations are justified since there are only small differences in absorption after oral and intranasal administration. Therefore, a specific long-term safety study for this population was not required.

#### *7.2.2 Explorations for Dose Response*

Please refer to section 6.1.8 regarding the doses utilized in the clinical studies.

#### *7.2.3 Special Animal and/or In Vitro Testing*

No special animal or in vitro testing was conducted as part of the sNDA.

#### *7.2.4 Routine Clinical Testing*

The routine clinical safety testing in the NDA 21450/S-008 clinical studies seemed appropriate and capable of identifying major safety signals.

#### *7.2.5 Metabolic, Clearance, and Interaction Workup*

No additional data was generated for this sNDA. No formal drug-drug interaction studies have been performed in pediatric subjects (<18 years of age).

#### *7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class*

Please see Review Section 2.4, for triptan class relevant safety issues. There were no major issues reported in NDA 21450/S-008.

### **7.3 Major Safety Results**

#### *7.3.1 Deaths*

There were no deaths reported in studies D1220C00001 and D1221C00005.

### 7.3.2 *Nonfatal Serious Adverse Events*

There were no reports of serious adverse events (21 CFR 312.32(a); 314.80(a)) reported in studies D1220C00001 and D1221C00005.

### 7.3.3 *Dropouts and/or Discontinuations*

No adolescent patient discontinued from Studies D1220C00001 and D1221C00005 due to an AE.

### 7.3.4 *Significant Adverse Events*

There were no treatment-emergent SAEs or other AEs (i.e., those that started on or after taking randomized treatment) reported during the study. There were 5 SAEs reported prior to receiving study drug, i.e., when the patients were in the single-blind placebo challenge period. All those events subsequently resolved (Module 5.3.5.1 Clinical Study Report D1220C00001 Table 11.3.4.2.1).

### 7.3.5 *Submission Specific Primary Safety Concerns*

Nose and throat examination results from baseline to final visit are summarized in Tables 11.3.8.1.3 -11.3.8.1.4 and abnormal findings are listed in Appendix 12.2.10.4.2. There were no notable changes in nose and throat results in any treatment group during the study, which have not been previously observed with nasal spray administration and with the ZOMIG nasal spray use in adults. No additional submission specific safety concerns were identified during this review.

## **7.4 Supportive Safety Results**

### 7.4.1 *Common Adverse Events*

Adverse events for the ZOMIG 5 mg nasal spray dose groups were pooled separately from the ZOMIG 2.5 mg and 0.5 mg dose groups from the two randomized controlled studies (D1220C00001 and D1221C00005). The middle and low doses were dropped (randomization ceased) following the interim efficacy analyses in study D1220C00001, although the placebo and high dose patients continued to end of study, hence the greater number of subjects in those dose groups in study D1220C00001. As discussed in section 6.1.4, post-interim (and futility) analysis, placebo patients with no contemporaneous middle dose parallel are assessed and they have no contemporaneous parallel in the middle and low dose cohorts.

The most commonly reported AEs (i.e., those preferred terms reported by  $\geq 2\%$  of patients in any treatment group) are presented Table 13.



<b>Table 13: NDA 21450/S-008 TEAEs ≥ 2% of Adolescent Patients</b>						
<b>D1220C00001</b>				<b>D1221C00005<sup>a</sup></b>		
<b>PT</b>	<b>ZOMIG 5mg (N=231)</b>	<b>ZOMIG 2.5mg (N=81)</b>	<b>ZOMIG 0.5mg (N=92)</b>	<b>Placebo (N=253)</b>	<b>ZOMIG 5mg (N=200)</b>	<b>Placebo (N=184)</b>
Unusual Taste (Dysgeusia)	12.6%	6.2%	6.5%	1.2%	6.5%	2.7%
Dizziness	2.6%	0%	1.1%	0.8%	1.5%	0.5%
Nasal Discomfort	3%	2.5%	1.1%	1.6%	2.5%	1.1%
Oropharyngeal Pain	3%	0%	1.1%	1.6%	0.5%	1.6%
Nausea	2.2%	1.2%	0%	1.2%	1.5%	0%

Ref: eCTD seq 0040; Module 2.7.4; Sponsor's Table 6  
<sup>a</sup> Adverse event counts were based on the randomized treatment at the time of the AE. In study D1221C00005, if the headache pain continued at 2 hours after the 2nd ZOMIG device was used, the subject could use the 3rd ZOMIG device provided, which contained another dose of the randomized treatment  
 Derived from Module 5.3.5.1, Study D1220C00001 CSR, Table 15; and NDA 21-450/S-005, Module 5.3.5.1, Study D1221C00005 CSR, Table 47

Pooled data is presented from studies D1220C00001 and D1221C00005 for ZOMIG nasal spray 5 mg, which was the only dose evaluated in study D1221C00005. Please note that subjects in study D1221C00005 were randomized to 1 of 2 crossover sequences to treat 2 moderate or severe migraine headaches during a 12-week study period, which included the safety analysis population.

<b>Table 14: NDA 21450/S-008 TEAEs ≥ 2% of Adolescent Patients, Pooled Safety Analysis Study D1220C00001 and D1221C00005</b>		
<b>PT</b>	<b>ZOMIG 5 mg (N=431)</b>	<b>Placebo (N=437)</b>
Unusual Taste (dysgeusia)	9.7%	1.8%
Dizziness	2.1%	0.7%
Nasal Discomfort	2.6%	1.1%
Oropharyngeal Pain	1.9%	1.6%
Nausea	1.9%	0.7%

Ref: eCTD seq 0040; Module 2.7.4; Sponsor's Table 8  
<sup>a</sup> Adverse event counts were based on the randomized treatment at the time of the AE.

AEs reported in adolescents treated with a single dose of ZOMIG in studies D1220C00001 and D1221C00005 were similar in nature to AEs reported in adults treated with a single dose of ZOMIG nasal spray (ZOMIG nasal spray labeled information). In the controlled trial of ZOMIG nasal spray in adults, AEs were coded to PTs using the Coding Symbols for Thesaurus of Adverse Reactions Terms (COSTART) dictionary (Study 1 in ZOMIG Nasal Spray label [Module 1, Section 1.14.2.2]). Preferred terms for AEs in adults were not mapped to MedDRA PTs, but similar PTs were compared.

<b>Table 15: NDA 21450 AEs ≥ 2% of Adult Patients in any ZOMIG Nasal Spray Treatment Group (ZOMIG Label)</b>			
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms by Body system	<b>ZOMIG 5 mg (N=236)</b>	<b>ZOMIG 2.5 mg (N=224)</b>	<b>Placebo (N=228)</b>
<b>Atypical Sensations</b>			
Hyperesthesia	5%	1%	0%
Paraesthesia	10%	5%	6%
Warm Sensation	0%	4%	2%
<b>Ear/Nose/Throat</b>			
Disorder/Discomfort of nasal cavity	3%	1%	2%
<b>Pain and Pressure Sensations</b>			
Pain Location Specified	4%	2%	1%
Throat Pain	4%	4%	1%
Throat Tightness	2%	<1%	1%
<b>Digestive</b>			
Dry Mouth	2%	3%	<1%
Nausea	4%	1%	1%
<b>Neurological</b>			
Dizziness	3%	6%	4%
Somnolence	4%	1%	2%
<b>Other</b>			
Unusual Taste	21%	17%	3%
Asthenia	3%	3%	1%

#### 7.4.2 Laboratory Findings

The review of shift plots and tables did not identify clinically relevant differences in laboratory measurements exceeding the predefined limits between the ZOMIG and placebo treatment groups.

#### 7.4.3 Vital Signs

During the study D1220C00001, vital signs were collected at screening (Visit 1) and at the end-of-study visit (Visit 3). There were no clinically significant changes identified evaluating the mean data compared to placebo treatment or for change from baseline values.

#### 7.4.4 Electrocardiograms (ECGs)

During the study D1220C00001, a 12-lead resting ECG was obtained at screening (Visit 1) and the end-of-study visit (Visit 3). There were no patients with shifts from normal at baseline to abnormal clinically significant ECG findings with no differences between treatment groups (reference: Module 5.3.5.1 study report D1220C00001, End-of-Text Table 11.3.8.1.2.3. and Figure 11.3.8.1.2.4 to 11.3.8.1.2.10).

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted for NDA 21450/S-008.

7.4.6 *Immunogenicity*  
 N/A

**7.5 Other Safety Explorations**

7.5.1 *Dose Dependency for Adverse Events*

There was increased incidence of AEs reported with the higher ZOMIG 5 mg dose compared to the lower doses, and the trend was similar to that observed with the AE incidence observed in adults.

7.5.2 *Time Dependency for Adverse Events*

The Sponsor described events within 24 hours of dosing for study D1221C00001 for non-serious adverse events and throughout the study for serious adverse events.

7.5.3 *Drug-Demographic Interactions*

Treatment emergent adverse events were analyzed by subgroups based on gender and race. Since the majority of subjects were Caucasians (93%), and with a higher proportion females (62%), any meaningful differences are difficult to determine regarding differential effects of gender and race on adverse events. Even though it appears females experienced comparatively increased AEs, there have been no differences observed for zolmitriptan products in product safety based on demographic differences.

<b>Table 16: NDA 21450/S-008 TEAEs ≥ 2% of Adolescent Patients Pooled Safety Analysis Study D1220C00001 and D1221C00005 by Gender</b>								
PT	ZOMIG 5mg		ZOMIG 2.5mg		ZOMIG 0.5mg		Placebo	
	Female N=248	Male N=183	Female N=49	Male N=32	Female N=58	Male N=34	Female N=264	Male N=173
Unusual Taste	10.5%	8.7%	4.1%	9.4%	5.2%	8.8%	1.9%	1.7%
Dizziness	3.2%	0.5%	0%	0%	1.7%	0%	0.8%	0.6%
Nasal discomfort	3.2%	1.6%	2.0%	3.1%	0%	2.9%	1.5%	0.6%
Oropharyngeal Pain	1.6%	2.2%	0%	0%	1.7%	0%	2.3%	0.6%
Nausea	2.8%	0.5%	2.0%	0%	0%	0%	0.4%	1.2%

Ref: eCTD seq 0040; Module 2.7.4; Sponsor's Table 7.8

Age subgroup analyses revealed no meaningful differences in AEs reported in 12-14 year old patients compared to 15-17 year old patients.

**Table 17: NDA 21450/S-008 TEAEs ≥ 2% of Adolescent Patients Pooled Safety Analysis Study D1220C00001 and D1221C00005 by Age Subgroup**

MedDRA Preferred term	12 to 14 Years				15 to 17 Years			
	Placebo (N=257) n (%)	ZOMIG			Placebo (N=180) n (%)	ZOMIG		
		0.5 mg <sup>a</sup> (N=41) n (%)	2.5 mg <sup>a</sup> (N=38) n (%)	5 mg (N=238) n (%)		0.5 mg <sup>a</sup> (N=51) n (%)	2.5 mg <sup>a</sup> (N=43) n (%)	5 mg (N=193) n (%)
Dysgeusia	6 (2.3)	3 (7.3)	2 (5.3)	25 (10.5)	2 (1.1)	3 (5.9)	3 (7.0)	17 (8.8)
Oropharyngeal pain	2 (0.8)	1 (2.4)	0	5 (2.1)	5 (2.8)	0	0	3 (1.6)
Throat irritation	1 (0.4)	0	0	5 (2.1)	1 (0.6)	0	0	1 (0.5)
Nasal discomfort	2 (0.8)	1 (2.4)	0	4 (1.7)	3 (1.7)	0	2 (4.7)	7 (3.6)
Nausea	2 (0.8)	0	0	3 (1.3)	1 (0.6)	0	1 (2.3)	5 (2.6)
Dizziness	1 (0.4)	1 (2.4)	0	2 (0.8)	2 (1.1)	0	0	7 (3.6)
Paresthesia	0	1 (2.4)	0	2 (0.8)	1 (0.6)	0	1 (2.3)	1 (0.5)
Abdominal pain upper	3 (1.2)	0	1 (2.6)	1 (0.4)	1 (0.6)	0	0	0
Administration related reaction	0	0	0	0	0	1 (2.0)	0	0
Chills	1 (0.4)	1 (2.4)	0	0	0	0	0	1 (0.5)
Feeling hot	0	0	0	0	0	1 (2.0)	0	0
Hypoesthesia	0	0	0	0	2 (1.1)	1 (2.0)	0	1 (0.5)
Influenza	0	1 (2.4)	0	0	0	0	0	0
Vertigo	0	1 (2.4)	0	0	1 (0.6)	0	0	0

Ref: eCTD seq 0040; Module 2.7.4; Sponsor's Table 10

#### 7.5.4 Drug-Disease Interactions

No formal drug-disease interaction studies have been conducted in adolescent subjects for NDA 21450/S-008. It relies on the recommendations and cautions described in the prescriber information ZOMIG nasal spray.

#### 7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted in adolescent subjects for NDA 21450/S-008.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted for this NDA.

#### 7.6.2 Human Reproduction and Pregnancy Data

The submission did not report of any pregnancies in studies D1220C00001 and D1221C00005, and no post-marketing pregnancies in adolescents have been reported as of 10 April 2014 (Post-Marketing data included Section 6 of the Summary of Clinical

Safety). Relevant information on use of ZOMIG nasal spray in pregnancy and lactation is provided in the ZOMIG nasal spray label.

#### 7.6.3 *Pediatrics and Assessment of Effects on Growth*

A comprehensive review of the literature did not reveal any information regarding zolmitriptan use in adolescent subjects that might be inconsistent with the product label for ZOMIG nasal spray.

#### 7.6.4 *Overdose, Drug Abuse Potential, Withdrawal and Rebound*

##### **Overdose**

The submission did not report of any overdose during the studies D1220C00001 and D1221C00005.

Although, there were two post-marketing cases of overdose, both serious, were reported in adolescents as of 10 April 2014 (Case IDs 2006CG01154 and 2002UW14534). In both cases, a suicide attempt was either confirmed or suspected.

For Case ID 2006CG01154, a 17- year old female adolescent patient described with comorbid depression and living in difficult social and familial environment ingested 6 tablets of ZOMIG, 40 tablets of Tardyferon (iron sulfate), and 4 blisters of magnesium/pyridoxine attempting suicide and hospitalized with vomiting. She is described as fully recovered the next day.

For Case ID 2002UW14534, a 16- year old male adolescent patient died after ingesting nine Imitrex 50 mg tablets over 2-days and an unknown amount of Sudafed 24-Hour sustained release along with a first dose of ZOMIG. After emergent acute medical care, the patient was declared brain dead, removed from the ventilator, and expired shortly afterwards. The cause of death was unknown.

##### **Drug abuse, withdrawal and rebound**

No additional studies have been conducted evaluating drug abuse, withdrawal, or rebound effects of ZOMIG nasal spray. There is no evidence of abuse potential based on the package insert for the reference listed product, ZOMIG nasal spray or for the class of drugs “triptans”.

Two post-marketing cases, 1 serious, in adolescents were reported as of 10 April 2014 (Case IDs 2008CG01690 and 2013SE33114). Both cases occurred in female adolescents who took ZOMIG via the oral route.

For Case ID 2008CG01690, the patient also experienced events (PT) of headache, ecchymosis, and vomiting. All events for this patient recovered or were recovering at the time of the report. However, AstraZeneca assessed the event of drug abuse in Case

2008CG01690 as unlikely to be related to ZOMIG. (Post-Marketing data included Section 7.2 of the Summary of Clinical Safety).

For Case ID 2013SE33114, the patient also experienced an event (PT) of medication overuse headache. Outcomes for the events reported in this patient were unknown and recovering for drug abuse and medication overuse headache, respectively. Both cases of drug abuse were assessed as related to ZOMIG by the reporter.

### 7.7 Additional Submissions / Safety Issues

The Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal risk was administered during study D1220C00001 at screening, randomization, and final visit. A trained rater administered the C-SSRS, and the same rater performed the assessment at each visit (Module 5.3.5.1, Study D1220C00001 CSR, Tables 11.3.8.1.5.1 and 11.3.8.1.5.3).

Treatment-emergent suicidality (suicidal ideation and behavior) has been identified in recent years in CNS drugs as a concern for a number of drugs and drug classes and the prospective assessment for suicidality provides information to allow additional analyses to be conducted in the future aggregating findings and comparing findings across drugs and drug classes. Such prospective assessments will help ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed. The risk of suicidality in adolescent migraineurs suggests monitoring for triptan use and any suicidal behavior.

The C-SSRS (Posner et al 2007) assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide. Protocol D1220C00001 specified all events of suicidality including events of suicide attempts, suicidal ideation, completed suicides, and suicidal behavior. The last category includes behavioral AEs or SAEs in which the investigator cannot rule out underlying suicidal thinking, e.g., motor vehicle accident or behaving in a dangerous or unsafe way, and other self-injurious behaviors.

**Table 18: NDA 21450/S-008 Suicidal Behavior and Ideation based on C-SSRS; Study D1220C00001**

Visit	Suicidality	Zomig 5mg (%)	Zomig 2.5mg (%)	Zomig 0.5mg (%)	Placebo (%)
Screening	N	230	81	92	253
	Suicidal ideation	10 (4.3%)	0	2 (2.2%)	5 (2%)
	Suicidal behavior	1 (0.4%)	1 (1.2%)	0	0
Final Visit	N	230	80	91	252
	Suicidal ideation	1 (0.4%)	0	1 (1.1%)	0
	Suicidal behavior	0	0	0	0

**Table 18: NDA 21450/S-008 Suicidal Behavior and Ideation based on C-SSRS; Study D1220C00001**

Visit	Suicidality	Zomig 5mg (%)	Zomig 2.5mg (%)	Zomig 0.5mg (%)	Placebo (%)
Ref: NDA 21450 (Module 5.3.5.1 Study Report D1220C00001; Table 11.3.8.1.5.1 Suicidal ideation is considered present if the response to at least one of the two suicidal ideation items (wish to be dead and non-specific active suicidal thoughts) is 'Yes'. Suicidal behavior is considered present if the response to at least one of the four suicidal behavior items (i.e., actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) is 'Yes'.					

Suicidal ideation was reported prior to the first dose of study drug at the screening visit in two patients (2.2%) in the ZOMIG 0.5 mg group, 10 patients (4.3%) in the ZOMIG 5 mg group, and 5 patients (2.0%) in the placebo group. At the final visit, only 1 patient each in the ZOMIG 0.5 and 5 mg groups (1.1% and 0.4%, respectively) who reported suicidal ideations at the screening visit reported the suicidal ideation of wish to be dead with non-specific active suicidal thoughts.

Even though there were subjects with actual prior attempt and/or a prior interrupted suicidal behavior/attempt, there were no patients with suicidal response or any type of suicidal behavior in any treatment group at the final visit. Information reviewed in the post-marketing reported cases of suicide attempt and death described in section 7.6.4 do not suggest any changes to labeling.

## 8 Postmarket Experience

AstraZeneca estimated exposure as approximately 1.6 million patients to ZOMIG nasal spray for all age groups based on sales figures and the assumption that one patient uses 90 mg ZOMIG per year (number of migraine attacks per year=18; use of 5 mg per attack). There is no specific information available regarding exposure to ZOMIG in adolescents.

AstraZeneca searched all spontaneous reports relevant to the safety of zolmitriptan in the pediatric population (12 to 17 years of age) through their global patient safety database that contains all AE reports from spontaneous sources (including healthcare professionals, regulatory authorities, literature, consumers), beginning March 7, 1997 to April 10, 2014.

There were 111 case reports of AEs in the AstraZeneca ZOMIG database involving children 12 to 17 years, containing 254 AEs, 53 of which were serious events. One patient died related to an overdose of nine 50 mg tablets of Imitrex who had taken ZOMIG (section 7.6.4). All serious reports associated with unlisted events are reviewed that were also included in the PSURs (Appendix 7.2 of the summary of clinical safety (Module 2.7.4).

An analysis of these cases is consistent with the safety profile of ZOMIG in adolescents being consistent with the safety profile in adults. The most frequent non-serious AEs listed in case reports in adolescents using ZOMIG were summarized (Table 19) in the sponsor’s submitted summary of clinical safety (Module 2.7.4). Almost all reports involved exclusive use of the oral route of administration with 10 cases reported ZOMIG nasal spray use. The most frequently reported AEs in adolescents who took ZOMIG were consistent with those reported in adults and included drug ineffective, nausea, dizziness, headache, throat tightness, and vomiting. Although some of these symptoms (e.g., headache, nausea, vomiting) may be manifestations of migraine symptoms.

Frequently reported events with zolmitriptan in the pediatric population are listed in the table below.

<b>Table 19: NDA 21450/S-008 ZOMIG Post Marketing AEs in Adolescent</b>	
<b>Preferred term</b>	<b>Number of adverse events</b>
Drug ineffective	15
Nausea	14
Dizziness	10
Headache	10
Throat tightness	10
Vomiting	9
Dyspnea	7
Paresthesia	7
Migraine	6
Chest discomfort	5
Chest pain	5
Drug interaction	5
Muscle Tightness	5
Neck Pain	5
Pain in Jaw	5
Hypoesthesia	4
Blood pressure increased	3
Hypoesthesia oral	3
Oropharyngeal pain	3
Palpitations	3

Ref: eCTD seq 0040; Module 2.7.4; Sponsor’s Table 11  
 Most Frequently Reported Post Marketing AEs in Adolescent Patients Using ZOMIG  
 Cut-off for adverse events=3 events; Case reports include spontaneous reports and published reports

## 9 Appendices

### 9.1 Literature Review/References

Citations are noted as footnotes in the review.



## **9.2 Labeling Recommendations**

The labeling should be consistent with other 5HT<sub>1</sub> receptor agonists for the treatment of acute migraine headache, and the clinical sections should remain consistent with RLD, ZOMIG nasal spray with the exception of additional information in applicable sections of the label informing of pediatric use in 12-17 year old patients with information from NDA 21450/S-008. Several labeling meetings were held during the review cycle and the available data supports the use of ZOMIG 5 mg and 2.5 mg doses.

## **9.3 Advisory Committee Meeting**

No advisory committee meeting was held because the drug product has already been approved at similar doses for other routes of administration and there were no unexpected safety issues.

## **9.4 Summary of Regulatory Activity**

The following information is modified and adapted from Dr. Teresa Podruchny's review of sNDA 21450/S-005.

- November 25, 1997 ZOMIG 2.5 and 5.0 mg Tablets (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. Sponsor is conducting trials of ZOMIG Tablets in adolescents pursuant to a Written Request issued by the FDA on March 26, 1999. According to the meeting minutes (IND 53848 serial 015) submitted on March 22, 2000, the Division agrees to allow the Sponsor to defer studies of ZNS in pediatrics until the safety and effectiveness of ZOMIG Tablets have been evaluated in adolescents.
- Feb 13, 2001 (NDA 21231) ZOMIG-ZMT fast disintegrating formulation (2.5 mg) approved.
- 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* (b) (4)

*he 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 – Dr. Katz memo noted *Approvable Action Letter* once sponsor demonstrates the bioequivalence of the *clinical and commercial* (i.e., "to be marketed") *spray devices*. The active moiety in ZNS is the same found in ZOMIG Tablets (2.5 and 5.0 mg). Efficacy was shown with 5mg, 2.5mg, 1.0mg, and marginally effective for headache response at 2 hours with 0.5 mg dose. The ZNS 5.0mg dose was significantly better than placebo at two hours for all three associated symptoms. All the other ZNS doses *failed on nausea* (it's interesting that the zolmitriptan tablet dose also failed on nausea), although they were all in the right direction of a dose response. Nasopharyngeal discomfort and unusual taste were common, generally mild, and non-serious, and dose-related (for the 5mg dose, NP discomfort occurred in 3%, vs. 1.8% in placebo, and unusual taste occurred in 21% vs. 3% in placebo). The pharmacokinetics, metabolism, and elimination profiles of zolmitriptan when taken orally or intranasally were similar. During development, the sponsor *changed the nasal spray device* used to deliver ZOMIG Nasal Spray. The pivotal trial Trial 311CUS/0077 (N=1547) was conducted using the earlier "clinical" device, (b) (4) was introduced during the course of the long-term study 311CIL/0078. Once the results of study 311CUS/0077 were available, the sponsor chose the most optimal dose (which in their estimation was the 5mg dose). At this point, all subjects still enrolled in study 311CIL/0078 were switched to the 5mg dose. This was the beginning of part 2 of the study and was exactly coincident with the switch to the commercial device. Potential biases could have been introduced with investigators knowledge of selection of optimal dosing and introduction of new device. Additionally, Subjects in study 0078 were permitted to treat mild attacks, and this was not permitted in 0077. It is expected that subjects

treating mild attacks will have higher response rates and subject's experience with the study medication from a previous attack can influence the response rate for subsequent attacks.

- 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 D1221c00005.
- 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. An interim analyses of study 311CUS/0022 using the commercial device fulfilled the deficiency relative to ZNS 5.0 mg devices. Study 311CUS/0022 was an ongoing, large (N=1384), multicenter, randomized, placebo controlled study to evaluate the early efficacy (15 minutes) of ZNS 5.0 mg. (b) (4)

The **phase 4 commitments** included evaluation of BE between the clinical and proposed commercial device for ZNS 2.5 and 0.5 mg to support approval of 2.5 mg and 0.5 mg to-be marketed spray devices.

Approaches included:

- Repeat the in vitro testing using either mechanical actuation or have the break ring remanufactured with more narrow specifications before repeating the study.
- Provide in vivo pharmacokinetic data to demonstrate bioequivalence.
- Provide efficacy data from a well designed, randomized controlled trial.
- 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 (b) (4)

- Pediatric Written request comments:

- (b) (4)  
*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.*

(b) (4)

- 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

(b) (4)

- December 2003-Pediatric Exclusivity granted to active moiety under NDA 20768
- January 7, 2004-teleconference between FDA and Company-FDA meeting minutes

(b) (4)

(b) (4) (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.

(b) (4)

- 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:



- 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.



- 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 t-con (signed 1-18-07)
- 10-14-08 – FDA communicated to the sponsor that the PREA obligation for NDA 21,450 was NOT MET

(b) (4)

(b) (4)

he Division required the sponsor to design and conduct an additional study of ZOMIG in adolescents (ages 12-17 years) and NEW requirement to study ZOMIG in ages 6-11 years. The submission of age 6-11 years study was deferred until additional safety and effectiveness data was available from the study in adolescents. Class Labeling changes were recommended pertaining to the risk for serotonin syndrome with the use of triptans.

- 03-19-09 – Sponsor submitted new protocol Study D1220C00001 for Division feedback and meeting for June 9, 2009.
- 06-09-2009 - Type B meeting to discuss protocol Study D1220C00001.
- 11-18-2009 - SPA protocol Review.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUHAIL KASIM  
06/05/2015

ERIC P BASTINGS  
06/12/2015