CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-450

MEDICAL REVIEW

Review and Evaluation of Clinical Data

IND (Serial Number)	**21-450**
Sponsor:	**AstraZeneca**
Drug:	**Zomig (zolmitriptan) Nasal Spray**
Proposed Indication:	**Acute Migraine**
Material Submitted:	**Labeling**
	edr \CDSESUB1N21450N_0002003-04-25
Correspondence Date:	**April 25, 2003**
Date Received / Agency:	**April 25, 2003**
Date Review Completed	**May 7, 2003**
Reviewer:	**Kevin Prohaska, D.O.**

I. Introduction

In this document I review the proposed labeling for Zomig Nasal Spray 5.0 mg submitted by the sponsor on April 25, 2003. The sponsor states that the revised labeling encompasses all the recommended changes to labeling contained in the Approvable Letter dated December 19, 2002. Additionally they have clarified the proposed labeling where requested, added a few new details, and completely reformatted the patient information sheet in the question/answer format presently recommended by the Agency. The sponsor states they used Relpax label as a guide in their reformatting. A DDMAC consult has been requested to review the proposed patient information sheet. My recommended changes are highlighted in red.

II. Proposed Professional Package Insert

Rev 01/03 SIC 28570-00

[redacted]

23 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Rev 01/03

Kevin Prohaska, D.O.
Medical Reviewer

A. Oliva, M.D. _____

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/s/

Kevin Prohaska
7/30/03 02:50:37 PM
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Clinical Review Cover Sheet

NDA:	**21-450**
Sponsor:	**AstraZeneca**
Drug:	**Zomig (zolmitriptan) Nasal Spray**
Proposed Indication:	**Acute Migraine**
Materials Submitted	**Response to Approvable Letter (edr \\CDSESUB1\N21450\N_000\2003-03-27**
Correspondence Date:	**March 27, 2003**
Date Review Completed:	**May 1, 2003**
Division:	**Neuropharmacological Drug Products**
Reviewer:	**Kevin Prohaska, D.O.**

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Clinical Review for NDA 21-450

Executive Summary

The sponsor is developing Zomig Nasal Spray (ZNS) 5.0 ———— mg for the treatment of acute migraine. The original NDA was submitted on February 27, 2002. An Approvable Letter was issued December 19, 2002. This executive summary and review only covers the material submitted by the sponsor in response to our Approvable Letter. My original review of the NDA submission can be found in DFS.

The active moiety in Zomig Nasal Spray (ZNS), zolmitriptan, is the same active moiety found in Zomig Tablets (2.5 and 5.0 mg) approved by the Agency on November 25, 1997 (NDA 20-768) for the acute treatment of migraine with and without aura in adults. Zolmitriptan is a selective 5-$HT_{1B/1D}$ receptor agonist (a.k.a. triptans) that has been developed for the acute treatment of migraine with and without an aura. Extensive clinical experience and multiple clinical trials has demonstrated that oral zolmitriptan is typical of members of its class in its risk/benefit profile.

The original application contained a single large (N=1547), double blind, placebo controlled, phase III efficacy trial (Trial 311CUS/077, hereafter trial 077) that clearly demonstrated efficacy for ZNS 5.0, 2.5, 1.0 and 0.5 mg using the clinical spray device. For the primary endpoint of headache response at 2 hours, all doses of zolmitriptan nasal spray were statistically superior to placebo ($p<0.02$ for ZNS 0.5 mg, all others <0.0001), with response rates of 68.9%, 55.3%, 59.1%, and 39.6% for the 5.0 mg, 2.5 mg, 1.0 mg, and 0.5 mg doses, respectively, compared with 30.7% for placebo[1]. Additionally 2 open label, long term safety trials were also conducted (Trail 311CIL/0078 and 311CIL/0122).

The Approvable Letter cites a single deficiency with the original application, the lack of bioequivalence between the devices used in the majority of trial 077 and the devices intended for marketing. Several of the in-vitro bioequivalence parameters were outside the acceptable limits. The Approvable Letter outlines the following options on how the sponsor could remedy the deficiency.

1. *Repeat the in vitro testing using either mechanical actuation or have the break ring re-manufactured with more narrow specifications before repeating the study.*
2. *Provide in vivo pharmacokinetic data to demonstrate bioequivalence.*
3. *Provide efficacy data from a well designed, randomized controlled trial.*

In addition the sponsor was requested to submit revised draft labeling and a safety update.

In a teleconference with the sponsor on February 11, 2003 we agreed that an interim analyses of the study 311CUS/0022 (hereafter trial 022) using the commercial device could possibly fulfill the deficiency relative to ZNS 5.0 mg. Trail 022 is an ongoing, large (N=1384), multicenter, randomized, placebo controlled study to evaluate the early efficacy (15 minutes) of ZNS 5.0 mg in the treatment of migraine. ————————————

[1] Source: Sponsor Table 6, 1st Attack Analysis.pdf, page 26 of original NDA submission.

As agreed this submission contains an interim efficacy analysis of trial 022, a safety update and revised draft labeling. For this review I use an abbreviated version of the suggested CDER template for NDA reviews. Specific details like PK/PD and chemistry summaries can be found in my original review and are not repeated here unless germane to the discussion. Primarily I will focus on the unblinded Interim Efficacy Analysis from trial 022 and the safety update report, most of which continues to be blinded. A review of the submitted revised labeling will be done in a separate document in order to facilitate team input.

1. Recommendations

1.1 Recommendation on Approvability

Considering the favorable risk-benefit balance seen with oral zolmitriptan use in migraine, and based on efficacy and safety data reviewed in this response to our Approvable Letter and the original NDA submission, and from a clinical perspective I recommend approval of Zomig (zolmitriptan) Nasal Spray 5.0 mg (NDA 21-450) for the treatment of acute migraine with and without an aura in adults.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

Phase IV commitments should include an evaluation of the bioequivalence between the clinical and proposed commercial device for ZNS [redacted] 0.5 mg. Acceptable approaches include the same options outlined in the original Approvable Letter:

1. *Repeat the in vitro testing using either mechanical actuation or have the break ring re-manufactured with more narrow specifications before repeating the study.*
2. *Provide in vivo pharmacokinetic data to demonstrate bioequivalence.*
3. *Provide efficacy data from a well designed, randomized controlled trial.*

Additionally as previously suggested in my original review the sponsor should continue with their development program to evaluate the safety and efficacy of ZNS in adolescent patients. The Sponsor has been granted a deferral for the pediatric migraine indication by agreement with the Agency.

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The efficacy database provided in this submission consist of an Interim Analysis of a single ongoing large efficacy trial (trial 022) using ZNS 5.0 mg in the proposed commercial device. Trial 022 is a multicenter, randomized, double-blind, placebo controlled trial involving 1384 patients to compare the efficacy and tolerability of ZNS 5.0 mg to placebo in the acute treatment of migraine using an early efficacy time point (15 minutes). The interim analysis was designed to evaluate the first 210 patients from 36 centers who treated the first migraine and provided efficacy assessments. The primary endpoint of the full study is to evaluate headache response at 15 minutes. The primary endpoint of the Interim Analysis is to evaluate headache response at 2 hours using first attack analysis.

The safety data base provided in this submission consists of 4 open label PK studies (SA-ZOB-0001, SA-ZOB-0002, 311CJP/0110, and 311CIL/0124) and two ongoing, double blinded, placebo-controlled efficacy and tolerability studies (Studies 311CUS/0022 and 311CIL/0120). A brief description of each trial design can be found in section 2.1 of this review. Additionally the sponsor provides a brief discussion of post marketing safety reports from countries where ZNS 5.0 mg is approved (Czechoslovakia, Iceland, Slovakia, Sweden, and the United Kingdom).

Overall, new safety data is presented from 121 patients in the 4 pharmacokinetic studies (259 exposures) and 1170 patients from blinded, placebo-controlled Studies 0022 and 0120 (2475 exposures). Safety data from the placebo-controlled studies in this update remains blinded and unvalidated; therefore no distinction is made between patients who received 5.0 mg zolmitriptan nasal spray and patients who received placebo. In the clinical pharmacology studies 89 subjects were given ZNS 5.0 mg, 46 subjects received ZNS 2.5 mg, 21 subjects received ZNS 1.0 mg and 12 subjects received zolmitriptan 10 mg. In trial 022 and 120 all subjects received ZNS 5.0 mg or placebo.

2.2 Efficacy

The Interim Analysis of trial 022 demonstrates statistical superiority of ZNS 5.0 mg, using the commercial device, for the primary endpoint of 2-hour headache response, when compared to placebo. The 2-hour headache response rate for the first treated migraine is demonstrated in the following sponsor table. As demonstrated in the table ZNS 5.0 mg using the commercial device was statistically better than placebo at relieving headache pain at two hours compared to placebo (p=0.0005).

Table 1 Headache response at 2 hours (first attack) Interim analysis

Population	Zolmitriptan 5-mg nasal spray group (N=108)		Placebo group (N=102)		Statistical comparison (logistic regression)		
	Number assessed	Headache response (n [%])[a]	Number assessed	Headache response (n [%])[a]	Odds ratio	95% confidence interval (L,U)	p-value
ITT	108	76 (70.4)	100[b]	47 (47.0)	2.84	1.58, 5.10	0.0005

[a] Percentages are based upon the total number of attacks in the ITT for which data were available at 2 hours. 95% CI (L,U) Lower and upper 95% confidence limits of odds ratio of headache response rates for patients treated with zolmitriptan versus patients treated with placebo.

[b] Two patients from the placebo group were not included in the analysis of 2-hour headache response: One patient had missing data at 2 hours; the other patient had taken escape medication before 2 hours when migraine headache pain was mild (these data were considered missing according to the SAP).

ITT Intent to treat.

Source: Sponsor table 13, interim analysis.pdf, page 45.

The response rate for ZNS 5.0 mg using the commercial device (70.4%) is similar to the response rate for ZNS 5.0 mg using the clinical device in trial 077 (68.9%). However the treatment effect between trials is appreciably different. In this trial the treatment effect is 23.4% whereas in trial 077 the difference in response rates between ZNS 5.0 mg (clinical device) and placebo was 38.2%. Most of this difference is accounted for by a lower placebo response rate in trial 077 (30.7% vs. 47.0% in trial 022). The reason for the difference in response rates in subjects that received placebo between the two trials is not apparent from my review.

The Interim Analysis of trial 022 does not demonstrate superiority for ZNS 5.0 compared to placebo in the percentage of subjects reporting resolution of their baseline nausea, photophobia or phonophobia ($p \geq 0.0736$). Despite this lack of superiority the response rate for ZNS 5.0 mg (clinical device) in trial 077 and ZNS 5.0 mg (commercial device) in trial 022 are nearly identical for each associated symptom. For some inexplicable reason the response rate for these endpoints in patients that received placebo in trial 022 were substantially larger than for the patients that received placebo in trial 077, resulting in a lower treatment effect. This as well as the small cohort size may explain the lack of significance for this secondary endpoint. The results did favor ZNS 5.0 mg numerically in trial 022 for each symptom.

However the Agency analysis of the proportion of subjects reporting nausea, photophobia, or phonophobia demonstrates a clear advantage to ZNS 5.0 mg over placebo at 2 and 4 hours. As demonstrated in Table 8, ZNS 5.0 mg was statistically superior to placebo in the proportion of subjects reporting photophobia at 2 hours ($p=0.0255$). Likewise ZNS 5.0 mg was nearly significantly better than placebo for nausea at 2 hours ($p=0.0796$) and numerically better than placebo in the proportion of subjects reporting phonophobia (35.6% vs. 26.9%) at 2 hours.

Although the analysis of associated symptoms results in mixed results it should be remembered this analysis only includes the first 210 subjects to complete the study. The efficacy of zolmitriptan against the associated symptoms of migraine has been demonstrated in other studies and is not the primary concern of this Interim Analysis.

2.3 Safety

The safety update report provides all new safety information between the period of the last update (June 27, 2002) up to the most recent cutoff date of December 31, 2002. Overall, new safety data is presented from 121 patients in 4 pharmacokinetic studies and 1170 patients from two blinded placebo controlled studies (trial 022 and trial 0120).

In the four clinical pharmacology studies there were no deaths, serious adverse events, or withdrawal due to adverse events in any healthy volunteer. Across all nasal spray doses the most common adverse event was dysgeusia. The vast majority of adverse events were mild in intensity and of short duration.

In the two controlled and blinded clinical trials (022 and 0120) the safety experience reported to date appears similar to the safety experience I previously reviewed for the full NDA. The sponsor uses the safety results from the cohort of subject receiving ZNS 5.0 mg (using the clinical device) in trial 077 as their primary comparison group for safety. A comparison of the blinded safety data from trial 022 and trial 0120 compared to trial 077 fails to demonstrate any new safety signals.

In the two blinded placebo controlled trial using ZNS 5.0 mg (commercial device) there were no deaths and very few serious adverse events (3 to date, all unrelated to treatment). Withdrawal rates have been reasonable and comparable to withdrawal seen in trial 077 (approximately 1%). The common adverse events seen in trial 022 and 0120 appear to be similar in nature and

incidence rates to the adverse events reported in trial 077. The most common adverse events was dysgeusia (unusual taste) in all studies (generally around 20%). Other common adverse events include dizziness, nasal passage irritation, and throat irritation. The majority of reports were generally rated as mild to moderate and were of short duration. Subgroup analysis by age, gender, weight and race did not demonstrate any clinically significant differences between cohorts.

Overall my review of the safety update report does not find any new safety concerns relative to the use of ZNS 5.0 mg using the commercial device. Since the majority of safety data provided in this safety update report is blinded or from open label uncontrolled PK/PD studies the new safety information is generally unacceptable for labeling purposes.

2.4 Dosing

The data provided in this submission supports the approval of ZNS 5.0 mg using the commercial device [redacted] The dosing regimen recommendations for ZNS 5.0 mg is unchanged from my original review, i.e., 1 spray at the onset of a migraine with a repeated dose at 2 hours if required. The total amount of Zomig, in any formulation, should not exceed 10 mg in any 24 hour period.

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Clinical Review

1. Introduction and Background

The sponsor is developing Zomig Nasal Spray (ZNS) 5.0, ——— mg for the treatment of acute migraine. The original NDA was submitted on February 27, 2002. An Approvable Letter was issued December 19, 2002. This submission contains the complete response to our Approvable Letter. My original review and the Approvable Letter can be found in DFS. In this review I will strictly focus on the new material submitted by the sponsor on March 27, 2003.

The original application contained a single large (N=1547), double blind, placebo controlled, phase III efficacy trial (Trial 311CUS/077, hereafter trial 077) that clearly demonstrated efficacy for ZNS 5.0, 2.5, 1.0 and 0.5 mg using the clinical spray device. For the primary endpoint of headache response at 2 hours, all doses of zolmitriptan nasal spray were statistically superior to placebo ($p<0.02$ for ZNS 0.5 mg, all others <0.0001), with response rates of 68.9%, 55.3%, 59.1%, and 39.6% for the 5.0 mg, 2.5 mg, 1.0 mg, and 0.5 mg doses, respectively, compared with 30.7% for placebo[2]. Additionally 2 open label, long term safety trials were also conducted (Trail 311CIL/0078 and 311CIL/0122). Additional details regarding the original NDA submission can be found in my original review in DFS.

The Approvable Letter (dated 12/19/02) cites a single deficiency with the original application, the lack of bioequivalence between the clinical and proposed commercial spray devices. The letter outlines the following options on how the sponsor could remedy the deficiency.

1. *Repeat the in vitro testing using either mechanical actuation or have the break ring re-manufactured with more narrow specifications before repeating the study.*
2. *Provide in vivo pharmacokinetic data to demonstrate bioequivalence.*
3. *Provide efficacy data from a well designed, randomized controlled trial.*

In addition the sponsor was requested to submit revised draft labeling and a safety update.

In a teleconference with the sponsor on February 11, 2003 we agreed that an interim analyses of the study 311CUS/0022 (hereafter trial 022) using the commercial device could possibly fulfill the deficiency relative to the 5-mg strength of Zomig Nasal Spray (ZNS). Trail 311CUS/0022 is an ongoing, large (N=1384), multicenter, randomized, placebo controlled study to evaluate the early efficacy (15 minutes) of ZNS 5.0 mg in the treatment of migraine. ———

[ ]

This submission contains an interim efficacy analysis of trial 022, a safety update and revised draft labeling. Statistical superiority of ZNS 5.0 mg using the commercial device was found for the primary endpoint of 2-hour headache response when compared to placebo according to the prespecified Interim Analysis of trial 022. The safety update report provides all new safety information between the period of the last update (June 27, 2002) up to the cutoff date of December 31, 2002. Overall, new safety data is presented from 121 patients in 4

[2] Source: Sponsor Table 6, 1st Attack Analysis.pdf, page 26 of original NDA submission.

pharmacokinetic studies and 1170 patients from two blinded, placebo controlled, studies. The sponsor claims that the report indicates no new safety concerns for ZNS 5.0 mg although the safety database for the controlled trials are presented in a blinded manner. The sponsor states the new revised draft labeling includes all the changes suggested by the Agency in our Approvable Letter as well as the requested clarifications and editing changes. Additionally the sponsor has reformatted the Patient Information Leaflet into the suggested question/answer format using the current Relpax Patient Information Leaflet as a guide.

For this review I use a truncated version of the suggested CDER template for NDA reviews. Specific details like PK/PD and chemistry summaries can be found in my original review and are not repeated here unless germane to the discussion. Primarily I will focus on the unblinded Interim Efficacy Analysis from trial 022 and the safety update report, most of which continues to be blinded. A review of the submitted revised labeling will be done in a separate document in order to facilitate team input.

1.1 Important Milestones in Product Development (Updated)

- December 19, 2002 Approvable Letter sent to the sponsor
- February 11, 2003 Teleconference with sponsor to discuss deficiencies.
- March 26, 2003 Complete Response to Approvable Letter Received

The Approvable Letter cites the lack of bioequivalence between the clinical and proposed commercial spray devices.

In a teleconference with the sponsor on February 11, 2003 we agreed that an interim analyses of the study 311CUS/0022 (hereafter trial 022) using the commercial device could possibly fulfill the deficiency relative to the 5-mg strength of Zomig Nasal Spray (ZNS) only.

2. Description of Clinical Data and Sources

The efficacy database provided in this submission consist of an Interim Analysis of a single ongoing large efficacy trial (trial 022) using ZNS 5.0 mg in the proposed commercial device. The safety data base provided in this submission consists of blinded safety data from trial 022 and trial 120 plus 4 open label PK studies. Each of the studies are briefly described below.

Clinical pharmacology studies:

- SA-ZOB-0001: This was an open-label, 2-panel, non-randomized study in healthy volunteers to study the distribution of 5.0 mg zolmitriptan nasal spray into the central nervous system in vivo using positron emission tomography.
- SA-ZOB-0002: This was an open-label, randomized, 4-way cross over, single-center study in healthy volunteers to determine the fraction intranasally absorbed of an intranasal dose of 5.0 mg zolmitriptan.
- 311CJP/0110: This was a Phase I, double-blind, placebo-controlled, randomized, incomplete, crossover study in healthy volunteers to determine the safety, tolerability, and pharmacokinetics of 5.0 mg zolmitriptan nasal spray.
- 311CIL/0124: This was a Phase I, open-label, randomized, single-dose, crossover study in healthy Japanese volunteers to determine the safety and pharmacokinetics of a 2.5 mg tablet

and 2.5 mg intranasal combined dose of zolmitriptan and a 5.0 mg tablet and 5.0 mg intranasal combined dose of zolmitriptan.

Placebo-controlled, efficacy, safety, and tolerability studies (ongoing):

- 311CUS/0022: This is an ongoing multicenter, randomized, placebo-controlled, double-blind, parallel-group study to evaluate the early efficacy and tolerability of a 5.0 mg intranasal dose of zolmitriptan in the acute treatment of adult subjects with migraine.
- 311CIL/0120: This is an ongoing multinational, multicenter, 2-phase study to assess the efficacy of and satisfaction with 5.0 mg intranasal zolmitriptan in the acute treatment of migraine when taken as required by the patient, by single attack comparison to placebo followed by an open-label treatment period with 5.0 mg intranasal zolmitriptan for 3 isolated attacks.

Only interim data from trial 022 will be reviewed for efficacy relative to ZNS 5.0 mg using the commercial device. All studies will be included in my safety discussion. The study reports for the 4 PK/PD studies are not included in this submission however the sponsor does include a summary of the safety findings from these studies in their Safety Report Update (SUR).

3. Integrated Review of Efficacy

In this section of my review I present the study design and efficacy results from the interim analysis of study 022 followed by my comments relative to this study only. Safety will be discussed in section 4. The first patient was enrolled on 10 September 2002. The study is presently ongoing.

3.1 Detailed Description of Trial 022

Title: "A multicenter, Randomized, Placebo-controlled, Double-Blind, Parallel-Group Trial to Evaluate Early Efficacy and Tolerability of Zolmitriptan (Zomig) Nasal Spray in the Acute Treatment of Adults Patients with Migraine"

Trial 022 is a multicenter, randomized, double-blind, parallel group, placebo controlled trial to compare the efficacy and tolerability of ZNS 5.0 mg to placebo in the acute treatment of migraine using an early efficacy time point (15 minutes). The trial is being conducted in 162 centers in the United States. Evaluable patients can treat up to two migraines of moderate to severe intensity with study medication. Escape medication is prohibited for the first 4 hours after treatment. Following treatment subjects are instructed to return to the study site within 2 weeks of their last dose of study medication. The interim analysis was designed to evaluate the first 210 patients from 36 centers who treated the first migraine and provided efficacy assessments. Only the Interim Analysis statistician and the SAS programmers had access to the unblinded treatment information for these 210 patients.

The primary objective of the study is to evaluate the efficacy of ZNS 5.0 mg at 15 minutes in the acute treatment of migraine. The primary objective of the Interim Analysis is to evaluate efficacy at 2 hours of ZNS 5.0 mg compared to placebo in the acute treatment of migraine using first migraine attack data. Multiple attack analysis will be presented in the final report. Additionally efficacy relative to the associated symptoms will be assessed.

The full trial is expected to enroll approximately 1592 subjects meeting IHS criteria for migraine with and without aura to obtain 1384 evaluable patients (692 per cohort). It is estimated this sample size will provide 90% power to show a difference in headache response rate between ZNS 5.0 mg and placebo 15 minutes after treatment. Calculations were based on the assumption that the headache response rate at 15 minutes would be 6% for placebo and 11% for ZNS 5.0 mg. Although it is not relevant to the interim analysis, which uses a traditional 2-hour response rate, I am not inclined to believe a treatment effect of 5% at 15 minutes is clinically relevant.

The inclusion and exclusion criteria for this trial are typical for most migraine trials. Included adult subjects are expected to have a migraine history of at least 1-year duration, be generally in good health and meet the IHS criteria for migraine with or without aura. Migraine frequency is not to exceed 6 migraine per month hence debilitated subjects with severe frequently recurring migraine were excluded.

Restricted medications include the following:

- MAOIs within 2 weeks of randomization.
- Unstable migraine prophylaxis within 2 months of randomization.
- Propranolol or cimetidine use.
- SSRI use within 2 months of randomization.
- Use of other migraine therapies (analgesics, anti-emetics, ergots, opiates, or other triptans) within 24 hours of use of study medication. Naratriptan is not to be used within 36 hours of treatment and Frovatriptan is not to be used within 5 days before trial treatment.

The primary endpoint for the full study is headache response at 15 minutes after treatment. Headache response is defined as an improvement in headache pain from moderate to severe to none or mild using the 4-point scale typically seen in migraine studies. The sponsor should be encouraged to look at sustained early response as the primary endpoint.

The primary endpoint for the Interim Analysis is headache response at 2 hours only using first attack data. Secondary endpoint for the Interim Analysis include:

- Headache response at 15 and 30 minutes, and 1 and 4 hours.
- Resolution of associated symptoms (nausea, photophobia and phonophobia) at 2 hours after treatment.

The Interim Analysis plan was originally submitted to the Agency on February 28, 2003. The interim analysis includes the first 210 evaluable subjects who treated the first migraine with study medication. This sample size is estimated to provide approximately 90% power of showing a difference in headache response rate between ZNS 5.0 mg and placebo at 2 hours. Calculations were based on the assumption that the headache response rate at 2 hours would be 39% for placebo and 69% for ZNS 5.0 mg.

The alpha spending function methodology based on Hwang, Shih, and deCani (1990) γ-family approach was used to control the overall two-sided type I error at 5% for both the interim and final analysis. The 2-sided significance boundaries for the p-values were calculated and pre-

specified to be 0.0027 and 0.0479 (based on γ=-2 and information fraction of t=15%) for the interim and final analysis, respectively. That is, the statistical significance of the analysis results for the primary efficacy parameter of 2-hour headache response was tested against a significance level of 0.0027 for the interim analysis and 0.0479 for the final analysis.

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

Resolution of associated symptoms (nausea, photophobia, and phonophobia) are analyzed at 2 hours using the same logistic regression method with treatment, region, and baseline intensity in the model as for the analysis of the primary endpoint. The sponsor did not analyze the associated symptoms in the manner generally requested by the division that being a comparison of the proportion of subjects with each symptom at various timepoints. No formal statistical analysis or summary of other efficacy endpoints are performed for this Interim Analysis. The prestated Interim Analysis plan did not include an algorithm for missing data.

3.2 Efficacy Results, Interim Analysis of Trial 022

Unblinded efficacy results from 210 patients were analyzed using the Interim Analysis plan submitted to the Agency in an e-mail dated February 28, 2003. Only first migraine treated results are presented.

3.2.1 Demographics and Migraine History

The Intent to Treat (ITT) population is the primary population and is defined as all patients who used trial treatment and provided baseline and post-baseline efficacy data.

The following sponsor table demonstrates the baseline demographics of the patient population in the Interim Analysis group. As is demonstrated there does not appear to be any significant differences between cohorts relative to age, gender, race, or average number of attacks per month. The mean age of patients in this study is 39.6 years of age, the majority (67.1%) are Caucasian, and the vast majority (83.8%) are women.

Table 2 Baseline Demographics, ITT population

Demographic characteristic	Treatment group		Total
	Zolmitriptan 5-mg nasal spray (N=108)	Placebo (N=102)	(N=210)
Age (y) at entry			
Mean	38.6	40.4	39.5
SD	9.6	10.0	9.9
Minimum, maximum	21, 63	18, 64	18, 64
Age group, number of patients (%)			
18 to 39 y	52 (48.2)	48 (47.1)	100 (47.6)
40 to 65 y	56 (51.9)	54 (52.9)	110 (52.4)
Sex, number of patients (%)			
Women	89 (82.4)	87 (85.3)	176 (83.8)
Men	19 (17.6)	15 (14.7)	34 (16.2)
Race, number of patients (%)			
Caucasian	72 (66.7)	69 (67.7)	141 (67.1)
Black	28 (25.9)	29 (28.4)	57 (27.1)
Hispanic	4 (3.7)	3 (2.9)	7 (3.3)
Asian	2 (1.9)	1 (1.0)	3 (1.4)
Other[a]	2 (1.9)	0	2 (1.0)

[a] Other includes any special subgroups.
Source: Sponsor Table 9, interim analysis.pdf, page 42.

The historical characteristics of patient migraines are similar between treatment groups, however, a slightly higher percentage of patients in the ZNS group had nausea with their migraines (85.2% ZNS vs. 80.4% placebo), and a slightly higher percentage of patients in the placebo group had phonophobia with their migraines (89.8% ZNS vs. 94.1% placebo). The historical average age at onset of migraine attacks is 21.9 years across both treatment groups and the average number of migraine attacks/month for both groups is 3.6.

Two hundred and ten patients are included in the ITT population. Of these 108 patients were randomized to ZNS 5.0 mg and 102 patients were randomized to placebo. Although all patients met the definition of the ITT population the sponsor did not include 2 subjects (both placebo) in the analysis of the primary endpoint since one subject did not provide data at 2 hours and the other patient took escape medication before 2 hours.

The baseline migraine characteristics were well balanced between cohorts with approximately 75% of the subjects reporting headache pain of moderate intensity at baseline for both cohorts (75.9 for ZNS vs. 74.5 for placebo) and the remainder reporting severe migraine headache pain.

3.2.2 Primary endpoint results

The 2-hour headache response rate for the first treated migraine is demonstrated in the following sponsor table. As demonstrated in the table ZNS 5.0 mg using the commercial device was statistically better than placebo at relieving headache pain at two hours compared to placebo (p=0.0005).

Table 3 Headache response at 2 hours (first attack) Interim analysis

Population	Zolmitriptan 5-mg nasal spray group (N=108)		Placebo group (N=102)		Statistical comparison (logistic regression)		
	Number assessed	Headache response (n [%])[a]	Number assessed	Headache response (n [%])[a]	Odds ratio	95% confidence interval (L,U)	p-value
ITT	108	76 (70.4)	100[b]	47 (47.0)	2.84	1.58, 5.10	0.0005

[a] Percentages are based upon the total number of attacks in the ITT for which data were available at 2 hours. 95% CI (L,U) Lower and upper 95% confidence limits of odds ratio of headache response rates for patients treated with zolmitriptan versus patients treated with placebo.

[b] Two patients from the placebo group were not included in the analysis of 2-hour headache response: One patient had missing data at 2 hours; the other patient had taken escape medication before 2 hours when migraine headache pain was mild (these data were considered missing according to the SAP).

ITT Intent to treat.

Source: Sponsor table 13, interim analysis.pdf, page 45.

The response rate for ZNS 5.0 mg using the commercial device (70.4%) is similar to the response rate for ZNS 5.0 mg using the clinical device in trial 077 (68.9%). However the treatment effect between trials is appreciably different. In this trial the treatment effect is 23.4% whereas in trial 077 the difference in response rates between ZNS 5.0 mg (clinical device) and placebo was 38.2%. Most of this difference is accounted for by a lower placebo response rate in trial 077 compared to trial 022 (30.7% in trial 077 vs. 47.0% in trial 022). The reason for the difference in response rates in subjects that received placebo between the two trials is not apparent from my review.

The above sponsor analysis excludes two placebo subjects from the ITT population. One patient due to missing data at the 2 hour time point and a second patient due to the use of rescue medication prior to 2 hours. The following Agency table demonstrates the analysis of the primary endpoint using a "last observation carried forward" analysis and treating subjects that use rescue prior to 2 hours as treatment failures. As can be seen our results are nearly identical to those of the sponsor.

Table 4 Headache Response at 2 hours, ITT Population

	ZNS 5.0 mg N=108	**Placebo N=102**
Patients evaluated at 2 hours	108	102
Patients with 2 hours response (%)	76 (70.4)	48 (47.1)
p-value	0.0006[1]	

1 Chi-Square Analysis using LOCF algorithm and early escape use equal to failure.

The sponsor concludes that ZNS 5.0 mg (using the commercial device) is statistically superior to placebo (p=0.0005) for the treatment of migraine with and without aura. I concur with the sponsor's conclusion.

3.2.3 Secondary endpoint results

Headache response at other timepoints is summarized in the following sponsor table. As can be seen ZNS 5.0 mg was numerically superior to placebo for headache response at all timepoints starting at 15 minutes. This result is consistent with what was seen during trial 077 using ZNS 5.0 mg (clinical device) where actively treated subjects had significantly better response

patients that received placebo in trial 022. As can be seen in the following table the percentage of subjects taking ZNS 5.0 mg reporting resolution of their baseline associated symptoms are nearly identical between trial 022 and trial 077. The reason for the difference in response rates in subjects that received placebo between the two trials is not apparent from my review.

Table 7 Percentage of subjects reporting resolution of associated symptoms, trial 022/077

	Placebo		ZNS 5.0 mg	
	Trial 022	Trial 077	Trial 022	Trial 077
Nausea	60.0	43.7	67.9	60.8
Photophobia	44.2	27.9	58.0	57.7
Phonophobia	53.0	23.3	62.7	62.0

In the following table I present the Agency's analysis of the proportion of subjects reporting each of these associated symptoms at various timepoints. As demonstrated in the table ZNS 5.0 mg was statistically superior to placebo in the proportion of subjects reporting photophobia at 2 hours (p=0.0255). Likewise ZNS 5.0 mg was nearly significantly better than placebo for nausea at 2 hours (p=0.0796) and numerically better than placebo in the proportion of subjects reporting phonophobia (35.6% vs. 26.9%) at 2 hours. Although the results were not significant for all associated symptoms it should be remembered this analysis only includes the first 210 subjects to complete the study. The efficacy of zolmitriptan against the associated symptoms of migraine has been demonstrated in other studies and is not the primary concern of this Interim Analysis.

Table 8 Proportion of patients reporting an associated symptom by time, 1st Attack[1]

		Baseline	15 min	30 min	1 hour	2 hours	4 hours
Nausea							
Placebo N= 102	**n (%)**	41 (40.2)	38 (37.3)	35 (34.7)	25 (25.3)	28 (27.7)	27 (27.0)
ZNS 5.0 mg N= 108	**n (%)**	53 (49.1)	46 (43.0)	36 (33.6)	25 (23.6)	19 (17.6)	18 (17.1)
p-value		0.1960	0.3979	0.8781	0.7811	0.0796	0.0883
Phonophobia							
Placebo N= 102	**n (%)**	67 (65.7)	64 (62.8)	54 (53.5)	44 (44.4)	36 (35.6)	31 (31.0)
ZNS 5.0 mg N= 108	**n (%)**	75 (69.4)	66 (61.7)	55 (51.4)	49 (46.2)	29 (26.9)	15 (14.3)
p-value		0.5608	0.8741	0.7658	0.7979	0.1700	**0.0041**
Photophobia							
Placebo N= 102	**n (%)**	87 (85.3)	82 (80.4)	69 (68.3)	58 (58.6)	50 (49.5)	39 (39.0)
ZNS 5.0 mg N= 108	**n (%)**	88 (81.5)	80 (74.8)	70 (65.4)	55 (51.9)	37 (34.3)	23 (21.9)
p-value		0.4587	0.3302	0.6575	0.3352	**0.0255**	**0.0077**

[1] Using Pearson Chi-Square analysis.

3.3 Efficacy Conclusions

The primary objective of this Interim Analysis of trial 022 is to assess the efficacy of ZNS 5.0 mg (using the commercial device) for headache relief at 2 hours. The sponsor hopes to demonstrate that the efficacy seen with ZNS 5.0 mg using the commercial device is similar to the efficacy seen in trial 077 using the ZNS 5.0 mg in the clinical device in lieu of demonstrating bioequivalence of the two products. As was discussed in my original NDA review of trial 077 all

doses of ZNS using the clinical device were superior to placebo ($p<0.02$ for the first-attack analysis) for headache relief at 2 hours. In both the first-attack and multiple-attacks analyses of trial 077 there was evidence of a dose response for headache response at 2 hours with the highest efficacy seen with the highest dose of ZNS.

In the following table I present a brief overview of the Interim Analysis results of the primary and secondary endpoints of trial 022 presented in this review. The results summarized for the associated symptoms of nausea, photophobia and phonophobia are from the Agency analysis of the proportion of patients reporting each symptom at the various time points. As can be seen in the table, there is clear evidence that ZNS 5.0 mg using the commercial device is superior to placebo for headache relief at 2 hours. Although the treatment effect between trial 077 and 022 are different it appears most of the difference can be accounted for by a higher response rate for placebo in trial 022. The reason for this higher response rate is not clear from my review however it may be due to the small sample size or perhaps due to the nature of the subjects that enter and finish a trial early. Despite this difference in treatment effect between trials the response rates for ZNS 5.0 mg using the commercial device in trial 022 were nearly identical to the response rates for subjects taking ZNS 5.0 mg using the clinical device in trial 077.

For the associated symptoms of nausea, photophobia, and phonophobia there was a clear advantage to ZNS 5.0 mg over placebo in the proportion of subjects reporting each of these symptoms at 2 hours. The proportions of subjects reporting photophobia was significantly lower in subjects randomized to ZNS 5.0 mg than subjects randomized to placebo. The proportion of subjects reporting nausea nearly reached statistical significance in subjects taking ZNS 5.0 mg compared to subjects taking placebo at 2 hours. Finally phonophobia demonstrated a numerical advantage over placebo at 2 hours and a significant difference between cohorts at 4 hours.

Table 9 Brief summary of statistical analysis, ZNS vs. placebo/zolmitriptan tablet 2.5 mg

Endpoint	Comparison of ZNS 5.o mg vs. placebo at various times after treatment (p-values)				
	15 min	30 min	1 hr	2 hr	4 hr
Headache Response					
ZNS 5.0 mg	na	na	na	**0.0005**	na
Nausea (Proportion reporting)					
ZNS 5.0 mg	0.3979	0.8781	0.7811	0.0796	0.0883
Phonophobia (Proportion reporting)					
ZNS 5.0 mg	0.8741	0.7658	0.7979	0.1700	**0.0041**
Photophobia (Proportion reporting)					
ZNS 5.0 mg	0.3302	0.6575	0.3352	**0.0255**	**0.0077**

na: Not analyzed

The sponsor provides the following conclusions relative to efficacy

1. *Zolmitriptan 5-mg nasal spray* [using the commercial device] *was more efficacious than placebo in the treatment of migraine headache with or without aura in adults. Statistical superiority of zolmitriptan was found for the primary endpoint of 2-hour headache response when compared with placebo according to the prespecified Interim Analysis significance boundary of 0.0027.*

2. *The zolmitriptan 5-mg nasal spray group also achieved numerical superiority for headache response at the earlier and later timepoints. The headache response increased consistently at all timepoints from 15 minutes to 4 hours.*
3. *In the subset of patients with migraine-associated symptoms at baseline, the resolution of nausea, phonophobia, and photophobia occurred at numerically higher rates in the zolmitriptan 5-mg nasal spray group for all 3 symptoms at 2 hours. This separation from placebo did not achieve statistical significance; however, the sample size for each group was small.*
4. *These data provide evidence of the efficacy of the zolmitriptan 5-mg nasal spray commercial device.*

My review of the submission results in similar conclusions. Trial 022 was clearly positive for the primary endpoint headache response at 2 hours and clearly demonstrated clinically significant improvement in the proportion of subjects reporting nausea, photophobia and phonophobia at later times. Although the treatment effect using ZNS 5.0 mg in trial 022 using the commercial device was smaller than the treatment effect seen in trial 077 using the clinical devise the actual response rates were nearly identical for the 2 devices. In conclusion, with respect to efficacy, I recommend zolmitriptan nasal spray 5.0 mg be approved for marketing in the United States.

4. Integrated Review of Safety

My original safety review includes the safety results from 5 clinical pharmacology trials, 1 placebo controlled, dose-ranging trial (077), and 2 long-term uncontrolled safety trials (078 and 122). The last safety report update was submitted on 27 June 2002 and was reviewed during my original NDA review.

In this review I will present the safety results from the 4 recently completed pharmacokinetic studies (SA-ZOB-0001, SA-ZOB-0002, 311CJP/0110, and 311CIL/0124) and 2 ongoing, double blinded, placebo-controlled efficacy and tolerability studies (Studies 311CUS/0022 and 311CIL/0120). A brief description of each trial design can be found in section 2.1 of this review. Additionally the sponsor provides a brief discussion of post marketing safety reports from countries where ZNS 5.0 mg is approved (Czechoslovakia, Iceland, Slovakia, Sweden, and the United Kingdom).

The safety data base included in this submission is either blinded or from open label PK studies hence few details will be adequate for labeling purposes unless significant findings are demonstrated. When appropriate the sponsor includes summary results from trial 077 (usually 5.0 mg cohort) in their discussion of safety in order to provide a comparison of results seen in the blinded controlled trials which used ZNS 5 mg (commercial device) only.

The safety monitoring during trial 022 includes a screening physical with a nose and throat examination as well as an ECG, urine pregnancy test, and clinical laboratories (CBC, Comprehensive Metabolic Panel and Urinalysis). Post treatment assessments include an identical evaluation and could occur up to 2 weeks after treatment of the second migraine event. Hence the post treatment laboratory and ECG findings are most likely of minimal importance in assessing the safety of ZNS unless the evaluation occurred very soon after treatment. Adverse

events were recorded if they occurred within 24 hours of treatment unless they were severe or led to withdrawal. The details of the safety monitoring in trial 0120 are not provided by the sponsor but appear to be similar to the monitoring in trial 022.

4.1 Description of Patient Exposure

The exposure data presented in the original ISS included 922 patients treating 2311 migraine attacks with ZNS in controlled clinical trials, and 1584 patients treating 30,819 attacks with ZNS in two long term uncontrolled trials. This new safety update report provides a relatively small amount of additional safety data from the clinical trial program for ZNS collected since the 4-month safety update (submitted to FDA on 27 June 2002) up to the data cutoff date of 31 December 2002.

Overall, new safety data is presented from 121 patients in the 4 pharmacokinetic studies (259 exposures) and 1170 patients from blinded, placebo-controlled studies 0022 and 0120 (2475 exposures). Safety data from the placebo-controlled studies in this update remains blinded and unvalidated; therefore no distinction is made between patients who received 5.0 mg zolmitriptan nasal spray and patients who received placebo. The following sponsor table outlines new patient exposures included in this safety update.

Table 10 New Patient exposures included in safety update report

Study category (N)	Number of exposures to each treatment by study category			
	Zolmitriptan nasal spray	Zolmitriptan tablets	Placebo	Blinded
Clinical pharmacology (121)[a]	168	76	15	0
Placebo-controlled (1170)[b]	0	0	0	2475

[a] Represents data from clinical pharmacology Studies 0001, 0002, 0110, and 0124.
[b] Represents blinded data from placebo-controlled Studies 0022 and 0120.
N Number of patients.
Source: Sponsor Table 1, safetyupdate.pdf, page 18

In the clinical pharmacology studies 89 subjects were given ZNS 5.0 mg, 46 subjects received ZNS 2.5 mg, 21 subjects received ZNS 1.0 mg and 12 subjects received zolmitriptan 10 mg. In trial 022 and 120 all subjects received ZNS 5.0 mg or placebo.

The safety information provided by the sponsor is integrated. Individual study reports for the pharmacokinetic studies and trial 0120 are not provided.

4.2 Patient Demographics

The following sponsor table outlines the baseline demographics of all subjects included in this update. Since the controlled trial are still blinded it is not possible to determine whether the cohorts are balanced however the gender ratio, mean age, and racial breakdown are similar to the demographics I have seen in most controlled clinical trials in migraine. The table demonstrates the demographics of the ongoing, blinded, controlled studies are similar to the demographics from the original trial 077 although there was slightly more non-Caucasian subjects in trial 022 and trial 0120.

Table 11 Demographics of safety update population (all doses).

Demographic characteristic		Study category		
		Clinical pharmacology[a] N=121	Blinded, placebo-controlled[b] N=1170	Study 0077 all doses (N=922)
Gender (n, %)	Women	70 (57.9)	1019 (87.1)	
	Men	51 (42.1)	150 (12.8)	
	Not recorded	0	1 (0.1)	
Age (years)	Mean (SD)	24.6 (6.7)	41.4 (10.3)	40.5 (10.2)
Age group (years) (n, %)	18-40	116 (95.9)	530 (45.3)	443 (48.0)
	>40-60	5 (4.1)	611 (52.2)	468 (50.8)
	>60	0	25 (2.1)	11 (1.2)
	Not recorded	0	4 (0.3)	0
Weight (kg)	Mean (SD)	59.65 (11.47)	71.88 (15.85)	68.5 (13.5)
Weight group (kg) (n,%)	<50	31 (25.6)	23 (2.0)	NAV
	50-80	84 (69.4)	853 (72.9)	NAV
	>80	6 (5.0)	290 (24.8)	NAV
	Not recorded	0	4 (0.3)	NAV
Race (n, %)	White	21 (17.4)	1058 (90.4)	910 (98.7)
	Black	0	75 (6.4)	1 (0.1)
	Other[c]	100 (82.6)	36 (3.1)	11 (1.2)
	Not recorded	0	1 (0.1)	0

[a] Represents data from clinical pharmacology Studies 0001, 0002, 0110, and 0124.
[b] Represents blinded data from placebo-controlled Studies 0022 and 0120.
[c] Other includes Asian (Indian), Asian (Oriental, Japanese), and other races not included in White or Black.
N Number of patients, n Number of patients in category, NAV Not available.
Source: Sponsor table 2, safetyupdate.pdf, page 20.

4.3 Safety Review Findings

The primary source of data for this safety review is the safety update report submitted by the sponsor March 26, 2003. The safety data base was not provided by the sponsor however case reports for serious adverse events and deaths were provided by the sponsor and reviewed by me for this review. Case report forms and individual narratives summaries for adverse events were reviewed as needed. The adverse events discussed in this safety update were coded by the sponsor using MedDRA terminology and methodology. The adverse events in trial 077 were coded using COSTART terminology and methodology. All patient treated with study medication are included in this safety update report between the period of the last safety update report and the 31 December 2002 cutoff date for this safety update report.

4.3.1 Deaths

No deaths occurred in any study discussed in this safety update. No deaths occurred in trial 077.

4.3.2 Serious Adverse Events

There were no serious adverse events reported in any PK/PD study discussed in this safety update.

In the controlled clinical trial 022 and 0120 three subjects (0.3%) reported a serious adverse event within 24 hours of taking study medication. This compares to a 0.4% reporting rate for serious adverse events seen in trial 077. The following table briefly outlines the serious adverse events seen in trial 022 and 0120. None of the events were considered drug related by the investigators involved with the patient. All events are still blinded. My review of the events also suggests the events were unrelated to study medication.

Table 12 Serious Adverse Events within 24 hours of study mediation, Trial 022 and 0120.

Patient ID	Event	Comment
311CIL/0120/3032/3150	Subileus	A 41 year old female developed acute abdominal pain, requiring hospitalization, 30 minutes after treating with study medication. The event was considered unrelated and the subject continued in the study. Rechallenge did not result in similar events.
311CIL/0120/3209/3900	Skull fracture	A 36 year old female experienced a skull fracture secondary to a motor vehicle accident. The event was considered unrelated to study medication.
311CUS/022/0071/0004	Confusional state	A 58 year old female developed "nausea, vomiting, a dazed orientation with respect to time and place, racing thoughts (confusional state) and perspiration" approximately 7 hours after taking study medication. The patient had also taken 2 doses of escape medication (butorphanol nasal spray). The investigator did not consider the event related to study medication. The patient withdrew from the study.

4.3.3 Withdrawals

There were no withdrawals reported in any PK/PD study discussed in this safety update.

The safety update report lists the adverse events that led to withdrawal up to the time of the safety cutoff in the entire population for both trial 022 and trial 0120 . In the controlled clinical trials 022 and 0120, seventeen subjects (1.5%) withdrew from the study due to an adverse event in the all-attack analysis. This compares to a 1.3% withdrawal rate due to an adverse event seen in subjects randomized to ZNS 5.0 mg during trial 077. The following table briefly outlines the withdrawal due to adverse events seen within 24 hours of study drug administration. Other withdrawal not summarized here include 3 subjects that withdrew before taking study medication and a single subject that withdrew due to chest pain eleven day after taking study medication. A review of the events demonstrates no unusual safety concerns.

Table 13 Withdrawal due to AE within 24 hours of treatment (blinded trial 022 and 0120)

Patient ID	Event	Comment
311CIL/0120/2006/2106	Nausea, burning sensation NOS	A 34 year old female developed nausea and burning sensation immediately after treating her 2nd migraine with study medication. The event was rated severe and related to study medication by the investigator.
311CIL/0120/2008/2077	Paresthesia, malaise, somnolence	A 38 year old female developed paresthesia, malaise and somnolence 1 minute after treating a migraine with study medication. The event was considered moderate intensity and related to study medication.
311CIL/0120/3020/3148	Urticaria NOS, exanthema	A 36 year old female developed urticaria after treating her 1st migraine with study medication. The event was considered mild and related to study medication.
311CIL/0120/3025/3113	Nausea, throat and nasal passage irritation, foreign body sensation.	A 41 year old female developed nausea, throat and nasal passage irritation, and foreign body sensation after treating with study medication. The events were considered mild to moderate and related to study medication.
311CIL/0120/3057/3270	Dizziness, headache, neck pain, throat tightness, epistaxis.	A 19 year old female developed dizziness, headache, neck pain, throat tightness approximately 15 minutes after treating a migraine attack. The epistaxis occurred the following day. All events were considered mild to moderate and related to study medication.
311CIL/0120/3076/3354	Dizziness, nausea	A 63 year old female developed dizziness and worsening nausea 10 minutes after treating her 3rd migraine with study medication. The intensity of the events is not stated however the events were considered related to study drug.
311CIL/0120/3077/3367	Malaise, nausea, fatigue, somnolence	A 21 year old female developed malaise, nausea etc soon after treating her 2nd migraine with study drug. The event was considered severe and related to study medication.
311CIL/0120/3079/3376	Anxiety, dysgeusia, throat tightness	A 57 year old female developed dysgeusia and throat tightness 45 minutes after taking study medication. The anxiety occurred approximately 9 hours after taking study medication. The events were considered moderate intensity and related to study medication.
311CIL/0120/3089/3409	Dizziness, anxiety	A 55 year old female developed dizziness and anxiety approximately 2.5 hours after treating her 1st migraine with study medication. The events were considered mild and related study medication.
311CIL/0120/3128/3455	Arthralgia, panic reaction, tachycardia, restlessness, asthenia	A 40 year old female developed asthenia, arthralgia, restlessness and asthenia 4 hours after treating a migraine. Tachycardia and panic reaction occurred approximately 12 hours after treatment. The events were considered mild to moderate and related to study medication.
311CIL/0022/0002/0006	Tiredness	A 22 year old female developed acute tiredness 40 minutes after treating her 1st migraine. The event was considered moderate and related to study medication.
311CIL/0022/0010/0009	Joint aches, increased migraine, nasal congestion, sore throat, throat tightness	A 48 year old female developed severe joint pains, nasal congestion, sore throat, throat tightness and worsening of her migraine 15 to 60 minutes after treatment. The investigator only considered the ENT complaints related to study medication.
311CUS/0022/0018/0003	Serotonin Effect	A 28 year old female developed a moderate "serotonin effect" 2.5 hours after treatment. The event was considered related to study medication. (no other details provided)

4.3.4 Common Adverse Events

The most common adverse events seen during the 4 open label PK/PD studies involving healthy volunteers is summarized in the following sponsor table. Overall for the 76 healthy volunteers exposed to ZNS, 46 subjects (61%) reported an adverse event. Of the 168 ZNS exposures (across all doses, up to 10 mg), 125 (74.4%) exposures had adverse events. The vast majority of adverse events reported in these studies were rated as mild and none were rated as severe. Across all dose groups the most common AE was unusual taste (dysgeusia). No significant dose response for any adverse event is apparent from a review of the incidence rates for each adverse event except for

perhaps fatigue and headache. Fatigue was not reported in subjects receiving ZNS 1.0 mg but was reported in 2.2% of subjects receiving ZNS 2.5 mg and 5.3% of subjects receiving ZNS 5.0 mg. No volunteer receiving ZNS 10.0 mg complained of fatigue however the cohort size is very small. Headache occurred at a similar frequency in the ZNS 2.5 and 5.0 mg cohorts (approximately 15%) but was more prevalent in the ZNS 10 mg cohort (41.7%).

Table 14 All AEs (exposure level) by system occurring in more than 2 volunteers

System organ class[a]	Preferred term (MedDRA)	Zolmitriptan nasal spray[b]				
		1.0 mg (N=21)	2.5 mg (N=46)	5.0 mg (N=76)	5.0 mg[c] (N=13)	10.0 mg (N=12)
		n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions	Fatigue	0	1 (2.2)	4 (5.3)	2 (15.4)	0
Nervous system disorders	Dizziness	0	0	4 (5.3)	0	1 (8.3)
	Dysgeusia	7 (33.3)	35 (76.1)	43 (56.6)	1 (7.7)	6 (50.0)
	Headache	0	7 (15.2)	12 (15.8)	1 (7.7)	5 (41.7)
Respiratory, thoracic, and mediastinal disorders	Cough	0	3 (6.5)	1 (1.3)	0	0
	Intranasal paresthesia	0	5 (10.9)	2 (2.6)	0	0
	Nasal passage irritation	2 (9.5)	0	3 (3.9)	0	0
	Nasopharyngitis	0	0	2 (2.6)	3 (23.1)	0
	Pharyngitis	1 (4.8)	5 (10.9)	4 (5.3)	0	2 (16.7)
	Pharyngo-laryngeal pain	1 (4.8)	3 (6.5)	3 (3.9)	1 (7.7)	0
	Throat irritation	3 (14.3)	0	2 (2.6)	0	1 (8.3)

[a] A patient may have an adverse event reported in more than 1 category.
[b] Represents nasal spray data from clinical pharmacology Studies 0001, 0002, 0110, and 0124.
[c] The 5.0 mg dose of zolmitriptan in this group was given with charcoal.
Note: One subject each in Studies 0110 and 0124 had pre-treatment adverse events, which were ongoing at the time of treatment; these patients are included in the table.
N, n Number of adverse events.
Source: Sponsor table 4, safetyupdate.pdf, page 23

The most common nasopharyngeal adverse events for volunteers in the 2.5 mg nasal spray dose groups were intranasal paresthesia and pharyngitis (each 10.9% of volunteers). Because of the nature of the study (i.e., the addition of charcoal), the most common adverse event in the 5.0 mg plus charcoal dose group was nasopharyngitis (23.1% of volunteers [primarily due to charcoal]); in the ZNS 5.0 mg (without charcoal) dose group, pharyngitis (5.3% of volunteers) was the most common adverse event. The number of volunteers with specific nasopharyngeal adverse events across all dose groups was small. All except a single nasopharyngeal adverse event was reported as mild.

The following sponsor table provides an overview of adverse events seen to date in the placebo controlled trials 022 and 0120. As can be seen there is little difference between reporting rates

and withdrawal seen during these trial compared to the previously completed and reviewed trial 077 (5.0 mg cohort). However care should be made in making this comparison since the reported rates are blended incidence rates for both placebo and ZNS 5.0 mg. Despite this problem there does not appear to be any signal for concern.

Table 15 Overview of AEs in placebo controlled trials

Adverse event category[a]	Blinded Studies 0022 and 0120 First attack	Blinded Studies 0022 and 0120 All attacks		Study 0077 All attacks Patient level
	Patient level (N=1170)	Patient level (N=1170)	Attack level (N=2475)	5.0 mg Zolmitriptan nasal spray (N=236)
	n (%)	n (%)	n (%)	n (%)
All adverse events	385 (32.9)	500 (42.7)	868 (35.1)	116 (49.2)
Drug-related adverse events	325 (27.8)	439 (37.5)	762 (30.8)	109 (46.2)
All serious adverse events	2 (0.2)	2 (0.2)	3 (0.1)	1 (0.4)
Within 24 hours of treatment	1 (<0.1)	2 (0.2)	3 (0.1)	0
Outside of 24 hours of treatment	1 (<0.1)	0	0	1 (0.4)
Drug-related, serious adverse events	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Adverse events leading to withdrawal	14 (1.2)	17 (1.5)	NA	3 (1.3)
Adverse events leading to death	0	0	0	0
Nasopharyngeal adverse events	165 (14.1)	237 (20.3)	384 (15.5)	48 (20.3)
Local irritation or soreness	27 (2.3)	49 (4.2)	74 (3.0)	10 (4.2)

[a] Patients may fall into more than 1 category.

N, n Number of patients. NA Not applicable. Note: One patient (2 attacks) in Study 0120 was listed as having serious adverse events at data cutoff, which were included in the table. After data cutoff, the investigator downgraded these adverse events to nonserious and not drug-related.

Source: Sponsor table 7, safetyupdate.pdf, page 26

The following sponsor table summarizes all adverse events seen in 1% or more of patients that received ZNS 5.0 mg or placebo in trial 022 and 0120. As can be seen in the table the most commonly reported adverse event in trial 022 and 0120 is dysgeusia (MedDRA term) at 14.3%. This compares to 21.2% of subjects receiving ZNS 5.0 mg in trial 077 reporting unusual taste (COSTART term for dysgeusia). Other common adverse events included dizziness, nasal passage irritation, and throat irritation. In general the reporting of each adverse event was similar between trial 022 and 0120 compared to trial 077 although a direct comparison is complicated by the fact the studies used different coding dictionaries and trial 012 and 022 are blended results of both placebo and ZNS 5.0 mg cohorts. Despite this problems there does not appear to be any new safety concerns apparent from this comparison.

Table 16 All AEs in placebo controlled studies occurring ≥1% of patients by system

System organ class	Preferred term (MedDRA)	Blinded studies 0022 and 0120		
		First attack (N=1170)	All attacks Patient level (N=1170)	All attacks Attack level (N=2475)
		n (%)	n (%)	n (%)
Gastrointestinal disorders	Dry mouth	15 (1.3)	21 (1.8)	25 (1.0)
	Dysphagia	11 (0.9)	20 (1.7)	35 (1.4)
	Nausea	21 (1.8)	50 (4.3)	60 (2.4)
	Vomiting NOS	6 (0.5)	13 (1.1)	15 (0.6)
General disorders and administration site conditions	Asthenia	12 (1.0)	18 (1.5)	23 (0.9)
	Fatigue	30 (2.6)	43 (3.7)	55 (2.2)
Musculoskeletal and connective tissue disorders	Arthralgia	8 (0.7)	14 (1.2)	16 (0.6)
	Sensation of heaviness	10 (0.9)	13 (1.1)	17 (0.7)
Nervous system disorders	Dizziness	48 (4.1)	70 (6.0)	85 (3.4)
	Dysgeusia	111 (9.5)	167 (14.3)	308 (12.4)
	Headache	9 (0.8)	19 (1.6)	22 (0.9)
	Hypoesthesia	8 (0.7)	14 (1.2)	19 (0.8)
	Paresthesia	18 (1.5)	25 (2.1)	35 (1.4)
	Somnolence	18 (1.5)	29 (2.5)	33 (1.3)
Respiratory, thoracic, and mediastinal disorders	Dry throat	9 (0.8)	13 (1.1)	18 (0.7)
	Nasal passage irritation	45 (3.8)	72 (6.2)	103 (4.2)
	Pharyngitis	19 (1.6)	32 (2.7)	51 (2.1)
	Rhinorrhea	17 (1.5)	25 (2.1)	37 (1.5)
	Throat irritation	49 (4.2)	75 (6.4)	118 (4.8)
	Throat tightness	11 (0.9)	17 (1.5)	23 (0.9)

N, n Number of patients.
Source: Sponsor table 8, safetyupdate.pdf, page 28.

The intensity of the adverse events reported above were similarly distributed as the intensity of adverse events reported in trial 077. Specifically 63% of the reports (all attack level) were reported as mild, 27% were reported as moderate, and 9% were reported as severe in trial 022 and 0120. Likewise the mean duration of all adverse events were similarly distributed between trial 0120/022 and trial 077.

A subgroup analysis of adverse events by gender demonstrates that women have an overall higher incidence of adverse events then men. (35.8% vs. 30.6% respectively). These results are

again similar to the findings seen in trial 077 where 39.5% of the women and 30.6% of the men receiving ZNS 5.0 mg reported an adverse event. Although the reporting rates were higher in general in women the sponsor states there were no significant gender differences for adverse events reported by preferred term between genders. Women appeared to report more adverse event categories than men and women reported dizziness and fatigue somewhat more frequently (3.8% and 2.6%, respectively, for all attack data) than men (1.2% and 0%, respectively). In Study 0077, women reported a slightly higher incidence of asthenia, nausea, hyperesthesia, and unusual taste than men. None of the reported difference appears to be clinically relevant.

A subgroup analysis of all adverse events by age (< 40 years of age vs. ≥ 40 years of age) and weight (<50 kg vs. ≥50 kg) demonstrates no clinically relevant difference in trends between populations. Similarly, a subgroup analysis of all adverse events by race demonstrates no clinically relevant difference in trends between populations although the non-Caucasian population was very small (6% Black, 4% other). These findings are similar to the results seen in trial 077.

4.3.5 Clinical Laboratories

The sponsor does not present any clinical laboratory data for review. No laboratory data were collected for trial 0120 and data available for trial 0022 was minimal at the data cutoff date for the Safety Update Report and were not considered by the sponsor to represent a meaningful sample. Since most laboratory data is collected days and weeks after treatment its relevance in the setting of acute treatment is limited.

4.3.6 Vital Signs

The available vital sign data from trial 022 demonstrates no clinically significant changes in vital signs between visit 1 and visit 2 for the patients evaluated. To date 5 patients (1.1%) had a least 1 abnormal value: 4 patients has systolic blood pressure ≤90 mm HG with a ≥20 mm HG decrease from baseline and 1 patient had a heart rate of ≥120 beats/minute and a ≥15 beats/minute increase from baseline.

4.3.7 Electrocardiogram

For those patients in blinded study 0022 who had at least 1 ECG assessment performed and provided data at the cutoff date, 288 (65.9%) had at least 1 post-baseline 12-lead ECG done. Of the 288 patients, 11 (3.8%) patients had treatment-emergent ECG abnormalities. A review of the data listings (table G5, safety update) for ECG findings at the follow up visit demonstrates no clinically significant malignant dysrhythmias (mostly non-specific t-wave abnormalities and sinus bradycardia).

4.3.8 Nose and Throat Examination

Of the 290 patients from trial 022 who had at least 1 post treatment nose and throat assessment, 17 (5.9%) had at least 1 treatment emergent abnormality. A review of the data listings (table G4, safety update) demonstrates the vast majority of the findings were consistent with an upper respiratory tract infection. None of the abnormalities warranted referral to a specialist for evaluation or follow up.

4.3.9 Post-Marketing Safety Data

Zomig Nasal Spray 5.0 mg is currently marketed in Austria, Germany, Sweden and the United Kingdom. The sponsor estimates that in 2002 there were approximately —— patient exposures to ZNS. The sponsor's search of the Clin Trace safety database failed to locate any reports of adverse events associated with the use of ZNS.

4.4 Summary of Critical Safety Findings and Limitations of Data

In the four clinical pharmacology studies there were no deaths, serious adverse events, or withdrawal due to adverse events in any healthy volunteer involving 244 exposures. Across all nasal spray doses the most common adverse event was dysgeusia. Interestingly the incidence of adverse events did not demonstrate a dose response with ZNS 2.5 mg having the highest incidence rate (87.0%) compared to 73.7% for ZNS 5.0 mg and 83.3% for zolmitriptan 10.0 mg. The vast majority of adverse events were mild in intensity and of short duration.

In the two controlled and blinded clinical trials (022 and 0120) the safety experience reported to date appears similar to the safety experience I previously reviewed for the full NDA. The sponsor uses the safety results from the cohort of subject receiving ZNS 5.0 mg (using the clinical device) in trial 077 as their primary comparison group for safety. A comparison of the blinded safety data from trial 022 and trial 0120 compared to trial 077 fails to demonstrate any new safety signals. However we must be careful when making this comparison since the two new trials are still blinded relative to safety, are still ongoing, and use a different terminology/methodology system to code adverse events than trial 077 (trial 077 used COSTART, trial 0120 and 022 uses MedDRA).

In the two blinded placebo controlled trial using ZNS 5.0 mg (commercial device) there were no deaths and very few serious adverse events (3 to date, all unrelated to treatment). Withdrawal rates have been reasonable and comparable to withdrawal seen in trial 077 (approximately 1%). The common adverse events seen in trial 022 and 0120 appear to be similar in nature and incidence rates to the adverse events reported in trial 077. The most common adverse events was dysgeusia (unusual taste) in all studies (generally around 20%). Other common adverse events include dizziness, nasal passage irritation, and throat irritation. For approximately 60% of exposures ZNS 5.0 mg did not result in any adverse event being reported. For the remainder the reports were generally mild to moderate and short duration. Subgroup analysis by age, gender, weight and race did not demonstrate any clinically significant differences between cohorts.

For first attack and all attacks, the most common nasopharyngeal adverse events in Studies 0022 and 0120 were nasal passage irritation (6.1%) and throat irritation (6.4%). In Study 0077, the most common nasopharyngeal adverse events after treatment with ZNS 5.0 mg were paresthesia (7.6%) and pain in throat (3.8%). For those patients who had nasopharyngeal adverse events, most were brief and of mild intensity.

Overall my review of the safety update report does not find any new safety concerns relative to the use of ZNS 5.0 mg using the commercial device. Since the majority of safety data provided in this safety update report is blinded or from open label uncontrolled PK/PD studies the new safety information is generally unacceptable for labeling purposes.

efficacy of zolmitriptan against the associated symptoms of migraine has been demonstrated in other studies and is not the primary concern of this Interim Analysis.

- The Interim Analysis of trial 022 supports the sponsor's contention that ZNS 5.0 mg in the commercial device is as efficacious as ZNS 5.0 mg using the clinical device in trial 077.

Relative to the safety of ZNS 5.0 mg (commercial device) I provide the following conclusions:

- Zolmitriptan nasal spray 5.0 mg using the commercial device appears to be well tolerated in the four clinical PK/PD and two placebo-controlled, blinded studies presented in this safety update. Although much of the data is still blinded and the controlled studies are still ongoing there does not appear to be any significant difference in the nature of adverse events reported compared to the previous safety information reviewed for this NDA.
- Serious adverse events were rare (0.3%) in this safety update and did not appear to be drug related.
- Withdrawal from the controlled clinical trials due to an adverse event was uncommon (1.5%) and similar to the rate seen in trial 077 (1.3%).
- Adverse events of all types, including nasopharyngeal adverse events, were typically mild-to-moderate, transient, and resolved without intervention.
- The types of adverse events seen were mainly known pharmacological effects of triptans (ie, paresthesia) or typical of drugs administered via the nasal route (ie, dysgeusia), and were consistent with those seen before in the zolmitriptan nasal spray clinical development.

The risk benefit evaluation is discussed in my original review and will not be repeated here other than stating the risk benefit equation favors the approval of ZNS 5.0 mg for the acute treatment of migraine.

6.2 Recommendations

From a clinical perspective I recommend the approval of Zomig Nasal Spray (zolmitriptan) 5.0 mg using the commercial device for the acute treatment of migraine with and without an aura.

7. Appendix

Appendix 1: List of Tables

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/s/

Kevin Prohaska
7/23/03 04:19:02 PM
MEDICAL OFFICER

Armando Oliva
7/24/03 01:35:38 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21450(000)**
Sponsor:	**AstraZeneca**
Drug:	**Zomig Nasal Srpay (zolmitriptan)**
Proposed Indication:	**Migraine**
Material Submitted:	**Revised labeling, edr \\Cdsesub1\n21450\N_000\2002-11-22**
Correspondence Date:	**11/22/02**
Date Review Completed	**12/9/02**
Reviewer:	**Kevin Prohaska, D.O.**

1. Introduction

The sponsor submits revised labeling to address multiple obvious formatting problems found in the previous revised labeling submitted November 5, 2002.

2. Label Review

2.1 Draft Retail Carton

The sponsor provides a copy of the Draft Retail Carton and immediate product label for each dose of Zomig Nasal Spray under "labeling" of the original submission (2/27/02). The proposed Retail Carton and immediate product label appear adequate.

2.2 Draft Professional Package Insert

As previously discussed in my original review of the label (Appendix B, NDA Clinical Review) the sponsor used the Zomig Tablet package insert as the template for the ZNS package insert and this is acceptable. An annotated version of the differences, with referenced explanations of the changes between the two labels can be found at the beginning of summary.pdf (2/27/02). On November 5, 2002 the sponsor submitted a supplement to the NDA application to provide for revised package insert. The intent of the update was to allow for consistency across zolmitriptan labels and included the addition of anaphylaxis and ischemic colitis to the post-marketing experience section. However the November 5, 2002 revised labeling has multiple formatting issues and has been replaced with the revised labeling contained in the November 22, 2002 submission. Additionally, this most recent label includes one change not contained in the November 5, 2002 submission. The NDC number has been updated due to a recent change. For the purposes of my review I used the annotated cross-referenced version of the package insert contained in "summary.pdf" as a tool to orient me to the sponsor's rationalization for each change however the supplement dated November 22, 2002 has the most recent proposed label. All page numbers referenced in the following sections refer to the final non-annotated clean version of the package insert, which can be found in "clean.pdf" (November 22, 2002).

2.2.1 Description

This section contains modifications to the description appropriate for the nasal formulation. I have no comments and defer to the chemistry reviewer for any recommended changes to this section.

2.2.2 Clinical Pharmacology

The sponsor maintains the ADME format used in the approved Zomig Tablet Label with changes appropriate for the nasal formulation. The format is acceptable and the changes are appropriately referenced.

- Under Clinical Pharmacokinetics and Bioavailability, page 3, the spacing between the first and second paragraph ("Food has no...") is missing
- Under special populations, Hypertensive Patients, I recommend the following clarification:

  From:

  To: "No differences in the pharmacokinetics of oral zolmitriptan or its effects on blood pressure were seen in mild to moderate hypertensive volunteers compared to normotensive controls."

This information is derived from clinical pharmacology study 013 in which oral doses of zolmitriptan up to 20 mg were given to volunteers with mild to moderate hypertension[1].

I have no other comments and defer to the biopharmaceutics review for any additional recommended changes to this section.

2.2.3 Clinical Studies

This section has been extensively rewritten to reflect the information derived from Study 077. All data is well referenced by the sponsor. However I have the following recommendations:

- In the first paragraph the following change is recommended:

  From:

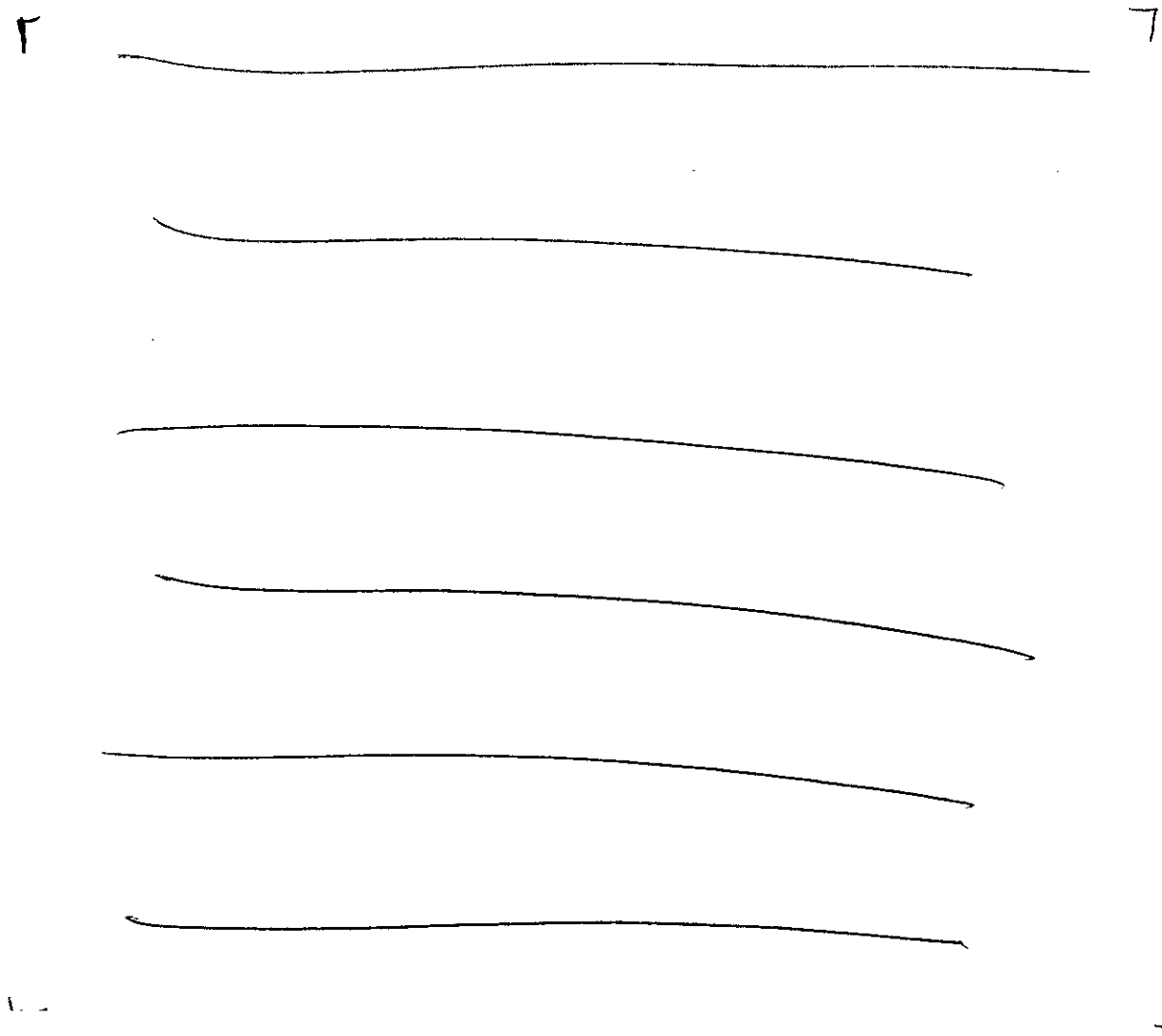
  To: "...placebo-controlled trial."

  The ZNS formulation used in Trial 077 included a different device than what is to be marketed.
- Table 1 depicts the results of the sponsor's multiple attacks analysis. The sponsor should use the data from their first attack analysis (Table 10, 1st attack analysis, page 31/295)

We should consider limiting the above table to the 2-hour time point only. This would be consistent with what is found in the Zomig Tablet and Zomig-ZMT Tablet labels. Likewise the labels for Imitrex Nasal, Frova, and Axert report only 2 hour results. The label for Imitrex Tablets reports 2 and 4 hours results and the label for Amerge reports only 4 hour results. The only label that reports early results for headache response is Imitrex Injection, which reports 10 minutes, 30 minutes, 1 hour, and 2 hour results

[1] Source: Dr. Armando Oliva's NDA 20768 (Zomig Tablet) review, page 16.

- To improve clarity I recommend the following revision to the proposed text (page 8, clean.pdf):



2.2.4 Indications and Usage

This section contains a modification to the product name appropriate for the nasal formulation and is acceptable.

2.2.5 Contraindications

The sponsor proposes no changes from the Zomig Tablet Label for this section. The proposed wording is acceptable.

2.2.6 Warnings

This section contains few modifications to the original Zomig Tablet label.

- Under the subsection "*Premarketing experience with zolmitriptan*" the sponsor adds information that there were no deaths or serious cardiac events reported in Trial 077. This change is acceptable.

- The sponsor adds a new subsection entitled "Local Adverse Reactions" to describe the nasopharyngeal effects seen during Trial 077. The content of the information is acceptable however I would recommend the following statement be added after the sentence ending "...approximately 60% resolved in 1 hour".

  "Nasopharyngeal examinations, in a subset of patients participating in two long term trials of up to one year duration, failed to demonstrate any clinically significant changes with repeated use of Zomig Nasal Spray."

- [redacted]

2.2.7 *Precaution*

This section contains modifications appropriate for the nasal formulation. The content changes are acceptable. The subsection "Carcinogenicity, Mutagenicity, Impaired Fertility" include new information derived from the preclinical studies using zolmitriptan nasal spray. The additional information appears acceptable however I defer to the pharmacotoxicology reviewer for additional comments.

2.2.8 *Adverse Reactions*

This section was extensively rewritten by the sponsor to reflect the data obtained from the clinical development program for Zomig Nasal Spray.

- [redacted]

- On page 19 the statement [redacted] should be changed to "The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age (18 – 39 vs. 40 – 65 years of age) of patients, or presence of aura".
- Under "Urogenital" (page 21) change [redacted] to the more common abbreviation, "PAP smear", for a Papanicolaou smear.

2.2.9 *Dosage and Administration*

This section has been extensively rewritten from the oral Zomig label to reflect prescribing information for Zomig Nasal Spray. The changes are acceptable.

2.3 *Draft Patient Information Sheet*

As with the profession package insert the sponsor submits a revised Patient Information Sheet for Zomig Nasal Spray electronically under "clean.pdf" (page 25, November 22, 2002 submission) to correct the multiple formatting problems seen in the November 5, 2002 submission. The sponsor used the Zomig Tablet Patient Information sheet as the template for the ZNS Patient Information sheet and this is acceptable. An annotated version, with referenced explanations of the changes between the two labels can be found in summary.pdf (page 37) of the original submission (February 27, 2002).

Most of the changes involve appropriate modifications needed for the ZNS formulation and are acceptable. However I recommend the following:

- [redacted]

Kevin Prohaska, D.O.
Medical Reviewer

A. Oliva, M.D. _____

cc:
HFD-120
NDA 21450

APPEARS THIS WAY
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/s/

Kevin Prohaska
12/16/02 02:49:57 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Clinical Review Cover Sheet

NDA:	21-450
Sponsor:	AstraZeneca
Drug:	Zomig (zolmitriptan) Nasal Spray
Proposed Indication:	Acute Migraine
Materials Submitted	Original NDA (edr \\CDSESUB1\N21450\N_000
Correspondence Date:	February 27, 2002
Date Received	February 28, 2002
Date Review Completed:	December 6, 2002
Division:	Division Of Neuropharmacological Drug Products
Reviewer:	Kevin Prohaska, D.O.

Table of Contents

Executive Summary Section

Clinical Review for NDA 21-450

Executive Summary

1. Background

The active moiety in Zomig Nasal Spray (ZNS), zolmitriptan, is the same active moiety found in Zomig Tablets (2.5 and 5.0 mg) approved by the Agency on November 25, 1997 (NDA 20-768) for the acute treatment of migraine with and without and aura in adults. Zolmitriptan is a selective 5-$HT_{1B/1D}$ receptor agonist (a.k.a. triptans) that has been developed for the acute treatment of migraine with and without an aura. Extensive clinical experience and multiple clinical trials has demonstrated that oral zolmitriptan is typical of members of its class in its risk/benefit profile.

The sponsor's rationale for developing a nasal formulation is to provide migraine patients with an alternative treatment option when oral zolmitriptan may not be appropriate. Studies have shown that oral absorption of triptans is diminished during an acute migraine attack due to the gastroparesis often seen during a migraine attack. It is the sponsor's belief that a nasal formulation of zolmitriptan might provide improved absorption and earlier efficacy than oral zolmitriptan with an acceptable adverse event profile. A pharmacokinetic study utilizing PET scans demonstrated that zolmitriptan nasal spray is to a great extent directly absorbed through the nasal mucosa (see section 3.1.5).

As agreed to by the Division, the clinical development program consists primarily of a single short-term efficacy trial (Trial 077) and two long-term safety trials (Trial 078 and 0122). Trial 077 demonstrates that ZNS 0.5, 1.0, 2.5 and 5.0 mg (all doses tested) was effective for Headache Relief at 2 hours (the pre-stated primary endpoint) using the sponsor's results. The sponsor seeks approval of ZNS 5.0 mg

The most common adverse events seen during the clinical development program for ZNS was bad taste in the mouth or unpleasant local sensations, however these were generally mild, self-limited and rarely led to discontinuations in the clinical trials. The incidence of serious adverse events (e.g., cardiovascular) was low in the ZNS clinical program and was no greater than what was seen during the Zomig Tablet clinical development program. The two long-term trials failed to demonstrate any additional safety concerns with repeated use over a 1 year period.

1.1 Recommendation on Approvability

Considering the favorable risk-benefit balance seen with oral zolmitriptan use in migraine, and based on efficacy and safety data reviewed for this NDA, and from a clinical perspective I recommend approval of Zomig (zolmitriptan) Nasal Spray 5 mg, NDA 21-450) for the treatment of acute migraine with and without an aura in adults. My recommendations for changes to the proposed label are contained in Appendix B.

Executive Summary Section

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

The Sponsor has been granted a deferral for the pediatric migraine indication by agreement with the Agency.

. However the sponsor informs us they plan the following clinical trials using Zomig Nasal Spray in the near future (some may have already begun):

1. **Trial 311CIL/0120**: A multicenter, randomized, 2-phase study to assess the efficacy, safety, and patients' satisfaction with ZNS 5.0 mg in the acute treatment of a single migraine when taken as required by the patient. This is a multinational trial (non-U.S.) scheduled to begin in April 2002. Phase 1 of the study is a double-blind, placebo-controlled, parallel-group evaluation of the efficacy of ZNS 5.0 mg in a single migraine attack. Phase 2 is an open-label assessment of safety and patient satisfaction with ZNS 5.0 mg during the treatment of 3 attacks.
2. **Trial 311CUS/0022:** A multicenter, randomized, placebo-controlled, double-blind, parallel-group trial to evaluate the efficacy and tolerability of ZNS 5 mg in the acute treatment of adult subjects with migraine. This US trial was scheduled to begin in June 2002. Its primary objective is to assess whether ZNS 5.0 mg provides early relief (15 minutes) compared to placebo (protocol submitted July 29, 2002 to IND 53848, serial 029).
3. **Trial 311CIL/0121:** A trial to evaluate ZNS in the treatment of cluster headache. Protocol development is in progress.

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The clinical development plan for Zomig Nasal Spray included in this NDA consists of 1 placebo controlled efficacy study (Trial 311CIL/0077), 2 open-label, long-term safety studies (Trial 311CIL/0078 and 311CIL/0122), and 5 pharmacology studies (Trials 0032/GW, 311CIL/0041, 311CIL/0079, 311CIL/0102, and 311CIL/104). Since zolmitriptan is already approved in other formulations and has been well studied the Division agreed that efficacy of the nasal spray could be based on a single well conducted, controlled, clinical trial (311CIL/0077, hereafter 077).

The five pharmacology studies consists of 81 healthy subjects receiving ZNS up to 10 mg as a single or multiple dose. Trial 077 treated 1547 patients with moderate to severe migraine (with and without aura), equally randomized to placebo, ZNS 0.5 mg, ZNS 1.0 mg, ZNS 2.5 mg, ZNS 5.0 mg and zolmitriptan tablets 2.5 mg, treating up to three migraine attacks. Trial 078 is an open-label, long-term (1 year) extension of Trial 077 in which 1097 subjects were initially randomized to receive ZNS 0.5, 1.0, 2.5 or 5 mg however all subjects were crossed over to ZNS 5 mg once the safety results from Trial 077 were known. Trial 0122 is an ongoing, open-label, long-term safety (1 year) study in which 536 subjects treat their migraines with ZNS 5.0 mg. In all, this program consists of approximately 2500 unique individuals receiving over 30,000 doses

of ZNS. This amount of data provides substantial evidence for the evaluation of safety and efficacy of ZNS in the treatment of acute migraine with and without aura in adults.

In addition to the clinical development plan cited above the sponsor also relies on the data derived from the clinical development program for Zomig Tablet and Zomig-ZMT (fast disintegrating oral formulation). Zomig Tablet (2.5 and 5.0 mg) was approved on November 25, 1997 (NDA 20-768) and Zomig-ZMT (2.5 mg) was approved on February 13, 2001 (NDA 21-231). In all, there were 31 clinical trials involving 4003 unique subjects supporting the approval of Zomig Tablets and an additional trial involving 380 patients supporting the rapidly dissolving oral tablet (Zomig ZMT).

As summarized above, zolmitriptan has been extensively studied for the indication of acute migraine with and without aura in adults. Additionally, a few studies have been conducted using zolmitriptan tablets in menstrually associated migraines and in adolescents with migraine. Overall, about 35,000 subjects have been exposed to zolmitriptan (all formulations) in clinical trials[1]. Based on sales figures, the Sponsor estimates the drug exposure to be approximately 1,603,000 patient-years between March 1, 2001 through February 2002[2].

2.2 Efficacy

The single efficacy trial, Trial 077 (N=1547), demonstrates that Zolmitriptan Nasal Spray (5.0, 2.5, 1.0 and 0.5 mg) is effective, compared to placebo, in the treatment of migraine with and without an aura. The primary endpoint of the trial was headache response at two hours. For the primary endpoint and most secondary endpoints there was clear evidence of a positive dose response, with increasing efficacy seen with increasing dose of ZNS. The trial also included a zolmitriptan tablet arm in order to determine whether ZNS provided additional benefit over the already approved zolmitriptan product.

All doses of ZNS studied demonstrated a statistically significant difference favoring ZNS, compared to placebo, for the proportion of patients reporting headache response at 2 hours ($p \leq 0.0223$ 1st attack analysis, $p<0.001$ multiple attacks analysis, see Table 11) using the sponsor's analysis. Similar results were seen using the Agency's analysis however the ZNS 0.5 mg cohort results ($p=0.053$) were slightly outside the predefined alpha of 5 percent. Generally there was evidence of a dose response, with increasing benefit seen with increasing dose.

For the multiple secondary endpoints there was a clear advantage for ZNS 5.0 mg and ZNS 2.5 mg over placebo. ZNS 1.0 and 0.5 mg also demonstrated improved efficacy over placebo however often at a later time point than what was seen for the higher doses of ZNS (typically by 2 hours). For the secondary endpoints of the proportion of patients reporting a photophobia, and phonophobia at various time points, all doses of ZNS performed quite well compared to placebo even as early as 15 minutes. For the secondary endpoint of the proportion of patient reporting nausea at various time points, only ZNS 5.0 mg demonstrated superiority over placebo at 2 hours. However efficacy over placebo was demonstrated for all ZNS doses at 4 hours. A detailed discussion of each secondary endpoint can be found in section 6.3.4.

[1] Source: Annual Report, NDA 20-768, 4/30/02, page 8
[2] Source: Annual Report, NDA 20-768, 4/30/02, page 9.

In discussing the results from these secondary analyses the Sponsor tends to stress how ZNS 5.0 mg is superior to zolmitriptan tablet 2.5 mg. However on dose for dose basis ZNS 2.5 mg failed to demonstrate any clinical benefit over zolmitriptan tablet 2.5 mg for most endpoints evaluated. A notable exception was for the endpoint headache pain relief at various times. ZNS 2.5 mg was superior to zolmitriptan tablet 2.5 mg for pain relief at 15 minutes (p=0.0303) however this finding was not sustained at 30 minutes or beyond and as such has little clinical implications.

In summary, Trial 077 demonstrates that all doses of ZNS were statistically superior to placebo for the primary endpoint of headache relief at 2 hours and for most secondary endpoints. The differences in responses are clinically relevant. ZNS 2.5 mg provides little clinical benefit over zolmitriptan tablet 2.5 mg. There is some suggestion that ZNS 2.5 mg may provide an earlier benefit for headache response compared to oral zolmitriptan 2.5 mg however this benefit does not appear to be sustained.

2.3 Safety

The safety of ZNS was evaluated in 8 trials involving 2536 individuals and over 30,000 doses. Of these 8 trials, 5 are pharmacology trials involving healthy volunteers and 3 are trials involving migraine patients. The 3 patient trials include the one efficacy trial cited above and 2 long-term, open-label safety trials. All ZNS trials include the same safety monitoring that was used in studies in support of zolmitriptan tablet (NDA 20-768) plus additional examinations of the nose and throats of those patients using ZNS long-term. These trial data therefore provide a fairly large safety population with adequate monitoring. Since very few adverse events (none serious) occurred during the 5 pharmacology trials, the bulk of my safety review will concentrate on the 3 clinical trials. In general, ZNS was well tolerated in all studies.

A combined total of 52 serious adverse events (0.2% of all exposures) occurred during Trial 077, Trial 0122 and Trial 078 with the majority (79%) occurring with an onset greater than 24 hours after trial drug administration. A discussion of serious adverse events with an onset after 24 hours is contained in the text of this review however due to the lack of temporal relationship to study medication and the nature of the event it is unlikely they were caused by ZNS. A serious adverse event within 24 hours of dosing occurred in 1 patient (0.1%) in Trial 077 and in 10 patients (0.8%) in the long term trials 078 and 0122. Only 2 of these events are likely to have been caused by ZNS, patient 0122/0001 experienced severe nausea and vertigo 23 hours after treatment with ZNS 5 mg, and patient 122/0005 experienced angina pectoris 15 minutes after treatment with ZNS 5 mg. A discussion of each of these events can be found in section 7.4.3. However there was no individual type of SAE that occurred in more than one patient and there was no evidence of serious adverse events becoming more frequent with increasing duration of treatment.

Adverse events (AEs) leading to withdrawal occurred in 0.7% in Trial 077 and in 2.8% in the 2 long-term safety trials. In none of the studies were there any apparent trends in withdrawal to suggest a problem with ZNS.

Common systemic adverse events (nausea, dizziness, paresthesias) with ZNS are similar in their intensity and frequency to those seen during the clinical trials for zolmitriptan tablet. The most

common adverse events seen with zolmitriptan nasal spray were due to its local effect in the nasopharynx and included "unusual taste", local paresthesia, throat pain and disorder/discomfort of the nasal cavity. The overall incidence of adverse events for ZNS increase in dose-related manner, as is seen with the zolmitriptan tablets. Up to 21.2% of patients treated with ZNS 5.0 mg complained of unusual taste and 7.6% of patients in the 5 mg dose group complained of paresthesia. Throat pain and disorder/discomfort of the nasal cavity occur less frequently. The majority of nasopharyngeal events at all doses resolved within 1 hour. Local irritation and soreness of the nasopharynx is dose-related and occurred in 2.9% of patients in controlled trials and resolved in about 4 hours. Systematic nose and throat evaluations conducted in a subset of patients undergoing long-term treatment showed no indication of clinically significant effects. Local effects were rarely rated as severe and generally did not result in withdrawal.

In the long-term trials there was no evidence of change in frequency, type, seriousness, or duration of AEs with increasing duration of treatment. Local irritation of nasopharynx was seen in 10.7% of patients in long-term trials, but only in 3.2% of attacks in long-term use. The incidence of AE's was not affected by gender.

The safety profile of ZNS is similar to that of the oral formulation of zolmitriptan with the added AEs of local nasopharyngeal complaints, but no increase in serious AEs. At all ZNS doses, all adverse events were typically mild and transient. Zolmitriptan nasal spray at the dose range studied (up to 10 mg in Study 136-032) did not reveal any clinically significant cardiac effects, changes in clinical laboratories, or changes in ECGs. The incidence of adverse events was not affected by gender, weight, or the presence of rhinitis. There was insufficient experience in non-Caucasian, geriatric or pediatric populations to assess the impact of race and age on the incidence of adverse events.

In summary, the eight clinical trials using ZNS demonstrate a safety profile consistent with that in the original NDA for the conventional oral tablet. Zolmitriptan Nasal Spray was well tolerated in the dose range studied (0.5 mg to 5.0 mg) during the three clinical trials. The overall incidence of adverse events increased in a dose-related manner, however serious adverse events and adverse events leading to withdrawal occurred in very few patients. There is no evidence to suggest that in widespread use, the tolerability profile of ZNS will differ from that of the conventional oral tablet except for the local nasopharyngeal effects. Therefore, the safety section of the prescribing information for the nasal spray and conventional oral tablet formulations should, in general, be similar but will require the addition of events related to the route of administration (e.g., unusual taste) to the list of most frequently reported events.

2.4 Dosing

The sponsor proposes in the label to dose ZNS [redacted] 5.0 mg at the onset of a migraine with and with an aura. Retreatment for migraine recurrence or treatment failure may occur at 2 hours after initial treatment if needed. Subjects should not take more than 10 mg of zolmitriptan in any form in any 24 hour period. This regimen is similar to the regimen found in the Zomig Tablet and Zomig-ZMT package insert.

Executive Summary Section

The safety and efficacy of ZNS in doses up to 5 mg was demonstrated in Trial 077. The safety of ZNS as a single 10 mg dose was demonstrated in Trial 136-032. The long-term safety of repeat dosing at 2 hours with ZNS 5 mg is demonstrated in Trial 0122.

The five pharmacokinetic trials for ZNS suggest that the regimen proposed is appropriate. ZNS has the same distribution, metabolism and elimination as Zomig Tablet. ZNS is directly absorbed through the nasal mucosa with a 41% bioavailability (compared to 40% for Zomig Tablet). Within 5 minutes of nasal administration zolmitriptan can be detected in plasma and about 40% of Cmax is reached by 10-15 minutes. Peak concentrations are reached in about 3 hours and plasma concentration is sustained for 4-6 hours after dosing. There appears to be no accumulation with repeat dosing and zolmitriptan displays predictable linear kinetics after multiple doses of 2.5 mg, 5 mg, or 10 mg.

Zolmitriptan tablet and nasal spray is metabolism by the liver to an active N-desmethyl metabolite. The metabolite's potency is 2-6 times that of the parent. The mean elimination half-life for zolmitriptan and the active metabolite after nasal spray administration are 3 hours, which is similar to the oral tablet.

Effects of impaired renal and hepatic function were not evaluated in the clinical program for ZNS however caution in dosing is recommended in the label. Effects of size, weight, gender, and race on metabolism were not evaluated.

The coadministration of sympathomimetic nasal decongestant with ZNS was evaluated in Study 311CIL/0102. The study was designed to determine whether the vasoconstrictive properties of decongestants would alter the absorption of ZNS. Intranasal absorption of ZNS was neither delayed nor reduced by coadministration of the decongestant.

Overall the pharmacokinetics, metabolism, and elimination profiles of ZNS are similar to the tablet formulation hence the proposed dosing regimen appears reasonable to this reviewer.

2.5 Special Populations

Because over 98% of the participants in the ZNS trials were Caucasian, no conclusions can be drawn about efficacy or safety among different ethnic or racial groups. Over 80% of the participants were women, reflecting the natural predilection for migraine in women. When the 234 men are analyzed separately for the same primary endpoints for efficacy, the result was the same as that obtained for women. Likewise, when men are analyzed separately for AEs, the nature and frequency of AEs is the same as for women.

Elderly and pediatric patients were not enrolled in the clinical trials for ZNS therefore no conclusion can be drawn about safety and efficacy of ZNS in these populations. Currently the 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[3] submitted on March 22, 2000, the Division agrees to allow the Sponsor to defer studies of Zomig Nasal Spray in

[3] IND 53,848, Serial 015

pediatrics until the safety and effectiveness of Zomig Tablets have been evaluated in adolescents.

There is no data on the efficacy and safety of ZNS in patients with hepatic or renal impairment.

There were 18 pregnancies reported in subjects who were administered ZNS during the long term trials. Of these 18 pregnancies, there were 10 normal births, 5 elective terminations (including 1 subject where an ultrasound examination at the end of the first trimester revealed a fetus with no heart activity) and 3 pregnancies with an unknown outcomes. Zomig Tablets and Zomig-ZMT is rated as Category C for pregnancy (i.e., only to be used if the benefits outweigh the risks when considering both mother and fetus). A similar designation is proposed for Zomig Nasal Spray. I agree with the category designation.

Clinical Review

1. Introduction and Background

1.1 Proposed Trade Name, Drug Class, Indication, Dose, Regimens, Age Groups

Zomig (zolmitriptan) Nasal Spray (abbreviated herein either ZNS or Zomig NS) is a 5-hydroxytryptamine$_{1B/1D}$ ($5HT_{1B/1D}$) receptor agonist often referred to as a "triptan". The Sponsor seeks Agency approval for the use of ZNS 5.0 mg [redacted] in adult patients with an acute migraine with and without an aura with repeat dosing at 2 hours if required. The drug substance in the nasal spray is the same active moiety approved in Zomig Tablets 2.5 and 5.0 mg (NDA 20-768, approved November 1997) and Zomig-ZMT (NDA 21-231, approved April 2001).

1.2 State of Armamentarium for Acute Migraine Indication

There are currently several approved triptan drug products for acute migraine, all of which are available in oral formulations. Sumatriptan (Imitrex®) is also available as a nasal spray and as a subcutaneously injectable formulation. All triptans are effective in relieving migraine pain and its associated symptoms (nausea, photophobia, and phonophobia). The triptans have similar, though not identical, risk profiles (see section 7.4.14 for additional information on triptan safety).

In addition to triptans, there are a wide variety of approved treatment options for acute migraine including non-steroidal anti-inflammatory drug products (OTC), aspirin (OTC-pain of migraine approval only), dihydroergotamines, and isometheptene (Midrin, labeled as "possibly effective in migraine").

Since acute migraine is often associated with nausea and gastric stasis, both making oral therapy problematic, the Sponsor has developed a nasal formulation of zolmitriptan in the hope it would provide additional benefit to migraine sufferers by bypassing gastrointestinal tract absorption. Additionally the Sponsor believes a nasal formulation of zolmitriptan will provide less discomfort, inconvenience and possible risks associated with injectable formulations of triptans such as sumatriptan injection.

1.3 Administrative History

The following milestones occurred during the clinical development program for ZNS:

- July 25, 1997: The Sponsor opens IND 53,848 for zolmitriptan nasal spray.
- September 4, 1997: The Agency issues a Clinical Hold Letter due to the presence of a degradant [redacted] not previously evaluated. The Sponsor was instructed by the Agency to perform several preclinical studies prior to starting Human Protocol 311CIL/0077.
- December 1997 through February 1999: The Sponsor conducts, non-IND (outside the United States), safety and efficacy trial 311C1L/0077 (hereafter Trial 077).
- March 27, 1998: The Sponsor and Agency meet to discuss CMC issues.
- March 1998 through February 2000: Trial 311CIL/0078 (hereafter Trial 078) is conducted. This trial is an open-label, long-term, safety study extension of Trial 077.

- June 17, 1999: The Sponsor submits a complete response to the Clinical Hold (serial 006). A review by Dr. Armando Oliva states that the "response to our clinical comments (non-Hold) are acceptable". A review by the pharmacotoxicology reviewer (Dr. Linda Fossom) recommends continued Hold due to a genetox study demonstrating possible increase incidence in micronuclei in rats treated with the "degraded" formulation.
- July 16, 1999: The Agency issues a continued Hold Letter. Results from study TQR/2894 suggests ZNS may be clastogenic. The Agency requests additional studies.
- November 23, 1999: The Sponsor and Agency meet for a pre-NDA meeting to discuss CMC issues.
- February 18, 2000: The Sponsor and Agency meet for a pre-NDA meeting. Concluded at the meeting was the following: (1) It was agreed that a single efficacy study would be sufficient. (2) The Sponsor was informed that the issues of clastogenicity was still problematic and if the repeated micronucleus assay was positive the Agency would require the formulation to be tested in the full in vivo carcinogenicity assay in 2 species. (3) It was agreed to defer pediatric studies until after approval. (4) It was decided that if in vitro bioequivalence study demonstrated device equivalence between the "commercial" nasal spray device and the "clinical trial" device, then an in vivo bioequivalence trial waiver could be requested. (5) [redacted] See minutes dated March 22, 2000 for additional details (serial 015).
- October 13, 2000: The Sponsor initiates non-IND (outside the United States), long-term safety trial 311C1L/0122 (hereafter Trial 0122). The trial is still ongoing.
- June 19, 2001: The Sponsor and Agency meet for a Type A meeting. Pre-clinical issues were discussed as well as what was needed to lift the Clinical Hold (see minutes serial 024).
- November 15, 2001: The Sponsor provides a complete response to the remaining Clinical Hold issues (serial 025).
- December 11, 2001: The Agency lifts the Clinical Hold.
- February 27, 2002: NDA 21-450 is submitted by electronic format.
- June 27, 2002: The sponsor submits a CMC amendment and a 4 month safety update to the NDA.
- October 9, 2002: A teleconference was held with the sponsor to discuss the lack of equivalence between the device used in the clinical program and the proposed to be marketed device.
- November 5, 2002 the sponsor submits revised labeling electronically.

1.4 Other Relevant Information

Background information on zolmitriptan can be obtained from NDA 20-768 (Zomig Tablet 5.0 mg and 2.5 mg) and NDA 21-231 (Zomig-ZMT).

2. Clinically Relevant Issues From Other Disciplines.

2.1 Chemistry Manufacturing and Control Issues

The active drug substance, zolmitriptan, is unchanged from Zomig Tablets (NDA 20-768). Zomig Nasal Spray will be packaged in unit dose nasal spray device that is designed to deliver 5.0 [redacted] mg zolmitriptan in a dose volume of 100 µl. [redacted] The device is comprised of a [redacted] vial holder

and actuator device, with an integral stainless steel needle and an [redacted] protection cap.

Zomig Nasal Spray is an aqueous solution composed of the following: zolmitriptan, anhydrous citric acid, dibasic sodium phosphate (pH=5), purified water and nitrogen. The product will be manufactured in United Kingdom.

ZNS has shown adequate stability after 6 months storage at [redacted] RH and 12 months storage at both [redacted] RH and [redacted] RH. The proposed expiration period is 24 months for ZNS 5.0 [redacted] mg. [redacted] when stored at normal room temperatures.

Additional information can be obtained from the review conducted by Dr. Martha Heimann.

2.2 Pharmacotoxicology Issues

The pharmacology of zolmitriptan was provided with NDA 20-768 (Zomig Tablet). No new pharmacology studies have been conducted in support of the ZNS NDA.

The following toxicology studies were conducted in support of this NDA.

- A 2-week oral toxicity study (E95376) in rats of degraded and non-degraded ZNS (125 mg/kg) resulted in minor clinical signs (salivation), reduced body weight gain, minor changes in clinical chemistry parameters (decreased potassium and increased hemoglobin), and a reduction in kidney weight (male only). Maximum plasma level of 311C90 at one hour was 4668 ng/ml.
- A 28-day, repeat-dose, toxicity study (TAR2735) in rats demonstrated that intranasal administration of ZNS was generally well tolerated. Males received an average dose of 23.4, 48.4, or 101.8 mg/kg/day and females received 31.2, 64.4, or 137.6 mg/kg/day. High dose males had reduced weight gain. Mid dose males and high dose rats of both sexes exhibited minor rhinitis and nasopharyngitis. There were no treatment related ophthalmoscopic changes or deaths. The NOEL for rhinitis and nasopharyngitis was 23.4 mg/kg/day for males and 64.4 mg/kg/day for females.
- A 28-day, repeat nasal-dose of degraded and non-degraded ZNS toxicity study (TAR2813) in rats demonstrated that ZNS was generally well tolerated. Males received an average dose of 72.9 mg/kg/day of nondegraded ZNS and 73.3 mg/kg/day of degraded ZNS, females received 104.9 and 105 mg/kg/day respectively. Post-dose observations included sniffing, salivation, paddling, squinting and noisy respiration in all groups. Local irritant effect included minor rhinitis and nasopharyngitis in both groups. There were no deaths. A 4-week treatment free period demonstrated reversibility of histopathologic changes.
- A 26-week, nasal administration toxicity study in rat (TPR2920) demonstrated that ZNS was generally well tolerated. Males received an average dose of 4.3, 12.3 or 52.3 mg/kg/day, females received an average dose of 6.8, 20.7 or 83.7 mg/kg/day. One high dose female died in week 23 of hemorrhage in the thoracic cavity of unknown cause. The investigator did not believe it was related to treatment. Post-dosing observations included sniffing, salivation, paddling and erect tail in all dose groups, and squinting and noisy respiration at the high dose group. The NOAEL is considered 52.3 mg/kg/day in males and 83.6 mg/kg/day in females.

- A 4-week, intranasal toxicity study in monkey (E95375) was conducted to assess local tolerance to TID administration of degraded (15 mg/day) and non-degraded (30 mg/day) ZNS. Animals from both treatment groups demonstrated salivation after dosing otherwise ZNS was well tolerated. There were no treatment related differences in hematology, urinalysis and clinical chemistry parameters. There were no histopathologic changes in either group.
- A 28-day, nasal administration toxicity study in monkey (TAP97) was conducted to assess the local tolerance and systemic toxicity of degraded ZNS. Each monkey received an average of 16.6, 33.1, or 66.2 mg/kg/day. In general the treatment was well tolerated. Post-dose observations included salivation and vomiting in the higher dose. There was no effect on food consumption, ophthalmoscopy, electrocardiography or clinical pathology parameters. Histopathology was negative for local and systemic effects.
- A histopathologic evaluation of monkey tongues (study TKP129) was conducted after 28 days of continuous treatment with ZNS (16.6, 33.1 and 66.2 mg/kg/day). Histopathologic evaluations were negative for change.
- A special toxicity study (CTL/P/5884) was conducted to evaluate the effect of ZNS in the eyes of rabbits. A single 0.1 ml drop of ZNS 50 mg/ml was instilled in a single eye of three rabbits and followed for three days. There were no corneal or iridial effects. There was slight conjunctival erythema in 2 animals that resolved within 2 days.
- A reproduction study in rats (TTR2980) was conducted to assess the teratogenic potential of degraded ZNS. Doses of degraded ZNS (0, 100, 400, or 1000 mg/kg/day) was given to pregnant rats on day 7 through 16 of pregnancy. The number of corpora lutea, live fetuses, implantation loss and fetal weight were similar between groups. There was an increase in placental weight in the highest dose group however there was some internal inconsistency with this finding. There were no major fetal abnormalities. There were no dosage related visceral or skeletal anomalies. Increased salivation was seen in animals at dose levels of 400 mg/kg/day and above.
- Two in-vitro genotoxicity studies (TMV752 and TMV902, Bacterial Mutation Assay) using degraded ZNS in S. typhimurium and E.coli was negative for any abnormal findings.
- An in-vitro cytogenetic study (TYX124) using cultured human lymphocytes exposed to degraded ZNS was performed. The results demonstrate that ZNS caused a dose related increase in the incidence of chromosomal aberrations following a 20 hour exposure in the absence of exogenous metabolic activation system (E9). The study included cyclophosphamide and mitomycin C as positive controls. There was no evidence of an increase in chromosomal aberrations with degraded ZNS in comparison with the non-degraded formulation.
- A mouse bone marrow micronucleus test using degraded ZNS was performed (TQM1216). A single oral dose was given to male and female mice at a dose level of 100, 350, and 1000 mg/kg. Bone marrow samples were collected at 24 and 48 hours after dosing. When degraded ZNS is administered orally there was no increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow of mice.
- A rat (male) bone marrow micronucleus test, using degraded ZNS was performed (TQR2894). A single oral dose of 100, 350 and 1000 mg/kg was administered and bone marrow was sampled at 24 and 48 hours. There was a slight but statistically significant increase against controls in micronucleated cells 48 hours after administration of degraded ZNS at 1000 mg/kg/day. The sponsor felt this observed increase was of no biological

significance because the values for all groups that received ZNS fell well within the historical control range for the testing laboratory. [Note: this study resulted in a continued hold letter being issued on July 16, 1999.]

- A rat bone marrow micronucleus test using degraded and nondegraded ZNS was performed (TQR3080) to reevaluate the results from study TQR2894. Male and females rats received 100, 350 or 1000 mg/kg ZNS as a single oral dose. Bone marrow samples at 24 and 48 hours demonstrated no increase in the incidence of micronucleated polychromatic erythrocytes.
- A rat (female) bone marrow micronucleus test using either placebo or vehicle was performed (study TXR3098) in order to assess the incidence of micronucleated polychromatic erythrocytes (MPE) in females. Forty-eight after administration of vehicle or placebo to female rats, group mean values for the incidence of MPE/2000 polychromatic erythrocytes in bone marrow ranged from 0.4 to 1.2 MPE/2000 PE. For individual animals the range was 0 to 3 MPE/2000 PE.
- A rat bone marrow micronucleus test using degraded zolmitriptan was performed to further evaluate the potentially abnormal findings from Study TQR2894. The study included a positive control (cyclophosphamide) to assess test sensitivity. The results indicate that degraded ZNS administered orally up to 1000 mg/kg did not increase the incidence of MPE in rats.

Additional information regarding each study can be obtained from the review of the NDA conducted by Dr. Linda Fossom.

2.3 Biopharmaceutical Issues

On October 4, 2002 Dr. Oliva and I had a meeting with the biopharmacology review team to discuss their progress with the NDA review. At that time they informed us the sponsor's in-vitro bioequivalence study between the tested product and the proposed marketed product failed. The primary problem revolves around the size and dispersion of droplets from the proposed to-be-marketed nasal spray device. The formulation of ZNS is not changed. A proposed remedy included having the sponsor perform an in-vivo bioequivalence pharmacokinetic study comparing the tested product with the proposed marketed product. The sponsor was informed by teleconference of our concerns on October 9, 2002. Additional information regarding this problem can be found in the review done by the biopharmacology reviewer Dr. Andre Jackson.

2.4 Statistical Review Issues

I conferred with the Agency statistician (Yong-Cheng Wang Ph.D.) several times throughout my review of this NDA. Much of what we discussed is blended into the text of this review however a single finding should be emphasized. In the statistician's analysis of the primary endpoint the data for the ZNS 0.5 mg group failed to demonstrate significance ($p=0.053$). Part of the reason for the difference between his results and the sponsor's results ($p=0.023$) involve the way the analysis was performed. The sponsor analyzed the primary endpoint using a logistical regression model using "country' and "baseline headache intensity" as covariates and included patients in the zolmitriptan tablet cohort. The statistician's analysis does not include the zolmitriptan tablet cohort since he believes this introduces bias and he used the Bonferroni procedure to correct for multiple comparisons of the primary endpoint (not done by the sponsor). Additional details regarding this issue can be found in the review done by the statistician.

- Plasma concentrations of zolmitriptan and 183C91 (active metabolite) were broadly dose proportional based on C_{MAX} and AUC_{0-t}, but concentrations were too low at lower intranasal doses for statistical comparisons.
- Zolmitriptan was well absorbed from all formulations.
- Plasma concentrations were higher at earlier time points after ZNS 10 mg compared to zolmitriptan tablets 10 mg.
- Distribution, metabolism and excretion of zolmitriptan were consistent between formulations.
- Plasma concentrations profiles were broader and flatter after intranasal dosing than after oral dosing. Approximately 40% of C_{MAX} is reached within 15 minutes of intranasal administration compared to within 30 minutes of oral tablet administration. Zolmitriptan plasma concentrations are subsequently sustained for up to 6 hours. Peak plasma concentration is achieved by approximately 3 to 4 hours.
- The active metabolite 183C91 and inactive metabolites were delayed in appearance with ZNS compared to the oral formulation, but showed similar plasma profiles.

3.1.2 Clinical Pharmacology Trial 041 (N=12), PK and pH

Trial 041 is a randomized, 3-period crossover trial to determine the influence of pH (5.0 vs. 7.4) on the absorption of ZNS 2.5 mg and to compare the PK of ZNS 2.5 mg to zolmitriptan 2.5 mg in healthy subjects.

Conclusions:

- The absorption of zolmitriptan was not affected by pH in the range tested.
- Drug absorption was earlier after intranasal administration than after oral tablet dosing, with zolmitriptan detected in plasma at 5 minutes post-dose with the intranasal formulation.
- The appearance of 183C91 was delayed with the intranasal formulation suggesting delayed first pass expected with nasal absorption.
- The relative bioavailability of ZNS 2.5 mg, pH=5, was 102% and was subsequently chosen for further development. Mean absolute oral bioavailability of zolmitriptan tablet is approximately 40% (NDA 20-768). The bioavailability of intranasal zolmitriptan is approximately 41%.

3.1.3 Clinical Pharmacology Trial 079 (N=30), PK-multiple doses

Trial 079 is a randomized, double-blind, placebo-controlled, 2-period crossover trial to investigate the tolerability and PK of zolmitriptan (0.5, 1.0, 2.5 and 5.0 mg) when administered intranasally in single and multiple doses (2 doses, 2 hours apart) to healthy subjects. Each subject participated in 2 different cohorts.

Conclusions:

- ZNS is rapidly absorbed.
- C_{MAX} and AUC for zolmitriptan and 183C91 were proportional to zolmitriptan dose when administered either as single or multiple doses.
- Median values for T_{MAX} were similar (1.25 to 2.5 hours) after single or multiple dosing.
- Plasma levels during the multiple dose phase were predictable based on single dose kinetics and the dosing interval used. As expected, plasma concentrations of

zolmitriptan and 183C91 increased when a second dose is administered 2 hours after the first, but T_{MAX} and $T_{½}$ were similar after single- or multiple dosing.

- No accumulation with repeat dosing was seen.
- The appearance of 183C91 was delayed with the intranasal formulation suggesting delayed first pass expected with nasal absorption.

3.1.4 Clinical Pharmacology Trial 102 (N=18), Drug Interaction Study

Trial 102 is a randomized, 2-period crossover trial to evaluate the effect of a nasally-administered decongestant (xylometazoline 140 mg) on the absorption of ZNS 5 mg when given to healthy male subjects.

Conclusions:

- Absorption of ZNS was not affected by the coadministration (30 minutes prior) of a nasal decongestant.
- Plasma concentration of zolmitriptan were detectable at 5 minutes after dosing.

3.1.5 Clinical Pharmacology Trial 104 (N=9), Absorption and PET Scan

Trial 104 is a 2-phase trial to assess the distribution of intranasally administered of ^{11}C-labeled ZNS 2.5 mg to healthy adults. Phase I used a single dose ^{11}C-ZNS 2.5 mg. Phase II used multiple doses of ^{11}C- ZNS 2.5 mg.

Conclusions:

- The rapid increase in plasma concentrations immediately after dosing demonstrated that initial absorption of intranasal ^{11}C-zolmitriptan was via the nasopharynx.
- The initial concentration of ^{11}C-zolmitrptian in the nasopharynx were seen to decrease with time as the drug was cleared through swallowing. As a direct result, concentrations of ^{11}C-zolmitrptan observed in the stomach increased during the first 20 to 60 minutes.
- Concentrations of radiolabeled ZNS in the lung were very low with only 0.2 and 0.3% of the initial dose present in the lungs at 20 and 80 minutes respectively.
- PET scan at 32 minutes demonstrates that there is some direct penetration of ZNS into brain tissue.

3.1.6 Summary

C^{11}-labeled zolmitriptan, instilled in the nasopharynx of volunteers and tracked with positron emission tomography, is directly absorbed through the nasal mucosa. Within 5 minutes of nasal administration zolmitriptan can be detected in plasma and about 40% of Cmax is reached by 10-15 minutes. Peak concentrations are reached in about 3 hours and plasma concentration is sustained for 4-6 hours after dosing.

Zolmitriptan is metabolism by the liver to an active N-desmethyl metabolite (183C91). Elimination is primarily through the kidneys. The metabolite's potency is 2-6 times that of the parent. The mean elimination half-life for zolmitriptan and the active metabolite after nasal spray administration are 3 hours, which is similar to the oral tablet.

Zolmitriptan displays linear kinetics after multiple doses of 2.5 mg, 5 mg, or 10 mg. Mean absolute bioavailability of the spray is 102%. Zolmitriptan and its active N-desmethyl metabolite display dose proportionality after single and multiple dosing.

Effects of impaired renal and hepatic function on ZNS metabolism and elimination have not evaluated. Effects of size, weight, gender, and race on metabolism were not evaluated.

The coadministration of sympathomimetic nasal decongestant with ZNS was evaluated in Study 311CIL/0102. The study was designed to determine whether the vasoconstrictive properties of decongestant would alter the absorption of ZNS. Intranasal absorption of ZNS was neither delayed nor reduced by coadministration of the decongestant.

Overall the pharmacokinetics, metabolism, and elimination profiles of ZNS are similar to the tablet formulation.

4. Description of Clinical Data and Sources

4.1 Overall Data

The data used in this review are exclusively from the 8 trials conducted by the Sponsor (see Table 3 Clinical development program for ZNS). The single double blind, placebo-controlled efficacy trial for Zomig Nasal Spray, 311C1L/0077, will be referred to as Trial 077 in this review. The two large, open-label, long-term safety trials are 311C1L/0078 and 311C1L/0122, referred to as Trial 078 and 0122, respectively. The remaining trials are Phase I pharmacokinetic and bioavailability trials involving small groups of healthy volunteers. Data was submitted electronically and can be found at edr\\CDSESUB1\N21450\N_000\2002-02-27.

4.2 Table Listing of Clinical Trials

Table 3 Clinical development program for ZNS

Trial #	ZNS dose (mg)	Type of Trial	N	Duration	Notes
Clinical Pharmacology Trials					
136-032	2.5, 5.0, 10	PK	12	single doses	Dose-escalation & bioavailability study
311CIL/0041	2.5	PK	12	single doses	Bioavailability (effect of pH on NS absorption)
311CIL/0079	0.5, 1.0, 2.5, 5.0	PK	30	multiple doses	Single & multiple dose proportionality study
311CIL/0102	5.0	PK	18	single doses	Effect of nasal decongestant on ZNS absorption
311CIL/0104	2.5	PK	9	single doses	Nasopharyngeal absorption study using ^{11}C-labeled ZNS monitored by PET scan
Clinical Safety and Efficacy Studies					
311CIL/0077	0.5, 1.0, 2.5, & 5.0	Efficacy	1383	3 attacks	Acute migraine treatment using ZNS, placebo and oral 2.5 mg Zomig Tablets
311CIL/0078	Phase I: 0.5, 1.0, 2.5, 5.0 Phase II: 5.0	Long-Term Safety	1096	12 months	Open-label extension of 077. Patients initially randomized to 0.5, 1, 2.5, or 5 mg (Phase I) then later switched to 5 mg (Phase II).
311CIL/0122	5.0	Long-Term Safety	536	12 months*	Open-label; all patients used 5 mg, able to repeat dose if needed.

*At the time of this review, only the 6-month interim data from Study 0122 (which is still ongoing) are available

4.3 Postmarketing Experience

Zolmitriptan Tablets have been approved in the United States for the treatment of acute migraine since 1997 in doses up to 5 mg. Since then, the marketing experience has been typical for triptan type products.

Zomig Nasal Spray has been approved in Sweden since November 30, 2001[4]. Since approval, 1800 patient exposures to ZNS have occurred and no reports of adverse events have been received.

5. Clinical Review Methods

5.1 How the Review was Conducted

The materials reviewed for this NDA review include the original electronic NDA submission, dated February 27, 2002, and several updates. A CMC and 4-month safety update was submitted on June 27, 2002.

The emphasis of this review with respect to efficacy is Trial 077, the single placebo-controlled efficacy trial conducted for this NDA. The use of a single efficacy trial was agreed to by the Agency on February 18, 2000. The study report for Trial 077 includes two separate analyses, the protocol specified multiple-attacks analysis and the FDA requested "first-attack" analysis. In my review of efficacy I will primarily use the FDA-specified "first-attack" analysis to present results. Results from the "multiple attacks analysis" will be discussed where appropriate however in general the two analysis are nearly identical and do not change the final recommendations.

My safety review consists of data provided from all 8 trials included in this NDA. Since the pharmacokinetic and bioavailability studies (0032, 0041, 0079, 0102, and 0104) include close monitoring of vital signs, ECG, and laboratory values, they provide useful safety data despite the small numbers of subjects involved. However because of their limited size and exposure the adverse events experienced during the conduct of these trials have limited utility and will be summarized only if relevant. The majority of my review of adverse events will be derived from the data obtained during the efficacy and long-term safety trials (077, 078 and 0122). Trial 0122, is not yet complete however greater than 6 months of data from the 12-month trial are available.

The pharmacokinetic data from the early studies is reviewed in detail by the Biopharmacology reviewer however I briefly summarize the results in section 3 of this review.

Data used in this review were submitted in electronic form and are available in the Electronic Document Room on the FDA intranet. Historical information was obtained from review of the Division File for IND 52,848 (zolmitriptan nasal spray).

In summary, the major emphasis in this review will be the Sponsor's single efficacy trial 077. The two long-term safety trials will be described in detail, the pharmacokinetic trials will be described briefly, and all 8 trials will be used as the safety database.

5.2 Data Quality and Integrity

A DSI audit of data quality was done during the DSI Audit and was determined to be sufficient.

[4] Source: summary.pdf, page 49.

5.3 Ethical Standards Statement and Issues

The Sponsor states that their clinical trials provided in support of this NDA comply with the ethical principals of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

The original IND was initially placed on Hold at the recommendation of Dr. Jessop (Pharmacotoxicology reviewer) due to the presence of a degradant not previously qualified. Appropriate preclinical studies were requested and performed however the genetox study demonstrated an increase incidence of micronuclei in rats exposed to the degradant. There was some debate about the quality of the study however it was agreed to not lift the Hold and to repeat the study. The recommendation for the continued Hold was from Dr. Powell (Pharmacotoxicology reviewer). A second complete response was submitted and the Hold was removed in December 0f 2001.

However while the IND was on Hold in the United States (see section 1.3 for details about sequence of events) several clinical studies were conducted in Human subjects in Europe, Canada, and in South Africa. From a review of the sample informed consent form (Appendix E, IL0077.pdf, page 942) and the patient information sheet (Appendix E, IL0077.pdf, page 943) it does not appear subjects were informed of the Clinical Hold or the concern about potential clastogenicity. A review of the minutes from previous meetings with the sponsor fails to demonstrate any discussion about this issue.

It is the opinion of the present Pharmacotoxicology reviewer of this NDA (Dr Fossom) that the original analysis of the genetox findings was faulty and probably should have not resulted in a continued Hold. I defer to her review for complete details about the genetox study however in light of this opinion I do not believe there are any ethical issues that would prohibit the acceptance of the data from the Human trials conducted while the NDA was on Hold.

5.4 DSI Audit (by Ni A. Khin, M.D.)

DSI selected for audit one site in the United Kingdom [redacted] and one site in Canada [redacted]. No special concerns were noted that affected the choice of site. Both centers were found to have "sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoints captured as specified in the protocol." Both sites were deemed acceptable for use in support of this NDA.

5.5 Evaluation of Financial Disclosure

The Sponsor certifies[5] that they have not entered into any financial arrangements with any investigator associated with the clinical development program for ZNS, whereby the value of compensation was tied to study outcome as defined in 21 CFR 54.2(a). The Sponsor also certifies that all investigators report no proprietary interests in the product under development or any significant equity in the Sponsor as defined in 21 CFR 54.2(b). Finally, the Sponsor certifies that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

[5] Source: FDA Form 3454 (3/99) completed by Sponsor, financial.pdf, page 1.

6. Integrated Review of Efficacy

6.1 Brief Statement of Conclusions Relative to Proposed Claim

Zomig Nasal Spray demonstrated efficacy at its protocol specified primary endpoint, headache relief at 2 hours (HR2), for each dose tested (0.5, 1.0, 2.5, and 5.0 mg) compared to placebo, and from a clinical perspective should be approvable. The Sponsor seeks Agency approval of ZNS 5.0 mg for marketing in the United States for the acute treatment of migraine with and without aura in adults.

6.2 General Approach to Review of Efficacy

The Integrated Summary of Efficacy consists of a single placebo and active controlled, double blind, multicenter study, trial 311CIL/0077 (Trial 077). This was agreed to by Division of Neuropharmacological Drug Products in the pre-NDA meeting with the Sponsor on February 18, 2000.

6.3 Detailed Review of Trial 077

In this section I will first describe the protocol design and patient demographics, then summarize the efficacy results from Trial 077.

6.3.1 Description of Protocol 077

Trial 077 was an international, multicenter, randomized, placebo and active controlled, double blind, double-dummy, parallel group study to evaluate the efficacy and tolerability of ZNS 5.0, 2.5, 1.0, and 0.5 mg in the acute treatment of adult patients experiencing a migraine of moderate to severe intensity. Each subject was expected to treat three migraines. The nasal spray formulation used in this trial is the same as that planned for commercial use however the device was different. The primary objective of Trial 077 was to compare the efficacy of ZNS 5.0, 2.5, 1.0, and 0.5 mg to placebo in the acute treatment of migraine headache. The zolmitriptan tablet 2.5 mg cohort was included to enable the Sponsor the opportunity to determine whether the nasal formulation provides any additional benefit over the original tablet formulation.

The study intended to treat approximately 1440 subjects equally randomized to one of six cohorts (ZNS 0.5, 1.0, 2.5, 5.0 mg, placebo and zolmitriptan tablet 2.5 mg) in approximately 40 centers in Western Europe, Australia and Canada. Eligible patients had to be male or non-pregnant females, 18 to 65 years of age, with an established diagnosis of migraine with or without aura (IHS criteria), have an age of initial migraine onset of less than 50 years, and a migraine frequency of 1 to 6 per month for the previous two months prior to screening. Patients with a history of basilar, ophthalmoplegic, or hemiplegic migraine were excluded, as were those with a history of any serious medical condition or illness (including heart disease, uncontrolled hypertension, hepatic or renal impairment). Also excluded were subjects with non-migraine headaches greater than 10 days per month during the 6 months prior to screening. In summary subjects were expected to be in good health with at least a 1-year history of migraines not exceeding 6 per month. Therefore, by protocol design, this study did not include any geriatric patients, pediatric patients, debilitated patients with complicated migraines, or unique special populations such as subjects with renal or hepatic insufficiency. These inclusion/exclusion criteria are typical of migraine studies I have reviewed.

Not allowed within 2 weeks of treatment with study medication was the use of MAO-A Inhibitors, methysergide, or methylergonovine. Not allowed within 24 hours of study medication treatment were any $5HT_{1B/1D}$ agonists, ergot derivatives or opiates. Not allowed within 6 hours were any analgesics. Patients were instructed that escape medications for the treatment of unresolved or recurrent migraine could be taken 4 hours after administering trial medication if needed. If headache pain was severe, subjects were permitted to take escape medication at 2 hours if needed. Any patient that took escape medications prior to 4 hours was considered a treatment failure at subsequent time points. Escape medications could include NSAIDs, anti-emetics, analgesics or sedatives. Medication taken by the patient before entry into the trial (other than those listed above) could be continued during the trial provided it was for a stable condition and not adversely affected by trial participation.

After the initial screening visit, patients received enough randomized medication to treat 3 migraine attacks with a single dose of study medication for each attack. Patients were required to return to the clinic within 2 weeks of treating their 3rd migraine headache, or 3 months after they were first dispensed trial medication, whichever was the earlier, for follow-up assessments and for inspection of the diary cards by the investigator. Patients who completed the trial were eligible to enroll in the long-term safety and tolerability trial 078, provided they continued to fulfill the entry criteria.

Patients were issued four diary cards at randomization and were instructed to record the appropriate data on each migraine headache immediately before and at specified times after taking trial medication. Pre-defined time windows were used to group the data for headache response presented on the diary cards as outlined in the following Agency table. As evident from the permitted range it appears the primary endpoint time point of 2 hours ranged from 91 minutes to 180 minutes. In my review of the data I will evaluate the spread of the data from this critical assessment period. If the data is widely dispersed over this 90 minutes period I will reevaluate the primary endpoint results using a more reasonable ± 15 minutes window.

Table 4 Trial assessment times and permitted range

Assessment Time (minutes)	15	30	45	60	120	240
Assessment window (minutes)	0-22	23-37	38-52	53-90	91-180	181-360

The primary endpoint for Trial 077 is headache response at 2 hours (HR2) after treatment, defined as moderate (Grade 2) to severe (Grade 3) headache pain at baseline with no (Grade 0) or mild (Grade 1) pain at 2 hours and no use of escape medication. In the original protocol the primary endpoint also included headache response at 30 minutes however this was amended on October 27, 2002 since it was deemed too stringent by the Sponsor. Secondary endpoints include the following:

- Headache response at 15, 30 and 45 minutes, and at 1 and 4 hours
- Absence of pain at 15, 30 and 45 minutes, and at 1, 2 and 4 hours

- Reduction in pain at 15, 30 and 45 minutes, and at 1, 2 and 4 hours
- Meaningful migraine relief (MMR) at 15, 30 and 45 minutes, and at 1, 2 and 4 hours
- Use of escape medication
- Time to resumption of normal activities
- Incidence and time to headache recurrence within 24 hours
- Incidence and nature of all serious adverse events (irrespective of dosing) and non-serious adverse events (occurring within 24 hours of dosing)

Additional endpoints not defined in the original protocol include the following (no formal statistical analyses where performed):

- Patient global satisfaction rating (global impression)
- Improvement of photophobia, phonophobia, nausea and somnolence
- Consistency of headache response

Headache response is defined as a reduction in intensity of migraine headache pain from severe or moderate at baseline to mild or none at each post-treatment assessment using a 4-point scale (0 to 3). Absence of pain is defined as a rating of "none" (0) for migraine headache pain intensity at the respective post-treatment assessment time point. Reduction in pain is defined as a reduction of ≥1 point in the intensity of migraine headache pain at each post-treatment assessment compared with the pre-treatment assessment.

Meaningful migraine relief (MMR) is defined as the patient's self-assessment of the overall benefit of acute anti-migraine therapy. Patients record on the diary card the actual time at which they feel they achieved MMR. The time between taking trial medication and experiencing MMR was derived from the data on the diary cards within the time windows 0 to 15 minutes (15 minutes), 0 to 30 minutes (30 minutes), 0 to 45 minutes (45 minutes), 0 to 60 minutes (1 hour), 0 to 120 minutes (2 hour) and 0 to 240 minutes (4 hour). The time windows were cumulative therefore once a patient experienced MMR they were included in all subsequent time windows whether or not the migraine returned.

Patients recorded on their diary card any use of escape medication, the drug used, the time of use, and the reason for use. Patients recorded on their diary card whether they had any recurrence of their migraine headache, and if so, the lowest intensity prior to recurrence, the actual intensity of the recurrence, and the time of recurrence.

Patients were requested to record in the diary the presence/absence of migraine associated symptoms of photophobia, phonophobia, nausea and somnolence. The Sponsor did not originally plan to include this assessment in their original protocol however an assessment of "improvement of photophobia, phonophobia, nausea and somnolence" was included in the protocol amendment of 27 October 1999. The Sponsor did not propose any statistical analysis for this endpoint. The Sponsor also did not define "improvement" however from the patient diary it appears they mean resolution of the baseline symptom. This approach is not typical of what the Agency requests for migraine studies. Generally we require the Sponsor to analyze the proportion of subjects complaining of each of these associated symptoms at the various time points. Special emphasis is then given to the primary endpoint time point (in this case 2 hours)

since it is generally considered important that a migraine product show some efficacy for nausea, photophobia, and phonophobia (somnolence is usually not considered). In my review of the dataset I will include an analysis of the proportion of subjects with nausea, photophobia and phonophobia at 2 hours using the dataset for the first attack.

Patient's Global Satisfaction was recorded by each investigator in the case report form (CRF). Patients were asked to rate their general satisfaction with study medication using a 4-point rating scale (excellent, good, fair, poor).

A migraine headache was defined as being menstrually related if the onset of the migraine headache was 2 days or less prior to the onset of menses or if the onset of the migraine headache was 3 days or less after the onset of menses. A complete response was defined as a 2-hour headache response for which recurrence or use of escape medication did not occur in the 24 hours after treatment. It is important to note that complete response does not mean absence of pain since subjects may continue to have mild pain during this period of time.

Patients were required to treat 3 migraine attacks of moderate or severe intensity with both a tablet and spray at each attack (double dummy). There were two statistical analyses done by the Sponsor. The first was protocol-specified and the second was requested by the Division of Neuropharmacological Drug Products. The protocol-specified efficacy analysis was based on the multiple attack data (three attacks, later reduced to two). The Division's plan is based on first attack data only. In my review of the efficacy results I will focus on the FDA-requested first attack analyses and comment on the protocol defined multiple attack analysis when appropriate. The two analyses have nearly identical results and lead to the same overall conclusions.

The Sponsor decided not to analyze all three attacks because the use of trial medication in the third attack did not appear to be independent of treatment (see Table 5). One of the assumptions of the statistical analysis model was that withdrawal from the trial or number of attacks treated was independent of treatment received. As is demonstrated in the table, the proportion of patients in each group treating a 3rd migraine attack, and to a lesser extent a 2nd migraine attack, appeared to be related to treatment. Clearly those subject treating a migraine with placebo were numerically more likely not to treat all three migraines with study medication compared to subjects randomized to active treatment. The Sponsor believes that treatment of attack 3 was dependent both upon the response to earlier attacks and treatment group, and that patients were more likely to treat a 3rd attack in the higher dose groups. The original assumption was therefore considered not to be fulfilled if all 3 attacks were included in the analysis, so the Sponsor argues that it is more appropriate to include only the first 2 attacks in the statistical analysis.

Table 5 Number of patients treating their migraine for each of 3 attacks

	ZNS 5.0 mg	ZNS 2.5 mg	ZNS 1.0 mg	ZNS 0.5 mg	Zolmitriptan Tab 2.5 mg	Placebo
1st migraine	235	224	236	221	229	226
2nd migraine	203	193	199	182	186	175
3rd migraine	165	156	149	136	150	113
2nd-1st attack	32	25	37	39	43	51
3rd-1st attack	70	68	87	85	79	113

Adapted from Sponsor Table 24, Study Report 007, Multiple-attacks analysis.

The primary endpoint, headache relief at 2 hours, was analyzed by the Sponsor as a binary response using a generalized linear mixed model (Wolfinger and O'Connell 1993) with a pseudo-likelihood approach to model the odds of headache response. Country-by-treatment interaction, treatment-by-attack interaction, and treatment-by-baseline-headache-intensity interaction were investigated. The effects on the primary endpoint of age, weight, gender and race were also investigated. In order to take account of the multiple testing of the treatment groups, a step-down approach was adopted by comparing the doses of zolmitriptan nasal spray with placebo starting from the highest dose.

Secondary comparisons of each intranasal dose of ZNS with oral zolmitriptan 2.5 mg were also undertaken. No step-down procedure was used for these comparisons. The results of each tested contrast were presented in terms of the odds ratio (OR) and the associated 95% confidence interval (95%CI) and significance level.

The secondary efficacy endpoints were analyzed in a similar manner as the primary endpoint. The effects of withdrawals and protocol violations or deviations on all analyses were examined and handled in such a way that any bias in the treatment comparison was minimized.

The protocol does not address how missing data was handled.

6.3.2 Population Demographics and Baseline Migraine Characteristics

Table 6 outlines the various populations from this study. A total of 1547 eligible subjects were randomized and 1383 patients (safety population) took study medication. The Intent-to-Treat Population (ITT) has 1371 subjects. It is important to note the Sponsor originally defined the ITT Population as all subjects that took study medication and completed some efficacy entries. However in a later amendment (27 October 1999) the Sponsor refined the definition to all randomized patients who treated at least 1 migraine of moderate to severe baseline headache intensity and returned to the clinic for a follow up visit. This resulted in 12 subjects being excluded from the ITT analysis because they treated a migraine of mild severity (1 subject from ZNS 5.0 mg, 2 subjects from ZNS 1.0 mg, 3 subjects from ZNS 0.5 mg, 3 subjects from zolmitriptan 2.5 mg, and 3 subjects from placebo).

The Sponsor argues that the original ITT definition made it impossible to define a headache response in those individuals that treated a migraine with baseline headache severity of mild. In my own analyses of the primary endpoint I will use the original ITT definition (hereafter ITT_{Agency}) and label subjects that treat a headache of mild severity as treatment failures at 2 hours. However when these 12 subjects are included in the analysis, and treated as treatment failures, the results are nearly identical to the results obtained by the Sponsor.

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Table 8 Recruitment by country, Trial 077

Country	Number of Centers	Number Recruited
Canada	9	357
Finland	5	310
United Kingdom	4	233
Australia	5	178
Germany	5	122
Sweden	3	113
Denmark	4	86
Holland	2	64
Belgium	2	49
Spain	2	19
Norway	1	16

Adapted from Sponsor's Appendix C, Trial 077 (multiple attack), IL0077.pdf, page 725 and Submission N(BM), dated 8/14/02

The demographic characteristics of the treated population are shown in the following Sponsor table. Approximately 83% were female, which is typical of adult migraine studies of this type. The mean age from all cohorts was 40.6 years of age, mean weight was 68.9 kg, and the mean height was 167.4 cm. The vast majority of subjects (98.6%) were Caucasian. The various treatment groups were well balanced with respect to all demographic characteristics.

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Table 9 Age, sex, height, weight, and race of patients, Trial 077 ITT Population

Demographic characteristic	Zolmitriptan nasal spray				Oral zolmitriptan	Placebo
	5.0 mg (N = 235)	2.5 mg (N = 224)	1.0 mg (N = 236)	0.5 mg (N = 221)	2.5 mg (N = 230)	(N = 226)
Age at trial entry (years)						
n	235	224	236	221	230	226
Mean	40.8	40.7	39.8	40.7	41.5	40.2
SD	10.3	9.8	10.4	10.2	10.7	10.5
Minimum	18	18	18	18	19	18
Maximum	63	65	64	65	63	65
Age distribution (n [%][a])						
≥18 to 39 years	103 (43.8)	92 (41.1)	112 (47.5)	98 (44.3)	88 (38.3)	112 (49.6)
≥40 to 65 years	132 (56.2)	132 (58.9)	124 (52.5)	123 (55.7)	142 (61.7)	114 (50.4)
Sex (n [%][a])						
Female	199 (84.7)	172 (76.8)	205 (86.9)	178 (80.5)	189 (82.2)	195 (86.3)
Male	36 (15.3)	52 (23.2)	31 (13.1)	43 (19.5)	41 (17.8)	31 (13.7)
Height (cm)						
n	234	220	234	218	229	225
Mean	167.5	168.2	167.2	167.6	166.9	167.1
SD	8.4	8.4	8.7	7.1	8.1	8.0
Minimum	150.0	149.0	143.0	152.0	150.0	150.0
Maximum	192.0	190.0	195.0	184.0	198.0	191.0
Weight (kg)						
n	234	220	235	218	229	225
Mean	67.7	69.5	68.7	68.3	69.8	69.4
SD	13.8	13.9	13.1	13.1	13.5	14.4
Minimum	43.5	40.0	45.0	45.5	44.3	41.0
Maximum	122.0	123.0	109.0	119.5	109.0	126.0
Race (n [%][a])						
Caucasian	231 (98.3)	221 (98.7)	234 (99.2)	218 (98.6)	226 (98.3)	223 (98.7)
Other[b]	4 (1.7)	3 (1.3)	2 (0.8)	3 (1.5)	4 (1.7)	3 (1.3)

[a] Percentages were calculated using the number of patients exposed in each treatment group as the denominator.
[b] Other includes Afro-Caribbean, Asian, Hispanic, Oriental, mixed and other.
N Number of patients exposed.
n Number of patients.
SD Standard deviation.
Source: Sponsor Table 5, IL0077.pdf (multiple attack analysis), page 49.

Table 10 summarizes the baseline migraine characteristics of the ITT population. Of the 1371 patients in the ITT population, the majority of migraine headache attacks were of moderate intensity (approximately 77%) and without an aura (approximately 73%). There was some imbalance between cohorts in the proportion of patients reporting a severe headache at baseline, which was lowest in the ZNS 5.0 mg group (16.6%) and highest in the ZNS 0.5 mg group (28.1%). This difference is accounted for in the Sponsor analysis plan.

There were no notable differences in the frequencies of associated symptoms of nausea, photophobia, phonophobia, or somnolence across the six treatment groups at baseline. The proportion of patients with these symptoms at baseline was as follows: photophobia, 75.5% (1035/1371); phonophobia, 60.5% (829/1371); nausea, 53.5% (734/1371); and somnolence, 52.3% (717/1371). Approximately 2 to 3% of the subjects did not enter the information for these baseline characteristics.

Table 10 Baseline migraine attack characteristics, 1st Attack, ITT population, Trial 077

	Zolmitriptan Nasal Spray				Zolmitriptan oral (N=229)	Placebo (N=226)
	5.0 mg (N=235)	2.5 mg (N=224)	1.0 mg (N=236)	0.5 mg (N=221)		
Pain Intensity						
Moderate n(%)	196 (83.4)	165 (73.7)	183 (77.5)	159 (71.9)	180 (78.6)	176 (77.9)
Severe n(%)	39 (16.6)	59 (26.3)	53 (22.5)	62 (28.1)	49 (21.4)	50 (22.1)
Aura						
Yes n(%)	49 (20.9)	50 (22.3)	42 (17.8)	48 (21.7)	46 (20.1)	45 (19.9)
No n(%)	172 (73.2)	160 (71.4)	181 (76.7)	161 (72.9)	168 (73.4)	169 (74.8)
Nausea						
Yes n(%)	128 (54.5)	126 (56.3)	125 (53.0)	114 (51.6)	118 (51.5)	123 (54.4)
No n(%)	104 (44.3)	94 (42.0)	107 (45.3)	102 (46.2)	105 (45.9)	100 (44.2)
Photophobia						
Yes n(%)	173 (73.6)	167 (74.6)	183 (77.5)	157 (71.0)	176 (76.9)	179 (79.2)
No n(%)	60 (25.5)	54 (24.1)	50 (21.2)	63 (28.5)	49 (21.4)	47 (20.8)
Phonophobia						
Yes n(%)	144 (61.3)	140 (62.5)	143 (60.6)	128 (57.9)	142 (62.0)	132 (58.4)
No n(%)	86 (36.6)	81 (36.2)	90 (38.1)	89 (40.3)	82 (35.8)	92 (40.7)
Somnolence						
Yes n(%)	127 (54.0)	123 (54.9)	112 (47.5)	110 (49.8)	124 (54.1)	121 (53.5)
No n(%)	102 (43.4)	99 (44.2)	120 (50.8)	104 (47.1)	98 (42.8)	99 (43.8)

Adapted from Sponsor tables: T12.1 through T12.4 (pages 181-196), Sponsor table 3 (page 20), T7.5 (page 135); analysis of 1st attack.pdf)

6.3.3 Sponsor's Primary Endpoint Efficacy Results from Trial 077

In this section I will describe the Sponsor' primary endpoint efficacy results from Trial 077. The Agency efficacy analysis (statistician's and medical officer's) can be found in Section 6.3.5.

In describing the results of the trial I will focus primarily on the first attack analysis provided by the Sponsor. The analysis of first-attack was not prospectively planned in the original protocol but was requested by the Agency at the pre-NDA meeting. When appropriate I will describe the results from the multiple-attacks analyses and my own analysis. However, all three analyses support the same conclusions. The results presented use the Sponsor's ITT population unless otherwise stated. The results were similar in the ITT_{AGENCY}, and the Per-Protocol Population. The main efficacy results are briefly summarized in Table 30.

The primary endpoint for this trial is a comparison of headache response at two hours (HR2) between each dose of ZNS compared to placebo. The proportion of subjects responding at 2 hours for each cohort is presented in the following Agency table. As can be seen every dose of ZNS was numerically superior to placebo for the proportion of patients reporting HR2.

Table 11 Headache response at 2 hours, 1st Attack Analysis, ITT population

	ZNS 5.0 mg (N=235)	ZNS 2.5 mg (N=224)	ZNS 1.0 mg (N=236)	ZNS 0.5 mg (N=221)	Zolmitriptan Tab 2.5 mg (N=229)	Placebo (N=226)o
Patients evaluated at 2 hrs	228	219	232	217	220	218
Patients with 2 hrs response (%)	157 (68.9)	121 (55.3)	137 (59.1)	86 (39.6)	133 (60.5)	67 (30.7)
Treatment comparison: ZNS dose vs. placebo						
Odds Ratio	5.13	3.05	3.47	1.60		
95% CI	(3.40, 7.73)	(2.04, 4.56)	(2.33, 5.17)	(1.07, 2.41)		
p-value	0.0001	0.0001	0.0001	0.0223		

Adapted for Sponsor Table 6, 1st Attack Analysis.pdf, page 26

As can be seen from the above table, all doses of ZNS are associated with a significantly greater relief of headache pain at 2 hours compared to placebo (p=0.0001 for ZNS doses ≥1.0 mg; p=0.0223 for ZNS 0.05 mg). The Sponsor points out there was a slight imbalance across the treatment groups in the proportions of patients with severe headache pain at baseline, however this was accounted for in the statistical plan by the inclusion of baseline severity term into the model used by the Sponsor. The results were similar for the multiple attack analyses (see the following Agency table) where all doses of ZNS were significantly better than placebo in the treatment of headache pain at 2 hours (p<0.001).

Table 12 HR2, Multiple-Attacks Analysis of HR2, ITT population

	ZNS 5.0 mg	ZNS 2.5 mg	ZNS 1.0 mg	ZNS 0.5 mg	Zolmitriptan Tab 2.5 mg	Placebo
Number treating 2 attacks	203	193	199	182	185	175
Number of attacks treated	438	417	435	403	415	401
Number of attacks with HR2 n(%)	300 (70.3)	239 (58.6)	234 (54.8)	165 (41.5)	245 (61.3)	119 (30.6)
Treatment comparison: ZNS dose vs. placebo						
Odds ratio	5.69	3.56	2.96	1.77		
95% CI	(4.05, 7.99)	(2.54, 4.99)	(2.14, 4.09)	(1.27, 2.48)		
p-value	0.0001	0.0001	0.0001	0.008		

Adapted from Sponsor tables 12, 13, and 14 Study report 007, multiple-attack analysis (IL0077.pdf, page 60).

In both analyses there was evidence of a dose response for pain relief at 2 hours with the highest efficacy seen with the highest dose of ZNS. This was slightly more obvious in the multiple-attacks analysis where the percentage of subjects reporting headache relief at 2 hours was 70.3, 58.6, 54.8, and 41.5 for ZNS 5.0, 2.5, 1.0, and 0.5 respectively compared to 30.6 for placebo.

The following Sponsor table evaluates the proportion of patients reporting a 2-hour pain response broken down by the following baseline characteristics; pain severity, association of menses, migraine upon awakening, and the presence of an aura or nausea. No consistent differences in headache response between subgroups were observed except for baseline pain intensity where the proportion of patients with baseline severe headache pain at baseline reported less HR2 than the subjects reporting moderate pain at baseline. This intuitively make some sense since these patients by definition treated a more severe migraine, at least for pain intensity.

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Table 13 HR2 by baseline migraine characteristics, 1st Attack Analysis, ITT Population

Characteristic	Zolmitriptan nasal spray												Oral zolmitriptan			Placebo		
	5.0 mg			2.5 mg			1.0 mg			0.5 mg			2.5 mg					
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Baseline intensity																		
Moderate	189	136	(72.0)	163	100	(61.3)	179	115	(64.2)	155	72	(46.5)	171	118	(69.0)	170	58	(34.1)
Severe	39	21	(53.8)	56	21	(37.5)	53	22	(41.5)	62	14	(22.6)	49	15	(30.6)	48	9	(18.8)
Pre-treatment nausea																		
Yes	121	81	(66.9)	122	68	(55.7)	124	69	(55.6)	112	43	(38.4)	113	61	(54.0)	119	36	(30.3)
No	102	75	(73.5)	93	50	(53.8)	104	67	(64.4)	100	42	(42.0)	102	69	(67.6)	96	30	(31.3)
Pre-treatment aura																		
Yes	49	34	(69.4)	50	23	(46.0)	42	25	(59.5)	48	18	(37.5)	46	26	(56.5)	45	18	(40.0)
No	172	121	(70.3)	160	93	(58.1)	181	105	(58.5)	161	64	(39.8)	168	103	(61.3)	169	48	(28.4)
Presence of migraine on awakening																		
Yes	111	76	(68.5)	120	66	(55.0)	93	54	(58.1)	105	39	(37.1)	100	56	(56.0)	103	31	(30.1)
No	118	81	(69.2)	94	52	(55.3)	139	83	(59.7)	111	46	(41.4)	120	77	(64.2)	115	36	(31.3)
Temporal relationship to menses[a]																		
Yes	55	39	(70.9)	37	16	(43.2)	52	32	(61.5)	46	16	(34.8)	42	20	(47.6)	50	21	(42.0)
No	138	94	(68.1)	131	74	(56.5)	151	89	(58.9)	132	52	(39.4)	139	93	(66.9)	139	37	(26.6)

[a] Female patients only. Defined as onset of migraine ≤2 days before, or ≤3 days after, the onset of menses.
N Number of attacks evaluated with baseline condition; n Number of attacks with headache response at 2 h. Headache response was defined as a reduction in headache intensity from moderate or severe to mild or none.

Source: Sponsor Table 9, analysis of 1st attack data.pdf, page 29.

As can be seen from the table above, the numerical results demonstrate ZNS efficacy (1mg and above) over placebo regardless of baseline status for all these characteristics. ZNS 0.5 mg performed better than placebo in all subgroups except for migraines associated with menses (34.8% ZNS 0.5 mg vs. 42.0% placebo). This would suggest that ZNS 0.5 mg is no better than placebo in the treatment of migraine associated with menses (a pseudo-specific indication). As would be expected clinically, the response to therapy was lower for subjects with severe pain at baseline for all cohorts compared to subjects reporting moderate pain at baseline. Likewise subjects with baseline nausea numerically tended to have a lower response to therapy in all cohorts, except ZNS 2.5 mg, than subjects without this symptom. This trend was also seen for baseline aura however it was not as consistent or pronounced. This would suggest that subjects with a more symptomatic migraine at baseline tended not to respond as well as subjects with a simple migraine without many associated symptoms.

There were no consistent findings that suggest any difference in HR2 response rates for the various ZNS doses whether or not the subjects have a migraine upon awakening or were on their menses. However, despite this finding there was clear numerical evidence that all ZNS doses 1 mg and higher and zolmitriptan tablet 2.5 mg was superior to placebo in the treatment of migraine irrespective of baseline aura or nausea, pain severity, associated menses or migraine upon awakening. In all sub-groups there was a general trend for ZNS to be more effective at treating attacks with increasing doses.

Likewise there was no evidence of any relationship between HR2 response rate and age, weight or gender as demonstrated in the following Agency table. Similar results were also seen in the multiple-attack analysis.

Table 14 HR2 by baseline age, gender and weight (ITT population, First Attack Analysis)

Headache Response at 2 hours		Randomized Treatment					
		ZNS				Zomig Oral	Placebo
		5.0 mg	2.5 mg	1.0 mg	0.5 mg	2.5 mg	na
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age Group							
18-39 years	Yes	70 (71.4)	53 (58.2)	66 (59.5)	39 (39.8)	47 (56.0)	34 (30.9)
	No	28 (28.6)	38 (41.8)	45 (40.5)	59 (60.2)	37 (44.0)	76 (69.1)
	Total	98 (100.0)	91 (100.0)	111 (100.0)	98 (100.0)	84 (100.0)	110 (100.0)
40-65 years	Yes	87 (69.9)	69 (53.1)	71 (58.7)	47 (39.5)	86 (63.2)	33 (30.6)
	No	43 (33.1)	60 (46.9)	50 (41.3)	72 (60.5)	50 (36.8)	75 (69.4)
	Total	130 (100.0)	128 (100.0)	121 (100.0)	119 (100.0)	136 (100.0)	108 (100.0)
Gender							
Female	Yes	133 (68.9)	90 (53.6)	121 (59.6)	68 (38.2)	113 (62.4)	58 (30.7)
	No	60 (31.1)	78 (46.4)	82 (40.4)	110 (61.8)	68 (37.6)	131 (69.3)
	Total	193 (100.0)	168 (100.0)	203 (100.0)	178 (100.0)	181 (100.0)	189 (100.0)
Male	Yes	24 (68.6)	31 (60.8)	16 (55.2)	18 (46.2)	20 (51.3)	9 (31.0)
	No	11 (31.4)	20 (39.3)	13 (44.8	21(53.8)	19 (48.7)	20 (69.0)
	Total	35 (100.0)	51 (100.0)	29 (100.0)	39 (100.0)	39 (100.0)	29 (100.0)
Weight							
< 50 KG	Yes	10 (83.3)	5 (62.5)	5 (62.5)	2 (33.3)	2 (33.3)	2 (33.3)
	No	2 (16.7)	3 (37.5)	3 (37.5)	4 (66.7)	4 (67.7)	5 (71.4)
	Total	12 (100.0)	8 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)	2 (100.0)
50-80 KG	Yes	119 (67.6)	90 (54.5)	111 (60.7)	70 (41.2)	102 (61.4)	54 (31.6)
	No	57 (32.4)	75 (45.5)	72 (39.3)	100 (58.8)	64 (38.6)	117 (68.4)
	Total	176 (100.0)	165 (100.0)	183 (100.0)	170 (100.0)	166 (100.0)	171 (100.0)
>80 KG	Yes	27 (69.2)	23 (54.8)	20 (50.0)	14 (36.8)	28 (59.6)	11 (28.2)
	No	12 (30.8)	19 (445.2)	20 (50.0)	24 (63.2)	19 (40.4)	28 (71.8)
	Total	39 (100.0)	42 (100.0)	40 (100.0)	38 (100.0)	47 (100.0)	39 (100.0)

Adapted from Sponsor table T7.5.1 through T7.5.3 "analysis of 1st attack data.pdf" (page 124 through 126)

The Sponsor's per-protocol multiple-attacks analysis yielded results similar to their ITT analysis. The 2-hour headache response rate was significantly greater ($p<0.01$) for each ZNS dose than for placebo[6].

6.3.4 Sponsor's Secondary Endpoints Efficacy Results from Trial 077

6.3.3.1 Headache Response at 2 Hours, ZNS versus Zolmitriptan 2.5 mg

The Sponsor conducted a secondary analysis of HR2 comparing each dose of ZNS to zolmitriptan oral tablet 2.5 mg. The results are presenting in the following Agency table. Compared to zolmitriptan 2.5 mg oral tablet, all doses of ZNS, except ZNS 0.5 mg, failed to demonstrate a significantly better response for HR2. ZNS 0.5 mg demonstrated a significantly worse response for HR2 than zolmitriptan oral tablet 2.5 mg ($p=0.001$). ZNS 5.0 mg did demonstrate a numerically higher response rate than zolmitriptan tablet 2.5 mg (68.3 vs. 60.4) however this did not reach statistical significance ($p=0.0950$). In the multiple attacks analysis the difference between ZNS 5.0 mg and zolmitriptan tablet 2.5 mg did reach statistical significance favoring ZNS 5.0 mg (70.3 vs. 61.3, $p=0.027$[7]). However when comparing products on a milligram per milligram basis, ZNS 2.5 mg and zolmitriptan tablet 2.5 mg were not statistically

[6] Source: Study report Trial 007, Multiple-Attacks Analysis, page 41.
[7] Source: Table 14, Study Report IL077.pdf (multiple attack analysis), page 60

different in either the first-attack analysis (p=0.3718) or the multiple-attacks analysis (p=0.5641[8]) for HR2.

Table 15 Analysis of HR2, First Attack (ZNS vs. oral Zolmitriptan) using ITT population

Treatment comparison vs. Zolmitriptan Tablet 2.5 mg	Estimated Response Rate (%)	Odds Ratio	95% CI	p-value
ZNS 5.0 mg	68.3	1.41	(0.94-2.10)	0.0950
ZNS 2.5 mg	56.1	0.84	(0.57-1.24)	0.3718
ZNS 1.0 mg	59.3	0.95	(0.65, 1.40)	0.8088
ZNS 0.5 mg	40.2	0.44	(0.30, 0.65)	0.0001
Zolmitriptan Tablet 2.5 mg	60.4	na	na	na

Adapted from Sponsor Table 8 and Table T7.4.5 "Analysis of First Attack Data.pdf" (page 27 and 122)

6.3.3.2 Headache Response at Various Times

Headache response at 15, 30 and 45 minutes and 1 and 4 hours were evaluated as a secondary endpoint. Each dose of ZNS was compared to placebo and zolmitriptan oral tablet 2.5 mg. The results can be seen in the following Sponsor table.

The proportion of subjects reporting a headache response at all time points (15 minutes onward) were numerically higher for all doses of ZNS compared to placebo[9]. Statistical significance between ZNS and placebo was seen at all time points for ZNS 5.0 mg and from 45 minutes onward for ZNS 2.5 mg and ZNS 1.0 mg. ZNS 0.5 mg did not demonstrate significant efficacy over placebo until the 2 hours time point (p=0.0223). Similar results were seen in the multiple-attacks analysis[10].

Table 16 Analysis of HR at various times, 1st Attack Analysis, ITT Population

Time (after dosing)	Odds ratio, (95% confidence interval), p-value							
	Zolmitriptan nasal spray versus placebo*				Zolmitriptan nasal spray versus oral zolmitriptan 2.5 mg			
	5.0 mg	2.5 mg	1.0 mg	0.5 mg	5.0 mg	2.5 mg	1.0 mg	0.5 mg
15 min	2.09	2.17	1.55	na	2.15	2.24	1.60	1.51
	(1.02, 4.26)	(1.05, 4.51)	(0.73, 3.29)		(1.05, 4.38)	(1.08, 4.64)	(0.76, 3.39)	(0.69, 3.28)
	0.0430	0.0367	0.2496		0.0355	0.0303	0.2200	0.3004
30 min	3.30	1.71	na	na	2.36	1.22	1.10	1.05
	(1.99, 5.47)	(0.99, 2.96)			(1.48, 3.77)	(0.73, 2.04)	(0.66, 1.83)	(0.62, 1.78)
	0.0001	0.0559			0.0003	0.4432	0.7269	0.8537
45 min	3.92	1.84	1.99	1.48	2.37	1.11	1.20	0.90
	(2.54, 6.07)	(1.17, 2.90)	(1.27, 3.11)	(0.93, 2.37)	(1.57, 3.58)	(0.72, 1.72)	(0.79, 1.84)	(0.57, 1.40)
	0.0001	0.0088	0.0026	0.0991	0.0001	0.6313	0.3961	0.6298
1 h	4.35	2.27	2.18	1.43	1.60	0.84	0.81	0.53
	(2.88, 6.56)	(1.49, 3.46)	(1.45, 3.30)	(0.93, 2.19)	(1.09, 2.35)	(0.57, 1.24)	(0.55, 1.18)	(0.35, 0.79)
	0.0001	0.0001	0.0002	0.1065	0.0153	0.3744	0.2683	0.0017
2 h	5.13	3.05	3.47	1.60	1.41	0.84	0.95	0.44
	(3.40, 7.73)	(2.04, 4.56)	(2.33, 5.17)	(1.07, 2.41)	(0.94, 2.10)	(0.57, 1.24)	(0.65, 1.40)	(0.30, 0.65)
	0.0001	0.0001	0.0001	0.0223	0.0950	0.3718	0.8088	0.0001
4 h	6.81	4.08	3.51	1.93	1.24	0.74	0.64	0.35
	(4.45, 10.41)	(2.71, 6.13)	(2.35, 5.23)	(1.29, 2.89)	(0.81, 1.90)	(0.49, 1.12)	(0.43, 0.95)	(0.23, 0.53)
	0.0001	0.0001	0.0001	0.0013	0.3284	0.1507	0.0280	0.0001

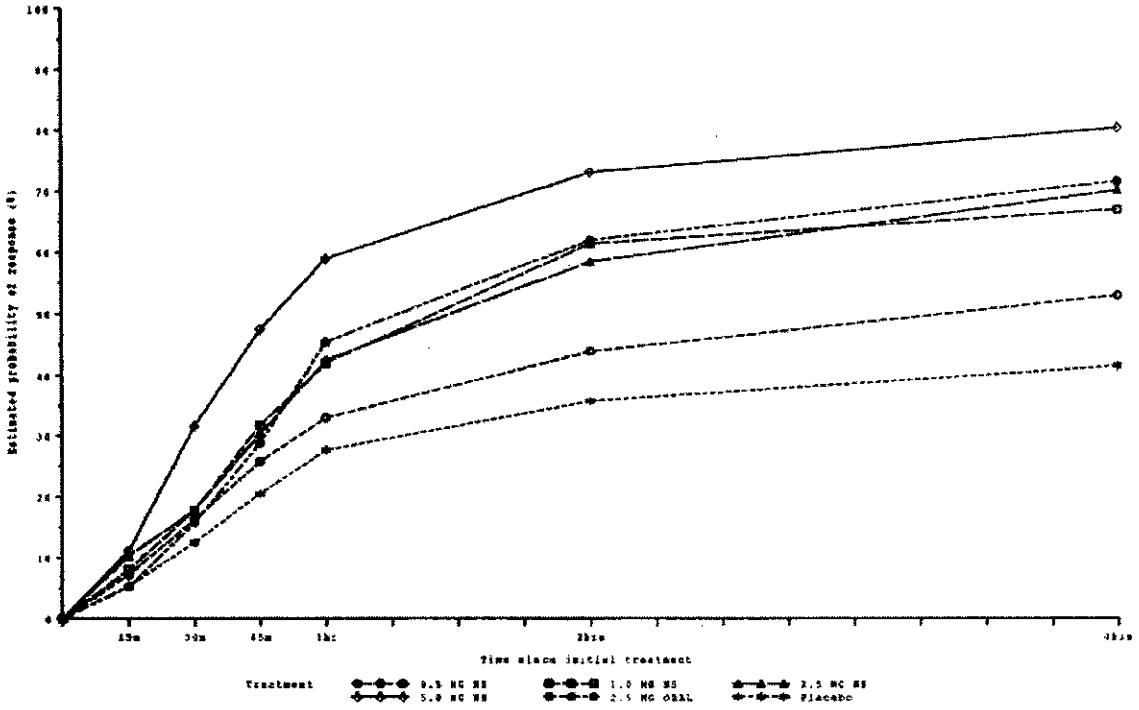
* The placebo treatment group includes patients treated with placebo nasal spray and oral placebo.
na Not analyzed - data were assessed using a step-down approach.
Source: Sponsor Table 11, analysis of 1st attack data.pdf, page 32

[8] Source: Table 14, Study Report IL077.pdf (multiple attack analysis), page 60.
[9] Source: Table 10, Study Report Analysis of 1st attack.data, page 32.
[10] Source: Table 7, Study Report IL0077.pdf (multiple attack analysis), page 65.

As seen in the above table ZNS 5.0 mg was the only nasal spray dose that consistently demonstrated significant superiority (from 15 minutes to 1 hour) in headache response over the zolmitriptan tablet 2.5 mg. At 2 hours and beyond there was a slight numerical difference favoring ZNS 5.0 mg over zolmitriptan tablet 2.5 mg, however this did not demonstrate statistical significance ($p \geq 0.0950$). This would suggest ZNS 5.0 mg may provide quicker relief of headache pain associated with migraine than does zolmitriptan tablet 2.5 mg however the benefit over the tablet is not maintained past 2 hours. It would be interesting to see whether this would hold true if the a comparison were made between ZNS 5.0 mg and zolmitriptan tablet 5.0 mg. The proportion of patients reporting headache relief early was numerically higher for ZNS 2.5 mg compared to zolmitriptan tablet 2.5 mg for the time points 15, 30 and 45 minutes. However this early time point comparison reached significance only at the 15 minutes time point (10.6% ZNS 2.5 mg vs. 5.4% zolmitriptan tablet, p=0.0303). The comparison between ZNS 2.5 mg and zolmitriptan tablet 2.5 mg was not statistically significantly different at 2 hours despite a numerical benefit (55.3 versus 60.5 respectively[11]) favoring zolmitriptan tablet 2.5 mg.

The following Sponsor figure demonstrates the estimated probability of time to first headache response within 4 hours of initial treatment. Clearly a dose response is evident for each of the ZNS doses compared to placebo. ZNS 5.0 mg demonstrates an improved response compared to zolmitriptan tablet 2.5 mg at all time points. ZNS 2.5 mg and zolmitriptan tablets 2.5 mg are nearly identical.

Figure 1 Estimated probability of time to 1st headache response within 4 hours, ITT



Source: Analysis of 1st attack data.pdf, page 242

[11] Source: Sponsor Table 10, analysis of 1st attack.pdf, page 32.

6.3.3.3 Absence of Pain

Absence of pain at various time points is defined as reporting no (0) pain at each of the time points and without the use of escape medication. The following Agency table outlines the analysis of the proportion of patients taking ZNS reporting no pain at various time points compared to patients taking placebo or zolmitriptan tablet 2.5 mg. All doses of ZNS had a greater proportion of patients reporting absence of pain at every time point compared to placebo (except ZNS 0.5 mg at 15 minutes).

Table 17 Analysis of the proportion of subjects reporting absence of pain, 1st Attack, ITT.

	Proportion of subjects reporting absents of pain (%)					
	15 min	**30 min**	**45 min**	**1 hour**	**2 hours**	**4 hours**
ZNS 5.0 mg	1.7	7.5	11.3	22.0	35.5	55.6
ZNS 2.5 mg	0.9	2.9	5.6	10.6	21.0	38.4
ZNS 1.0 mg	1.3	2.7	6.3	10.3	26.3	38.2
ZNS 0.5 mg	0.0	1.4	2.9	6.4	11.5	18.1
Zolmitriptan Tablet 2.5 mg	0.0	0.5	5.2	14.3	34.5	53.7
Placebo	0.0	0.5	2.3	3.6	6.4	9.8
Analysis of ZNS vs. Placebo (p-value)						
	15 min	**30 min**	**45 min**	**1 hour**	**2 hours**	**4 hours**
ZNS 5.0 mg	NA[1]	0.0066	0.0006	0.0001	0.0001	0.0001
ZNS 2.5 mg	NA	0.0885	0.0661	0.0049	0.0001	0.0001
ZNS 1.0 mg	NA	NA	NA	0.0070	0.0001	0.0001
ZNS 0.5 mg	NA	NA	NA	0.1539	0.0513	0.0082
Analysis of ZNS vs. Zolmitriptan Tablet 2.5 mg (p-value)						
	15 min	**30 min**	**45 min**	**1 hour**	**2 hours**	**4 hours**
ZNS 5.0 mg	NA	0.0065	0.0324	0.0524	0.9430	0.7680
ZNS 2.5 mg	NA	0.0871	0.8269	0.2819	0.0020*	0.0024*
ZNS 1.0 mg	NA	0.0993	0.6270	0.2007	0.0632*	0.0013*
ZNS 0.5 mg	NA	0.3127	0.2448	0.0110*	0.0001*	0.0001*

1. NA=not analyzed due to data analyzed using a step down approach or there was not enough data.
*Favoring zolmitriptan tablets over ZNS
Source: Sponsor Tables 12 and 13, analysis of 1st attack data.pdf, pages 35 and 36

The proportion of subjects reporting absence of pain was significantly greater for ZNS 5.0 mg than placebo ($p<0.0066$) at all analyzed time points except 15 minutes (when response rates were to low for analysis). ZNS 1.0 and 2.5 mg demonstrated statistically significant superiority over placebo ($p<0.0070$) at all time points from 1 hour onwards. ZNS 0.5 mg did not demonstrate superiority over placebo for absence of pain until the 4-hour time point ($p=0.0082$). As would be expected the magnitude of subjects reported absence of pain increased with time for all cohorts however it was dramatically lower for subjects taking placebo.

In comparison to zolmitriptan tablet 2.5 mg, ZNS 5.0 mg demonstrated statistically significant superiority for absence of pain at 30 and 45 minutes ($p\leq0.0324$). All other ZNS preparations demonstrated numerically higher but non-significant pain free rates compared to zolmitriptan tablet 2.5 mg at early time points, and were significantly inferior at later time points. This would suggest that ZNS 5.0 mg provides earlier complete relief of migraine pain compared to zolmitriptan tablet 2.5 mg however this difference is not sustained. ZNS 2.5 mg does not at any time provide superior efficacy for absents of pain compared to zolmitriptan tablet 2.5 mg and in fact is significantly inferior at 2 and 4 hours ($p\leq0.0024$). Similar results were seen in the multiple-attacks analysis.

6.3.3.5 Meaningful Migraine Relief (MMR)

The observed proportion of subjects reporting MMR at each time point is summarized in the following table. As would be expected the proportion of patients with MMR increased with time after dosing since the counting was cumulative. For ZNS 5.0 mg, 2.5 mg and 0.5 mg there appears to be a dose response at all time points for the proportion of subjects reporting MMR with the highest rates seen in the highest dose. As the dose of ZNS increased, statistically significant differences in the proportion of subjects reporting MMR compared to placebo were seen at earlier time points. (2 hours for ZNS 0.5 mg, 1 hours for ZNS 1.0 and 2.5 mg, and 30 minutes for ZNS 5.0 mg).

Comparisons between ZNS 5.0 mg and zolmitriptan tablet 2.5 mg demonstrated a statistically significant difference in the portion of patients reporting MMR, favoring ZNS 5.0 mg, at 30 through 60 minutes. No difference was seen at any time between ZNS 1.0 and 2.5 mg compared to zolmitriptan tablet 2.5 mg. The ZNS 0.5 mg was significantly worse than zolmitriptan tablet 2.5 mg for MMR at 2 hours and beyond.

Table 19 MMR rates (ZNS vs. zolmitriptan tablet and placebo, ITT)

Time post-dose	Zolmitriptan nasal spray												Oral zolmitriptan 2.5 mg	Placebo[a]
	5.0 mg			2.5 mg			1.0 mg			0.5 mg				
	Rate[b]	Significance vs		Rate[b]	Significance vs		Rate[b]	Significance vs		Rate[b]	Significance vs		Rate[b]	Rate[b]
		PBO	Oral		PBO	Oral		PBO	Oral		PBO	Oral		
15 min	3.7	na	ns	2.4	na	ns	3.8	na	ns	0.5	na	ns	1.9	2.1
30 min	11.6	+	+	7.3	ns	ns	10.4	ns	ns	3.8	na	ns	5.2	5.2
45 min	19.5	+	+	13.7	ns	ns	18.5	ns	ns	9.2	na	ns	11.8	9.4
1 h	35.3	+	+	25.4	+	ns	26.1	+	ns	18.5	ns	ns	22.2	15.1
2 h	57.7	+	ns	43.5	+	ns	47.2	+	ns	34.2	-	-	50.9	24.0
4 h	76.3	+	ns	60.8	+	ns	63.3	+	ns	47.3	-	-	69.3	27.7

[a] The placebo treatment group includes patients treated with placebo nasal spray and oral placebo.
[b] Rate of meaningful migraine relief (percentage of first attacks where meaningful migraine relief was recorded at specified time point).
PBO Placebo.
+ Statistically significant in favor of the zolmitriptan nasal spray dose ($p<0.05$).
- Statistically significant in favor of the oral zolmitriptan 2.5 mg dose ($p<0.05$).
ns Not significant.
na Not analyzed -- data were assessed using a step-down approach.
Data derived from Table T11.1 (rates), T11.3.1 through T11.4.6 (statistical significance).

Source: Sponsor Table 16, analysis of 1st attack data.pdf, page 40.

Global patient assessments of benefit are becoming more frequent in clinical trials and are frequently used by Sponsors to distinguish their product from their competitors. Unfortunately the clinical usefulness of MMR is limited by the subjective character of the endpoint and the fact that patients were not permitted to alter the MMR time point if they were to change their mind for some reason. However the results of this analysis suggests that patients are able to distinguish a subjective benefit from ZNS 5.0 mg earlier than what they perceive from taking zolmitriptan tablet 2.5 mg. Again this comparison would have more clinical strength if the comparator was zolmitriptan tablet 5.0 mg. It is interesting to note that patients where unable to perceive a difference between ZNS 2.5 mg and placebo until 1 hour and at no time where they able to perceive a difference for MMR when compared to zolmitriptan tablet 2.5 mg. Similar results were seen in the multiple-attacks analysis.

6.3.3.6 Use of Escape Medication

The proportion and analysis of patients using escape medication within 24 hours of treatment is outlined in the following Agency table. A clear dose response for the proportion of patients using escape medication was seen for all doses of ZNS with ZNS 5.0 mg using the least amount (32.8%) of rescue medication and ZNS 0.5 mg using the most (60.6%). The proportion of ZNS

patients using escape medication compared favorably to the proportion of placebo patients using escape medication. Statistical comparisons between ZNS and placebo showed that there was significantly greater use of escape medication in the placebo group than amongst all the ZNS cohorts ($p \leq 0.006$).

The comparison of ZNS cohorts to zolmitriptan tablet 2.5 mg is not as favorable. The proportion of subjects using escape medication from ZNS 5.0 mg and zolmitriptan tablet 2.5 mg were nearly identical numerically and showed no statistical difference ($p=0.9564$) and the ZNS 2.5 mg group used numerically and statistically ($p=0.0209$) more escape medication than the oral preparation cohort. This would suggest that patients with migraine taking ZNS 5.0 mg or 2.5 mg would require escape medication as frequently or potentially more frequently than patients taking zolmitriptan tablet 2.5 mg. Similar results were seen in the multiple-attacks analysis.

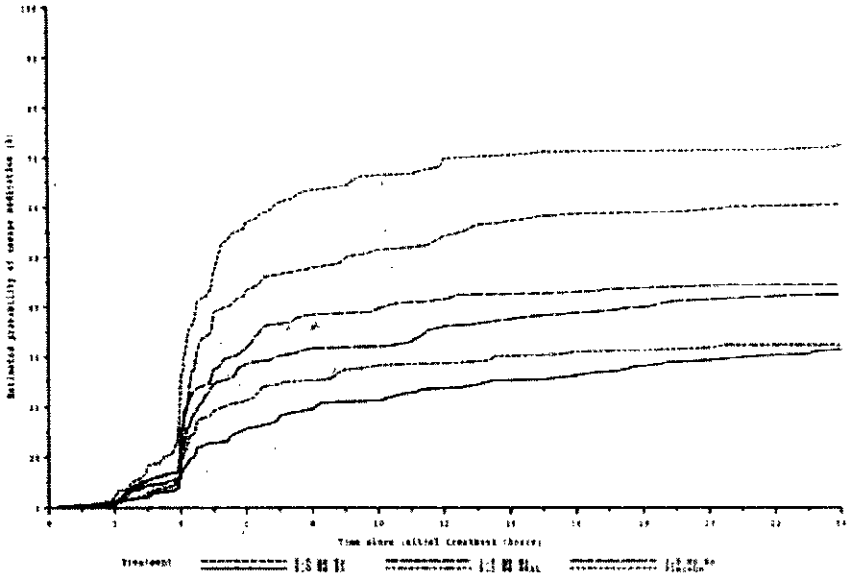
Table 20 Use of escape medication -- 1st Attack (ITT population)

	Treatment groups					
	ZNS 5.0	**ZNS 2.5**	**ZNS 1.0**	**ZNS 0.5**	**Zolmitriptan Tab 2.5 mg**	**Placebo**
Patients using escape medication n (%)	77 (32.8)	100 (44.6)	109 (46.2)	134 (60.6)	76 (33.2)	170 (75.2)
	Comparison ZNS treatment vs. placebo					
Odds Ratio	0.16	0.25	0.28	0.49	na	na
95 % CI	(0.11, 0.24)	(0.17, 0.38)	(0.19, 0.41)	(0.32, 0.73)	na	na
p-value	0.0001	0.0001	0.0001	0.0006	na	na
	Comparison ZNS treatment vs. Zolmitriptan Tablet 2.5 mg					
Odds Ratio	0.99	1.57	1.73	3.04	na	na
95 % CI	(0.67, 1.46)	(1.07, 2.31)	(1.18, 2.53)	(2.06, 4.48)	na	na
p-value	0.9564	0.0209	0.0046	0.0001	na	na

Adapted from Sponsor Tables 18, 19 and 20 from "Analysis of 1st Attack" study 077 (pages 42-43)

The following Sponsor table demonstrates the estimated probability of patients taking escape medication within 24 hours of treatment. A dose response is evident with ZNS 5.0 mg using the least amount of escape medication and ZNS 0.5 mg using the most.

Figure 2 Estimated probability of patients taking escape medication



Source: Sponsor Figure 2, page 243/295, "analysis of 1st attack data.pdf

6.3.3.7 Resumption of Normal Activity

The following Sponsor table demonstrates the proportion of subjects that were able to resume normal activity for each cohort. The results are only for those subjects reporting diminished activity at baseline. As with many of the other secondary endpoints there appears to be a dose response for each of the ZNS cohorts with patients in the highest dose group being able to resume normal activity sooner than patients in the lower dose groups.

At each time point the proportion of patients able to resume normal activity taking ZNS 5.0 mg was greater than the proportion of patients able to resume normal activity taking zolmitriptan tablet 2.5 mg. However, ZNS 2.5 mg, ZNS 1.0 mg and zolmitriptan tablet 2.5 mg all appeared to be equivalent until the 4 hour time point, when the oral dose was more effective than either dose of nasal spray. Similar results were seen in the multiple-attacks analysis.

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Table 21 Resumption of normal activity (1st attack, ITT)

Time point	Number (%) of attacks											
	Zolmitriptan nasal spray								Oral zolmitriptan		Placebo[a]	
	5.0 mg Patients = 235		2.5 mg Patients = 224		1.0 mg Patients = 236		0.5 mg Patients = 221		2.5 mg Patients = 229		Patients = 226	
	(N=188)		(N=204)		(N=191)		(N=176)		(N=184)		(N=191)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
15 min	13	(7.0)	11	(5.6)	12	(6.3)	4	(2.3)	3	(1.7)	6	(3.2)
30 min	29	(15.8)	22	(11.4)	18	(10.0)	12	(7.1)	16	(9.2)	9	(5.1)
45 min	51	(28.7)	34	(17.8)	35	(19.3)	20	(11.9)	28	(16.8)	22	(11.8)
1 h	71	(38.2)	50	(25.3)	47	(25.0)	36	(20.6)	50	(27.8)	25	(13.5)
2 h	94	(51.1)	81	(41.3)	81	(43.1)	55	(32.0)	77	(43.0)	32	(17.1)
4 h	118	(66.3)	95	(49.0)	102	(55.7)	54	(31.8)	110	(63.6)	48	(26.5)

[a]The placebo treatment group includes patients treated with placebo nasal spray and oral placebo.
N Number of attacks evaluated with normal activities limited at baseline.
n Number of attacks evaluated in which resumption of normal activities was recorded, when normal activities were limited at baseline.
Data derived from Table T13.

Source: Sponsor Table 21, analysis of 1st attack data.pdf, page 44.

At each time point ZNS 5.0 mg numerically appears to provide some additional benefit over zolmitriptan tablet 2.5 mg for the resumption of normal activity however the oral preparation seems to provide additional benefit compared to equivalent and lower ZNS doses at later times.

6.3.3.8 Headache Recurrence within 24-Hours

The observed proportions of patients reporting a headache recurrence within 24 hours are presented in the following Sponsor table. For a headache to be defined as a recurrence the patient must have reported a headache response at 2 hours. The proportion of patients reporting a headache recurrence was similar in all treatment groups including placebo. There was however a clear dose-response for the various ZNS doses and time to recurrence after dosing with the highest ZNS dose having the longest period of time before headache recurrence (ZNS 5.0 mg, 540 minutes) and the lowest ZNS dose having the shortest (ZNS 0.5 mg, 240 minutes). Zolmitriptan tablet 2.5 mg was comparable to ZNS 5.0 mg for time to headache recurrence (525 minutes vs. 540 minutes respectively) but was better than ZNS 2.5 mg (424 minutes) in delaying the onset of a headache recurrence. This would suggest that on a milligram for milligram bases, nasal formulations of zolmitriptan dose not provide any benefit over oral formulation for headache recurrence. In fact, when comparing ZNS 2.5 mg to zolmitriptan tablet 2.5 mg it appears the oral formulation may be better at delaying the onset of headache recurrence although both cohorts tended to have the same proportion of patients reporting a recurrence within 24 hours.

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Table 22 Headache recurrence within 24 hours (1st attack, ITT population)

Headache recurrence	Number (%) of attacks					
	Zolmitriptan nasal spray				Oral zolmitriptan	Placebo[a]
	5.0 mg (N=235)	2.5 mg (N=224)	1.0 mg (N=236)	0.5 mg (N=221)	2.5 mg (N=229)	(N=226)
Number of attacks with response at 2 h	157	121	137	86	133	67
Number (%[b]) of attacks with recurrence	42 (26.8)	33 (27.3)	40 (29.2)	25 (29.1)	35 (26.3)	21 (31.3)
Time to recurrence[c] (minutes)	540	424	241	240	525	175

[a] The placebo treatment group includes patients treated with placebo nasal spray and oral placebo.
[b] The number of 1st attacks with recurrence is expressed as a percentage of 1st attacks with response at 2 h.
[c] Kaplan-Meier estimate of time to recurrence at 10th percentile.
N number of patients.
Data derived from Tables T16.1 (recurrence rate), T16.3 (time to recurrence).
Source: Sponsor table 22, analysis of 1st attack data.pdf, page 45

In the multiple-attacks analysis, the placebo cohort tended to have a larger proportion of subjects expereincing a migraine recurrence (34.0%) than subjects treated with any of the ZNS preparations (range 25.1 to 28.2)[12]. The conclusions are otherwise similar to that seen with the single-attack analysis.

6.3.3.9 Complete Response

Complete response is defined as 2-hour headache response for which recurrence or use of escape medication did not occur within 24 hours of treatment. Complete response includes subjects with persistent mild pain unlike the absence of pain endpoint. The results of the Sponsor's first-attack ITT analysis is presented in the following Sponsor table. As can be seen, all ZNS doses provided a clear advantage over placebo in the proportion of patients reporting a complete response over 24 hours. In comparison to zolmitriptan tablet 2.5 mg, ZNS 5.0 mg provided a slight benefit in the proportion of subjects reporting a complete response (42.3 % versus 47.4% respectively). However on a milligram for milligram bases zolmitriptan tablet 2.5 mg appears to provide a slight benefit over ZNS 2.5 mg in complete response (42.3% versus 35.6% respectively). Similar results were seen with the multiple-attacks analysis.

[12] Source: Sponsor Table 28, IL0077.pdf (multiple attack analysis) page 80.

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Table 23 Complete response, 1st attack, ITT population

Response	Number (%) of attacks											
	Zolmitriptan nasal spray								Oral zolmitriptan		Placebo[a]	
	5.0 mg (N=235)		2.5 mg (N=224)		1.0 mg (N=236)		0.5 mg (N=221)		2.5 mg (N=229)		(N=226)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Attacks with complete response	108	(47.4)	78	(35.6)	86	(37.2)	52	(24.0)	93	(42.3)	30	(13.8)

[a] The placebo treatment group includes patients treated with placebo nasal spray and oral placebo.
N Number of patients.
n Number of attacks with complete response.
Data derived from Table T17.

Source: Sponsor Table 23, analysis of 1st attack data.pdf, page 46

6.3.3.10 Improvement in Photophobia, Phonophobia, Nausea, and Somnolence

The proportion of attacks with an "improvement" (resolution of baseline symptom) in photophobia, phonophobia, nausea or somnolence at each time point is presented in the following Agency table. [redacted] Percentages are based on the number of patient experiencing each symptom at baseline and subsequently recording a response at the various time points. The Sponsor did not perform any statistical analyses of these results.

When comparing the percentages it is apparent that ZNS 5.0 mg provides a clear advantage over placebo for each symptom at each time point in the proportion of patients reporting resolution of their baseline symptom. For the 2-hour time point 57.7% of the ZNS 5.0 mg patients with photophobia at baseline reported no photophobia hours compared to 27.9% of the placebo patients. The results at 2 hours were similar for phonophobia (ZNS 5.0 mg 62.0% vs. placebo 23.3%), nausea (ZNS 5.0 mg 60.8% vs. placebo 43.7%), and somnolence (ZNS 5.0 mg 43.9% vs. placebo 23.3%). Similar results were seen at 2 hours for the comparison between ZNS 2.5 mg vs. placebo and ZNS 0.5 mg vs. placebo. When comparing ZNS 2.5 mg and ZNS 5.0 mg to zolmitriptan tablet 2.5 mg the results suggest there is little difference between these products except for a slight improvement of ZNS 5.0 mg over the other two products. Similar results were seen in the multiple-attacks analysis.

Table 24 Proportion of patients with improvement in associated symptoms by time

		15 min	30 min	45 min	1 hour	2 hours	4 hours
Photophobia							
ZNS 5.0 mg	N	172	168	166	170	168	162
	n (%)	17 (9.9)	37 (22.0)	54 (32.5)	63 (37.1)	97 (57.7)	107 (66.0)
ZNS 2.5 mg	N	160	157	160	161	163	162
	n (%)	11 (6.9)	22 (14.0)	33 (20.6)	52 (32.3)	75 (46.0)	93 (57.4)
ZNS 0.5 mg	N	154	149	152	156	154	154
	n (%)	5 (3.2)	12 (8.1)	17 (11.2)	29 (18.6)	53 (34.4)	60 (39.0)
Zolmitriptan Tab 2.5 mg	N	171	164	159	172	169	165
	n (%)	10 (5.8)	26 (15.9)	32 (20.1)	61 (35.5)	82 (48.5)	104 (63.0)
Placebo	N	175	166	176	175	172	172
	n (%)	7 (4.0)	12 (7.2)	20 (20.1)	36 (20.6)	48 (27.9)	45 (26.2)
Phonophobia							
ZNS 5.0 mg	N	143	143	142	144	142	135
	n (%)	18 (12.6)	40 (28.0)	54 (38.0)	68 (47.2)	88 (62.0)	97 (71.9)
ZNS 2.5 mg	N	133	130	132	135	137	136
	n (%)	15 (11.3)	20 (15.4)	43 (32.6)	59 (43.7)	78 (56.9)	81 (59.6)
ZNS 0.5 mg	N	126	122	124	126	123	123
	n (%)	6 (4.8)	14 (11.5)	24 (19.4)	32 (25.4)	45 (36.6)	54 (43.9)
Zolmitriptan Tab 2.5 mg	N	138	133	131	138	139	130
	n (%)	10 (7.2)	23 (17.3)	33 (25.2)	46 (33.3)	74 (53.2)	86 (66.2)
Placebo	N	132	122	130	130	129	125
	n (%)	4 (3.0)	7 (5.7)	12 (9.2)	26 (20.0)	30 (23.3)	32 (25.6)
Nausea							
ZNS 5.0 mg	N	125	123	117	121	120	117
	n (%)	16 (12.8)	30 (24.4)	49 (41.9)	57 (47.1)	73 (60.8)	83 (70.9)
ZNS 2.5 mg	N	119	120	120	123	120	119
	n (%)	17 (14.3)	33 (27.5)	40 (33.3)	49 (39.8)	64 (53.3)	74 (62.2)
ZNS 0.5 mg	N	111	106	108	114	111	111
	n (%)	12 (10.8)	25 (23.6)	29 (26.9)	38 (33.3)	51 (45.9)	55 (49.5)
Zolmitriptan Tab 2.5 mg	N	116	110	112	114	112	111
	n (%)	17 (14.7)	23 (20.9)	32 (28.6)	47 (41.2)	55 (49.1)	73 (65.8)
Placebo	N	119	116	121	122	119	116
	n (%)	13 (10.9)	22 (19.0)	32 (26.4)	42 (34.4)	52 (43.7)	47 (40.5)
Somnolence							
ZNS 5.0 mg	N	125	121	115	124	123	121
	n (%)	13 (10.4)	22 (18.2)	31 (27.0)	40 (32.3)	54 (43.9)	66 (54.5)
ZNS 2.5 mg	N	118	114	117	117	119	118
	n (%)	9 (7.6)	16 (14.0)	20 (17.1)	27 (23.1)	44 (37.0)	55 (46.6)
ZNS 0.5 mg	N	109	106	107	110	109	109
	n (%)	10 (9.2)	16 (15.1)	23 (21.7)	27 (24.5)	39 (35.8)	45 (41.3)
Zolmitriptan Tab 2.5 mg	N	119	116	110	122	116	115
	n (%)	13 (10.9)	20 (17.2)	22 (20.0)	25 (20.5)	39 (33.6)	55 (47.8)
Placebo	N	115	115	117	116	116	117
	n (%)	9 (7.8)	18 (15.7)	24 (20.5)	27 (23.3)	27 (23.3)	29 (24.8)

Adapted from Sponsor Table 24, Study Report 077, analysis of 1st attack data.pdf, pages 47-49.
"N" Number of patients experiencing the symptom at baseline, and recording a response at this time point
"n" Number of patients who recorded an improvement in symptom for specific time point

The manner in which the Sponsor chose to present these important associated symptoms is generally not what we request for migraine studies in this Division. Typically we request a comparison of the proportion of subjects with each of these associated symptoms at the various time points with particular attention paid to the primary endpoint time point (i.e., 2 hours in this study). In section 6.3.5 I present my own analysis of this data using the Agency preferred method.

6.3.3.11 Global Impression

The following Sponsor table demonstrates patient's global impression of satisfaction with treatment collected at the completion of the study. Due to the limitations of the trial design it is

not possible to discuss Global Impression after the treatment of the first migraine hence the results reflect the patient's opinion at the end of the study. As can be seen from the table there is a clear dose response for patients reporting each response (excellent through poor) favoring ZNS 5.0 mg over placebo. The comparison of responses between ZNS 2.5 mg and zolmitriptan tablet 2.5 mg suggests patients were nearly equally satisfied/dissatisfied with both products.

Table 25 Global Impression

Global satisfaction rating	Number of patients (%)[a]											
	Zolmitriptan nasal spray								Oral zolmitriptan		Placebo	
	5.0 mg (N = 235)		2.5 mg (N = 224)		1.0 mg (N = 236)		0.5 mg (N = 221)		2.5 mg (N = 230)		(N = 226)	
Excellent	34	(14.5)	18	(8.1)	14	(5.9)	6	(2.7)	25	(10.9)	6	(2.7)
Good	101	(43.0)	82	(36.8)	64	(27.1)	40	(18.1)	79	(34.5)	24	(10.6)
Fair	56	(23.8)	54	(24.2)	58	(24.6)	55	(24.9)	63	(27.5)	45	(19.9)
Poor	44	(18.7)	69	(30.9)	100	(42.4)	120	(54.3)	62	(27.1)	151	(66.8)
Number of responders	235		223		236		221		229		226	

[a] Percentages calculated from the number of responders in each group.
N Number of patients.
Source: Sponsor Table 30, IL0077.pdf (multiple attack analysis) page 82.

6.3.3.12 Consistency of Headache Response

The consistency of headache response is defined as the proportion of patients who report a headache response at 1, 2, and 4 hours, in between 50 to 100% of the migraine attacks assessed. The following table demonstrates the Sponsor's results. As can be seen the consistency of response increased with increased dose of ZNS in comparison to placebo. The ZNS 5.0 mg group reported better consistency than the zolmitriptan tablet 2.5 mg group however the ZNS 2.5 mg group did not. This would suggest that on a milligram per milligram bases ZNS does not provide any additional benefit over zolmitriptan 2.5 mg for consistency of response.

Table 26 Headache response in patient responding in 50% or 100% of attacks[a]

Category	Zolmitriptan nasal spray												Oral zolmitriptan			Placebo		
	5.0 mg			2.5 mg			1.0 mg			0.5 mg			2.5 mg					
	N	n	(%)[b]	N	n	(%)[b]	N	n	(%)[b]	N	n	(%)[b]	N	n	(%)[b]	N	n	(%)[b]
≥50% of attacks																		
1 h	201	126	(62.7)	188	85	(45.2)	197	80	(40.6)	182	61	(33.5)	183	93	(50.8)	174	48	(27.6)
2 h	200	154	(77.0)	189	113	(59.8)	198	124	(62.6)	182	83	(45.6)	182	129	(70.9)	170	60	(35.3)
4 h	198	166	(83.8)	188	140	(74.5)	194	133	(68.6)	181	92	(50.8)	179	143	(79.9)	171	55	(32.2)
100% of attacks																		
1 h	201	59	(29.4)	188	42	(22.3)	197	24	(12.2)	182	16	(8.8)	183	42	(23.0)	174	15	(8.6)
2 h	200	93	(46.5)	189	64	(33.9)	198	43	(21.7)	182	34	(18.7)	182	76	(41.8)	170	16	(9.4)
4 h	198	113	(57.1)	188	72	(38.3)	194	54	(27.8)	181	38	(21.0)	179	93	(52.0)	171	14	(8.2)

n Number of patients responding
N Total number of patients
[a] Minimum of 2 attacks treated
[b] Percentages calculated from the number of responders in each group.
Source: Sponsor Table 32, IL0077.pdf (multiple attack analysis) page 85.

6.3.5 Agency's Efficacy Results

In this section I describe the efficacy analysis I performed. Results from the Agency statistician's analyses may be included as needed. My comments about the Sponsor's efficacy analyses can be found throughout the preceding sections. In my own analysis of the primary endpoint I use the data from the first migraine attack only. The sponsor's data file named "Diary V" was the primary dataset used. For headache response and associated symptoms I analyzed only data from

the first migraine treated and included all subjects that took study medication and provided at least a single post treatment efficacy assessment. Missing data was handled using an LOCF algorithm. Patients that took rescue medication were treated as treatment failures for all subsequent time points. My analysis is crude as it does not adjust for center nor correct for multiple endpoints.

The following table demonstrates my results for headache response at the various time points. As can be seen my results are nearly identical to those obtained by the sponsor (see sponsor Table 16). All doses of ZNS were significantly better than placebo in the proportion of patients reporting headache relief at 2 hours ($p \leq 0.03$). The cohort of subjects in the higher doses of ZNS reached significance as early as 15 minutes after treatment. This differs slightly from the Agency statistician's results where the comparison between placebo and ZNS 0.5 mg at 2 hours was just beyond the range of significance ($p = 0.053$). The statistician's method of analysis is discussed in detail in his review however he used a logistical regression method excluding the zolmitriptan tablet 2.5 mg cohort of patients. The sponsor did not exclude this cohort from their analysis, which the Agency statistician felt was faulty. Despite the failure of ZNS 0.5 mg to demonstrate significance at 2 hours in the Agency-statistician's analysis, I believe the totality of the results and the clinical utility of a low-dose treatment option would still favor the approval of ZNS 0.5 mg.

Table 27 Headache response at various time points, 1st attack, ITT_{AGENCY}

		Headache response					
		15 min	30 min	45 min	1 hour	2 hours	4 hours
ZNS 5.0 mg N= 236	**n (%)**	27 (11.5)	74 (31.5)	110 (46.8)	137 (58.3)	163 (69.0)	175 (74.5)
	p-value	**0.02**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
ZNS 2.5 mg N= 224	**n (%)**	23 (10.7)	39 (17.7)	65 (29.2)	90 (40.2)	124 (55.4)	142 (63.4)
	p-value	0.04	0.10	**0.02**	**<0.01**	**<0.01**	**<0.01**
ZNS 1.0 mg N= 236	**n (%)**	19 (8.2)	40 (17.0)	72 (30.6)	95 (40.3)	138 (58.5)	143 (60.6)
	p-value	0.25	0.13	**<0.01**	**<0.01**	**<0.01**	**<0.01**
ZNS 0.5 mg N= 223	**n (%)**	18 (8.2)	38 (17.0)	57 (25.6)	68 (30.5)	91 (40.8)	101 (45.3)
	p-value	0.25	0.13	0.11	0.13	**0.03**	**<0.01**
Zolmitriptan Tab 2.5 mg N= 232	**n (%)**	13 (5.7)	36 (15.6)	66 (28.6)	104 (44.8)	138 (59.5)	175 (74.5)
	p-value	0.89	0.28	0.02	<0.01	<0.01	<0.01
Placebo N= 226	**n (%)**	12 (5.4)	27 (12.1)	43 (19.2)	54 (24.1)	69 (30.8)	69 (30.8)

As part of my review of efficacy I also analyzed the range of actual times subjects recorded their 2 hour assessment. A 90 minute range (91 to 181 minutes) was permitted by protocol. During Trial 077 patients recorded their 2 hour assessment as early as 75 minutes after taking study medication and as late as 3 hours after taking study medication. However, approximately 93% of subjects (1274/1371) recorded their 2 hour assessment within ± 15 minutes of 2 hours. My analysis of 2 hour headache response for those subjects recording their response within 15 minutes of 2 hours is demonstrated in the following Agency table. This analysis is quite crude in that is does not include a correction for missing data or for taking escape medication. As can be seen my results are again nearly identical to the sponsor's results using their ITT population (see Table 11). The one difference is that with this subset of patients the comparison between ZNS 0.5

mg and placebo is no longer significant with a p-value equal to 0.0904 compared to the sponsor's result of 0.0223. Despite the failure of ZNS 0.5 mg to demonstrate significance at 2 hours in the proportion of patients reporting their 2 hour assessment within 15 minutes of 2 hours, I believe the totality of the results and the clinical utility of a low-dose treatment option would still favor the approval of ZNS 0.5 mg.

Table 28 Headache response at 2 hours, 1st Attack Analysis, Subset response recorded ±15 min of 2 hrs

	ZNS 5.0 mg (N=235)	ZNS 2.5 mg (N=224)	ZNS 1.0 mg (N=236)	ZNS 0.5 mg (N=221)	Zolmitriptan Tab 2.5 mg (N=229)	Placebo (N=226)o
Patients evaluated at 2 hrs ±15 mins.	222	203	223	210	207	209
Patients with 2 hrs response (%)	154 (69.4)	112 (55.2)	130 (58.3)	84 (40.0)	126 (60.9)	67 (32.1)
Treatment comparison: Treatment vs. placebo						
p-value	<0.0001	<0.0001	<0.0001	0.0904	<0.001	

As discussed earlier, the sponsor did not analyze the proportion of patients reporting an associated symptom at the various time points. Their approach for this critical secondary endpoint was to look at subjects that reported resolution of baseline symptoms at the various time points. In my analysis of these endpoints I analyze the proportion of subjects reporting each of these symptoms at the various time points and compare the results to placebo. To perform this analysis I only looked at data from the first migraine attack treated and included all subjects that took trial medication and recorded a post-treatment efficacy results for these endpoints (nausea, photophobia and phonophobia). A last-observation-carried forward algorithm was used for missing data.

The following table illustrates my results, using a Chi Square analysis, of the proportion of patients reporting an associated symptom the various time points. As demonstrated, the proportion of patients receiving ZNS (any dose) reporting photophobia at 2 hours was significantly less than the proportion of patients receiving placebo ($p \leq 0.03$). The results for phonophobia at 2 hours were nearly identical to the results for phonophobia however the ZNS 0.5 mg cohort did not precisely reach significance ($p=0.06$). It is possible this cohort would have reached significance if I had adjusted for center in my analysis.

Unfortunately the results for nausea are not as favorable at 2 hours where only the ZNS 5 mg cohort of patients reported significantly less nausea than subjects receiving placebo ($p<0.01$). The reason for this apparent lack of efficacy against nausea is not apparent but could lie in the fact that the ZNS formulation is known to cause abnormal taste perversion. Such an adverse event would certainly be expected to exasperate pre-existing nausea or cause nausea in subjects prone to nausea (i.e., migraine sufferers). Another point to consider is the fact that despite having previously been shown effective against migraine associated nausea, zolmitriptan tablet 2.5 mg also failed against placebo at 2 hours. The reason for this is not apparent but suggests perhaps the study itself may have had problems for this endpoint. Despite the failure of ZNS 2.5 mg and below to show efficacy for nausea at 2 hours there was evidence of a dose effect with all doses of ZNS being numerically better than placebo for the proportion of patients reporting nausea at 2 hours. The efficacy of ZNS against nausea was apparent at 4 hours where all doses were significantly better than placebo for the proportion of patients reporting nausea.

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Table 29 Proportion of patients reporting an associated symptom by time, 1st Attack[1]

		Baseline	15 min	30 min	45 min	1 hour	2 hours	4 hours
Nausea								
ZNS 5.0 mg N= 236	**n (%)**	127 (55.0)	114 (48.9)	104 (44.4)	**83 (35.3)**	**73 (31.1)**	**59 (25.1)**	**41 (17.5)**
	p-value	0.97	0.64	0.57	**0.05**	**0.05**	**<0.01**	**<0.01**
ZNS 2.5 mg N= 224	**n (%)**	126 (57.3)	116 (54.7)	101 (46.3)	92 (41.4)	89 (39.9)	67 (29.9)	**51 (22.8)**
	p-value	0.65	0.46	0.87	0.56	0.97	0.11	**<0.01**
ZNS 1.0 mg N= 236	**n (%)**	125 (53.9)	114 (49.8)	112 (48.1)	94 (40.3)	80 (34.2)	71 (30.3)	**62 (26.4)**
	p-value	0.78	0.77	0.83	0.40	0.22	0.13	**<0.01**
ZNS 0.5 mg N= 223	**n (%)**	116 (53.2)	105 (48.4)	103 (46.8)	98 (44.6)	88 (39.8)	76 (34.4)	**70 (31.5)**
	p-value	0.68	0.57	0.96	0.94	0.99	0.56	**0.06**
Zolmitriptan Tab 2.5 mg N= 232	**n (%)**	117 (51.8)	105 (47.5)	105 (46.3)	97 (42.7)	88 (38.6)	75 (32.9)	46 (20.2)
	p-value	0.47	0.45	0.86	0.75	0.80	0.35	0.04
Placebo N= 226	**n (%)**	123 (55.2)	112 (51.1)	105 (47.1)	99 (44.2)	89 (39.7)	83 (37.1)	90 (40.2)
Phonophobia								
ZNS 5.0 mg N= 236	**n (%)**	144 (62.6)	128 (55.4)	**107 (45.9)**	**93 (39.9)**	**77 (33.1)**	**61 (26.0)**	**42 (17.9)**
	p-value	0.42	0.32	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
ZNS 2.5 mg N= 224	**n (%)**	140 (63.4)	119 (56.4)	116 (53.0)	**95 (43.0)**	**80 (36.0)**	**62 (27.8)**	**57 (25.6)**
	p-value	0.34	0.45	0.19	**<0.01**	**<0.01**	**<0.01**	**<0.01**
ZNS 1.0 mg N= 236	**n (%)**	143 (61.4)	140 (61.1)	128 (54.9)	113 (48.5)	101 (43.4)	**83 (35.6)**	**65 (27.9)**
	p-value	0.59	0.81	0.36	0.07	0.14	**<0.01**	**<0.01**
ZNS 0.5 mg N= 223	**n (%)**	129 (59.2)	126 (58.3)	120 (54.6)	109 (49.6)	102 (46.4)	**90 (40.9)**	**81 (36.7)**
	p-value	0.96	0.72	0.32	0.12	0.42	**0.06**	**0.01**
Zolmitriptan Tab 2.5 mg N= 232	**n (%)**	142 (62.6)	129 (59.2)	118 (52.4)	105 (46.7)	95 (41.9)	69 (30.4)	51 (22.5)
	p-value	0.43	0.86	0.15	0.03	0.07	<0.01	<0.01
Placebo N= 226	**n (%)**	132 (59.0)	132 (60.0)	132 (59.2)	127 (57.0)	112 (50.2)	111 (49.8)	108 (48.3)
Photophobia								
ZNS 5.0 mg N= 236	**n (%)**	173 (74.3)	**156 (67.0)**	**135 (57.9)**	**118 (50.6)**	**109 (46.6)**	**75 (31.9)**	**57 (24.3)**
	p-value	0.21	**0.02**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	<0.01
ZNS 2.5 mg N= 224	**n (%)**	167 (75.6)	154 (72.0)	**145 (65.9)**	**135 (60.8)**	**115 (51.6)**	**92 (41.3)**	**72 (32.3)**
	p-value	0.36	0.24	**0.03**	**0.01**	**<0.01**	**<0.01**	**<0.01**
ZNS 1.0 mg N= 236	**n (%)**	183 (78.5)	177 (77.0)	166 (71.6)	151 (65.1)	138 (59.2)	**103 (44.2)**	**87 (37.3)**
	p-value	0.86	0.99	0.35	0.10	0.13	**<0.01**	**<0.01**
ZNS 0.5 mg N= 223	**n (%)**	159 (72.0)	157 (72.4)	154 (69.7)	147(66.5)	135 (61.1)	**111 (50.2)**	**99 (44.6)**
	p-value	0.07	0.27	0.17	0.18	0.27	**0.03**	**<0.01**
Zolmitriptan Tab 2.5 mg N= 232	**n (%)**	176 (77.2)	164 (73.5)	154 (67.5)	141 (61.8)	119 (52.0)	91 (39.7)	67 (29.3)
	p-value	0.60	0.41	0.06	0.02	<0.01	<0.01	<0.01
Placebo N= 226	**n (%)**	179 (78.2)	170 (76.9)	169 (75.5)	162 (72.3)	148 (66.1)	136 (60.7)	131 (58.5)

[1] Using Pearson Chi-Square analysis with LOCF for missing data.

In summary, my analysis of the primary endpoint and the interpretation of the results from the analysis of the associated symptoms supports the approval of ZNS 0.5 mg and higher.

6.4 Efficacy Conclusions

The primary objective of this efficacy trial is to assess the efficacy of ZNS 5.0, 2.5, 1.0, and 0.5 mg doses compared to placebo for headache relief at 2 hours. The Sponsor seeks Agency approval of ZNS 5.0 mg,

Table 30 Summary of statistical analysis, ZNS vs. placebo/zolmitriptan tablet 2.5 mg

Endpoint	Comparison of ZNS vs. placebo/ZNS 5.0 mg vs. zolmitriptan tablet 2.5 mg at various times after treatment					
	15 min	30 min	45 min	1 hr	2 hr	4 hr
Headache Response						
ZNS 5.0 mg	+/+	+/+	+/+	+/+	+/ns	+/ns
ZNS 2.5 mg	+/+	ns/ns	+/ns	+/ns	+/ns	+/ns
ZNS 1.0 mg	ns/ns	na/ns	+/ns	+/ns	+/ns	+/-
ZNS 0.5 mg	na/ns	na/ns	ns/ns	ns/-	+*/-	+/-
Absence of pain						
ZNS 5.0 mg	na/na	+/+	+/+	+/ns	+/ns	+/ns
ZNS 2.5 mg	na/na	ns/ns	ns/ns	+/ns	+/-	+/-
ZNS 1.0 mg	na/na	ns/ns	ns/ns	+/ns	+/ns	+/-
ZNS 0.5 mg	na/na	na/ns	na/ns	ns/-	ns/-	+/-
Reduction in Pain						
ZNS 5.0 mg	ns/ns	+/+	+/+	+/+	+/ns	+/ns
ZNS 2.5 mg	na/ns	ns/ns	+/ns	+/ns	+/ns	+/ns
ZNS 1.0 mg	na/ns	na/ns	+/ns	+/ns	+/ns	+/-
ZNS 0.5 mg	na/na	na/ns	ns/ns	+/-	+/-	+/-
Meaningful Migraine Relief						
ZNS 5.0 mg	ns/ns	+/+	+/+	+/+	+/ns	+/ns
ZNS 2.5 mg	na/ns	ns/ns	ns/ns	+/ns	+/ns	+/ns
ZNS 1.0 mg	na/ns	na/ns	na/ns	+/ns	+/ns	+/ns
ZNS 0.5 mg	na/ns	na/ns	na/ns	ns/ns	+/-	+/-
Nausea (Proportion reporting)						
ZNS 5.0 mg	-/na	-/na	+/na	+/na	+/na	+/na
ZNS 2.5 mg	-/na	-/na	-/na	-/na	-/na	+/na
ZNS 1.0 mg	-/na	-/na-	-/na	-/na	-/na	+/na
ZNS 0.5 mg	-/na	-/na	-/na	-/na	-/na	+/na
Phonophobia (Proportion reporting)						
ZNS 5.0 mg	-/na	+/na	+/na	+/na	+/na	+/na
ZNS 2.5 mg	-/na	-/na	+/na	+/na	+/na	+/na
ZNS 1.0 mg	-/na	-/na	-/na	-/na	+/na	+/na
ZNS 0.5 mg	-/na	-/na	-/na	-/na	+/na	+/na
Photophobia (Proportion reporting)						
ZNS 5.0 mg	+/na	+/na	+/na	+/na	+/na	+/na
ZNS 2.5 mg	-/na	+/na	+/na	+/na	+/na	+/na
ZNS 1.0 mg	-/na	-/na	-/na	-/na	+/na	+/na
ZNS 0.5 mg	-/na	-/na	-/na	-/na	+/na	+/na

+: Statistically significant difference in favor of ZNS
-: Statistically significant difference not in favor of ZNS
ns: Not significant/no difference between cohorts
na: Not analyzed
Adapted from Sponsor Table 26, Trial 007, First- attack Analysis
* sponsor's analysis p=0.02, Agency statistician's analysis p=0.053, my analysis p=0.03

However in discussing the results from these secondary endpoint analyses the Sponsor tends to stress how ZNS 5.0 mg is superior to zolmitriptan tablet 2.5 mg. For reasons previously discussed I do not feel this is a fair comparison and instead would stress the comparison between ZNS 2.5 mg and zolmitriptan tablet 2.5 mg which tended to show little difference between the two products. ZNS 2.5 mg does appear to provide quicker headache relief as evidenced by

superiority of ZNS 2.5 mg over zolmitriptan tablet 2.5 mg at 15 minutes. However this difference is not sustained and in fact zolmitriptan tablet 2.5 mg provides statistically greater total relief from headache pain (absence of pain) compared to ZNS 2.5 mg at 2 hours and 4 hours. Likewise, despite the fact that there was little difference between ZNS 2.5 mg and zolmitriptan tablet 2.5 for the proportion of subjects reporting headache recurrence over 24 hours (27.3% vs. 26.3% respectively), there was a relatively large difference in the time to recurrence with ZNS 2.5 mg cohort experiencing headache recurrence much sooner than with zolmitriptan tablet 2.5 mg (424 minutes vs. 525 minutes respectively).

In conclusion, with respect to efficacy, I recommend zolmitriptan nasal spray 5.0 mg, [redacted] be approved for marketing in the United States. [redacted]

7. Integrated Review of Safety

In this section I summarize the safety results from the clinical development program for zolmitriptan nasal spray. The ZNS clinical development program includes 5 clinical pharmacology trials (136-032, 311CIL/0041, 311CIL/0079, 311CIL/0102 and 311CIL/0104), 1 controlled clinical efficacy trial (311CIL/077), and two long term open-label safety trials (311CIL/0078, and 311CIL/0122). The clinical pharmacology trials resulted in 303 exposures to zolmitriptan nasal spray in 81 subjects. However the bulk of the clinical safety information is derived from the controlled efficacy study 077 (922 subjects, 2311exposures) and the two long term (1 year) uncontrolled safety studies 078 and 022 (1633 subjects combined, over 30,000 exposures combined). In total there are 2000 unique subjects in the clinical trials for ZNS.(Trial 078 is an extension of Trial 077). During the two long term trials subjects taking ZNS 5mg treated approximately 2.7 migraines per month (this included all subjects in Trial 0122, all post-crossover subjects in Trial 078 and the pre-crossover ZNS 5 mg cohort from Trial 078).

7.1 Brief Statement of Conclusions

The safety profile of Zomig Nasal Spray appears to be similar to that of the approved zolmitriptan formulations and is typical of the triptan class of drugs in general, with the exception of local nasopharyngeal complaints. No increase in cardiovascular or other serious adverse events compared to zolmitriptan tablets were noted in the trials of the nasal spray. Common, non-serious adverse events that are unique to the nasal spray formulation of zolmitriptan include local reactions such as nasopharyngeal discomfort and unusual taste however these complaints were generally mild, self-limiting and rarely resulting in withdrawal. In my opinion there are no safety concerns that would preclude the approval of ZNS 5.0, [redacted] for the acute treatment of migraine.

Clinical Review Section

7.2 Safety Population

The database evaluated in the safety review includes all patients who received trial medication (i.e., ZNS, zolmitriptan oral tablet, or placebo) in completed ZNS trials and in the ongoing open-label safety trial 0122. Data from NDA 20-768 (zolmitriptan oral tablet) were included by the Sponsor for comparison purposes.

With respect to long-term safety trial 078 the Sponsor outlines two groups of patients: those who received ZNS 5 mg throughout the study and those who received 5 mg only after crossover. During the pre-crossover phase, patients were randomized to take either 0.5, 1.0, 2.5, or 5.0 mg of ZNS. After the analysis of study 077, all subjects in study 078 were crossed over to ZNS 5.0 mg. In Trial 0122, only 5 mg was used throughout the trial and subjects were permitted to retreat a persistent or recurrent headache in 2 hours with ZNS 5 mg if needed. For simplicity my safety review will focus on long-term data from subjects receiving ZNS 5.0 mg however discussion about findings in other cohorts will be discussed if appropriate.

7.3 Patient Exposure and Demographics

The following Sponsor table provides a summary of the numbers of subjects exposed to study medication as well as their demographics for the entire clinical development program for ZNS. In Trial 077, 922 patients were given 2311 individual exposures to ZNS. In Trial 078, 1097 patients administered 20114 doses of ZNS. In Trial 0122 (ongoing), 536 subjects have administered 10705 doses of ZNS 5 mg as of the date of the interim analysis.

Table 31 Demographic characteristics of subjects exposed to ZNS

Demographic characteristic	Clinical pharmacology trials [a]		Placebo-controlled trials		Long-term uncontrolled safety trials	
	Nasal spray	Oral tablet (NDA 20-768)	Nasal spray Trial 0077	Oral tablet (NDA 20-768)	Nasal spray Trials 0078 and 0122	Oral tablet (NDA 20-768[b])
Number of subjects exposed	81	347	922	2633	1633	2058
Age (y)						
n	81	347	922	2633	1633	2058
Mean	33.4	33.9	40.5	40.3	41.6	40.9
Standard deviation	9.5	NC	10.2	NC	10.3	NC
Range	18 to 58	18 to 76	18 to 65	12 to 66	18 to 66	12 to 66
Age distribution; number (%) of subjects						
<18 y	0	0	0	18 (<1)	0	13 (<1)
≥18 to 40 y	63 (77.8)	267 (77)	443 (48.0)	1233 (47)	725 (44.4)	921 (45)
>40 to 60 y	18 (22.2)	55 (16)	468 (50.8)	1337 (51)	874 (53.5)	1087 (53)
>60 y	0	25 (7)	11 (1.2)	45 (2)	34 (2.1)	35 (2)
Sex; number (%) of subjects						
Male	46 (56.8)	192 (55)	163 (17.7)	378 (14)	281 (17.2)	288 (14)
Female	35 (43.2)	155 (45)	759 (82.3)	2255 (86)	1352 (82.8)	1769 (86)
Weight (kg)						
n	81	347	912	2624	1623	2046
Mean	72.4	70.8	68.5	68.4	69.5	68.0
Standard deviation	11.0	NC	13.5	NC	14.2	NC
Range	52 to 101	47 to 99	40 to 123	33 to 173	40 to 142	34 to 173
Race; number (%) of subjects						
White	79 (97.5)	313 (90)	910 (98.7)	2550 (97)	1601 (98.0)	2001 (97)
Black	0	15 (4)	1 (0.1)	50 (2)	4 (0.2)	31 (2)
Other [c]	2 (2.5)	19 (5)	11 (1.2)	33 (1)	28 (1.7)	25 (1)

[a] 12 subjects from Trial 0032 and 12 subjects from Trial 0041 are counted in both the nasal spray and oral tablet columns.
[b] Trial 136-015 (multiple attack outpatient trial).
[c] Other includes: Asian (Indian), Asian (Oriental), as well as other races not included in the categories of white or black.
NC Not calculated.
Data from Tables T2 and T3 (nasal spray) and Data Summary 7 of original ISS (oral tablet).
Source: Sponsor Table 8, iss.pdf, page 60.

All subjects were adult between 18 to 66 years of age. There were no pediatric or geriatric subjects (only a single subject was 66 years of age). The vast majority of subjects were women

(approximately 83%) with and average age of about 40 years. Most subjects were Caucasian (approximately 97%). As can be seen in the above table the demographic profile of these trials is similar to that used in NDA 20-768 (Zomig Tablets).

The following Sponsor table provides a breakdown of migraine attack frequency and 5 mg nasal spray exposure in the long term studies (note this has been updated to include additional data from 4 month safety update). The sponsor used a 350 day cutoff because subjects were permitted by protocol to have their 1 year follow up within 2 weeks of their full year anniversary. In both Trial 078 and 0122 there were no limits in the number of migraines that could be treated in a single month. A review of the datasets for both studies indicates good compliance with study medication with all migraines treated with study medications.

Table 32 Frequency of attacks for patients with 6 month and 1 year exposure in long-term safety trials (0078 and 0122) – patients exposed to doses of at least 5.0 mg at any time

Time in study (days)	Mean number of attacks per 30 days	Number (%) of patients	
		Doses of at least 5.0 mg zolmitriptan nasal spray at any time	
		ISS cutoff (N=1394)	4MSU cutoff (N=1396)
≥180	<1	232 (16.5)	**262 (18.8)**
	≥1 to <2	220 (15.8)	**260 (18.6)**
	≥2 to <3	134 (9.6)	**149 (10.7)**
	≥3	268 (19.2)	**326 (23.4)**
	All ≥2	402 (28.8)	**475 (34.0)**
≥350	<1	148 (10.6)	**187 (13.4)**
	≥1 to <2	116 (18.3)	**205 (14.7)**
	≥2 to <3	52 (3.7)	**124 (8.9)**
	≥3	63 (4.5)	**293 (21.0)**
	All ≥2	115 (8.2)	**417 (29.9)**

Source: Nasal –spray ISS, Table T1.14; 4MSU, Table T2.6.

Source: Sponsor Table 19, 4MSU.pdf, page 51.

In summary, the safety database for ZNS is large and the number of patients exposed to the highest (5 mg) dose of the spray is well in excess of that required under ICH guidelines.

7.4 Safety Review Findings

7.4.1 Methods Used to Evaluate Safety in this Review

The primary sources of data for this safety review include the Integrated Summary of Safety (ISS) submitted electronically (iss.pdf) by the Sponsor on February 26, 2002 and the SAS transport file datasets for the efficacy study (0077) and the two long-term safety studies (078 and 0122). Case report forms (CRFs) and individual narrative summaries for adverse events were consulted as needed. All documents in support of this NDA are available in the Electronic Document Room (EDR) at \\CDSESUB1\N21450\N_000. Additionally the most recent annual report (April 30, 2002) for Zomig Tablet was reviewed for an updated accounting of adverse events seen for all marketed formulations of zolmitriptan worldwide.

7.4.2 Deaths

No deaths have occurred in any trial with zolmitriptan nasal spray.

Clinical Review Section

7.4.3 Serious Adverse Events

Since the elimination period for zolmitriptan is significantly less than 24 hours, the Sponsor reviewed serious adverse events (SAEs) that occurred within 24 hours of a dose and those that occurred later separately. I reviewed all narrative summaries for SAE found in Appendix B of the ISS.

There were no SAEs reported during the clinical pharmacology trials. The integrated safety database of the three clinical trials included 30,819 exposures to ZNS. Of these exposures, there were 52 (0.2%) serious adverse events reported (combined for less than 24 hours and greater than 24 hours). Less than 0.01% (2/30819) of these events were considered drug-related by the investigator (patient 0122/0252/0001 and patient 0122/0953/0005).

Two serious adverse events from Trial 0122 were felt by the investigators to possibly be related to ZNS exposure. The first is a 37 year old female (patient 0953/0005, narrative page 1174, iss.pdf) who experienced angina pectoris 15 minutes after administering ZNS 5.0 mg. The patient was subsequently admitted to hospital and had a negative screen for myocardial infarction. This was her 5th attack treated with study medication. The patient had several cardiovascular risk factors including hypertension and family history. From my review of the narrative I would agree the event was probably related to study medication. The label for all triptans include the concern for cardiovascular events such as angina. A similar warning is included in the proposed label for ZNS. The second SAE considered possibly related to ZNS is a 53 year old female (patient 0252/0001, narrative page 1173, iss.pdf) who experienced nausea and vertigo 23 hours after treating the 29th migraine attack with ZNS 5 mg. The patient was hospitalized and treated with prednisone. The symptoms subsided in 5 days. Despite the complaint the patient was not withdrawn from the study. Although these symptoms occurred 23 hours after treatment with study medication I agree that they may have been related to treatment. The proposed label for ZNS and the present label for Zomig Tablets contains warnings about nausea and vertigo.

There was a single SAE, occurring within 24 hours of dosing, reported in trial 077. A 46 year old female patient (patient 0077/0001/0042) receiving ZNS 1.0 mg was hospitalized due to severe diverticular disease affecting the sigmoid colon the day after treating her third migraine attack with study medication. The condition was considered life threatening and required hospitalization for intravenous antibiotics and fluids. She was discharged three days later without sequelae. The investigator involved with her case did not consider the event to be drug-related. The case report form does not state whether the "diverticular condition" was due to ischemia. The label for all triptans contain the warning that ischemic colitis is possible with 5-HT$_1$ use. It is possible that the event was related to ZNS use. This represents an incidence of 0.1% of patients treated with ZNS (1/922) in this study.

Ten subjects receiving ZNS 5.0 mg in the long-term safety trials reported a SAE within 24 hours of treatment. This represents 0.8% of patients (10/1319) during the long-term trials of ZNS 5.0 mg. No individual type of SAE occurred in more than one patient. The SAEs that occurred within 24 hours of dosing during the long-term trials are summarized in the following Sponsor table. There is no evidence of SAEs becoming more frequent with increasing duration of treatment.

Clinical Review Section

Table 33 SAE (within 24 hrs) in patients receiving ZNS 5.0 mg in long-term trials.

COSTART body system / Adverse event	Number (%) of patients									
	0-90 days (N=1308)		91-180 days (N=971)		181-270 days (N=499)	271-360 days (N=203)	>360 days (N=80)	Total[a] (N=1319)	
Number (%) of patients with event[a, b]	4	(0.3)	5	(0.5)	0	0	0	10	(0.8)
Body/abdomen									
Pain abdominal	0		0		0	0	0	1	(<0.1)
Body/general									
Cyst	0		0		0	0	0	1	(<0.1)
Infection	0		1	(0.1)	0	0	0	1	(<0.1)
Injury accidental	0		1	(0.1)	0	0	0	1	(<0.1)
Reaction aggravation	1	(<0.1)	0		0	0	0	1	(<0.1)
Body/head									
Headache	0		1	(0.1)	0	0	0	1	(<0.1)
Cardiovascular									
Angina pectoris	1	(<0.1)	0		0	0	0	1	(<0.1)
Thrombophlebitis	0		1	(0.1)	0	0	0	1	(<0.1)
Digestive									
Nausea	1	(<0.1)	0		0	0	0	1	(<0.1)
Nervous/CNS									
Vertigo	1	(<0.1)	0		0	0	0	1	(<0.1)
Nervous/general									
Drug dependence	1	(<0.1)	0		0	0	0	1	(<0.1)
Psychosis	1	(<0.1)	0		0	0	0	1	(<0.1)
Urogenital/female genital									
Carcinoma breast	0		1	(0.1)	0	0	0	1	(<0.1)

[a] Patients with an event in more than 1 time window are counted only once in the 'Total' column. Adverse events that cannot be related to an attack are included in the 'Total' column only.
[b] A patient may have had more than 1 serious adverse event.
CNS Central nervous system.
N Number of patients.
Data derived from Table T56.2 and T27.1.
Source: Sponsor Table 70, iss.pdf, page 153

In the pre-crossover phase of Trial 0078, 7 patients experienced SAE within 24 hours of treatment. The events included one each of abdominal pain, neoplasm, accidental injury, local pain, depression, pneumonia, breast carcinoma, and 3 events of cysts. Based upon my review of the clinical narratives these SAEs were not plausibly related to the treatment drug.

In Table 72 of the ISS[13] the Sponsor tabulates the serious adverse events that occurred more than 24 hours after a dose of the treatment medication in Trial 077. In total, eleven patients experienced a serious adverse event 24 hours after treatment. From a review of each narrative it is my opinion that none of these events were plausibly related to study medication based upon the nature of the event and its timing with respect to the administration of study medication. Likewise, the Sponsor has presented serious adverse events outside of 24 hours in the long-term trials (078 and 0122) in Table 73 of the ISS[14]. They occurred at an overall frequency of 1.5%, were not thought to be drug-related by the investigators, involved random conditions, and were not, by my review of the clinical narratives, plausibly related to the study treatment.

7.4.4 Withdrawal Due to Adverse Events

The following Sponsor table tabulates the number of patients that withdrew from treatment in the single placebo-controlled efficacy study 077 and the two open-label, long-term safety studies

[13] Page 155, iss.pdf.
[14] Page 157, iss.pdf

078 and 0122. On the right side of the table the Sponsor includes a comparison of withdrawals seen in their clinical development program for oral zolmitriptan (NDA20-768). Unless appropriate I will not comment on this comparison. As can be seen in the placebo-controlled trial 077, a greater proportion of subjects in the placebo treated group withdrew from the study (13.6%) compared to patients enrolled in the ZNS cohorts (6.7%) or zolmitriptan tablet cohort (6.0%). No subject withdrew from any of the clinical pharmacology studies conducted for this NDA.

Table 34 Number of patients withdrawn from Study 077, 078 and 0122

Type of trial and trial ID	Nasal spray clinical trials		NDA 20-768	
Treatment	N of subjects exposed	N (%) withdrawn	N of subjects exposed	N (%) withdrawn
Placebo-controlled (0077)				
Zolmitriptan nasal spray	922	62 (6.7)	0	NA
Zolmitriptan oral tablet	233	14 (6.0)	2663	30 (1)
Placebo	228	31 (13.6)	401	1 (<1)
Other drugs	0	0 (0)	504	2 (<1)
Long-term uncontrolled (0078 and 0122)				
Zolmitriptan nasal spray			0	0 (0)
5.0 mg population [a]	1319	178 (13.5)	0	0 (0)
Pre-crossover population (0078 only)	1093	274 (25.1)	0	0 (0)
Zolmitriptan oral tablet	0	0 (0)	2058 [b]	755 (36.7)

[a] Includes 5.0 mg doses given pre- or post-crossover in Trial 0078, and results as of the data cut-off date for ongoing trial 0122.

[b] Only data for the oral tablet trial 136-015 are given; this trial provides the best comparison, as it used the same dose as Trial 0078 (5.0 mg).

Data from Tables T5.3 through T5.5 (nasal spray) and Tables 9.11 and 9.12 in text of original ISS (oral tablet).

Source: Sponsor table 14, iss.pdf, page 68.

The following Sponsor table demonstrates the various reasons why subjects withdrew from Trial 077. Again the Sponsor includes a comparison to NDA 20-768 which I will not comment on unless appropriate. As demonstrated in the table the most common reason for withdrawal was lack of efficacy, with placebo appropriately demonstrating the highest rate. Likewise there was an inverse dose relationship for withdrawal due to lack of efficacy with ZNS 0.5 mg demonstrating the highest rate (12%) and ZNS 5.0 mg demonstrating the lowest rate (3%). This is what would be expected from a product demonstrating efficacy. Otherwise there are no trends in withdrawal between cohorts that would suggest a problem with ZNS.

Table 35 Patient outcome, Trial 077

Reason for withdrawal	Number (%) of subjects [a]							
	Trial 0077						NDA 20-768	
	PBO	OT	Nasal spray				PBO	OT
	N=228	2.5 mg N=233	0.5 mg N=224	1.0 mg N=238	2.5 mg N=224	5.0 mg N=236	N=401	N=2633
Subjects who completed the trial	197 (86.4)	219 (94.0)	205 (91.5)	217 (91.2)	213 (95.1)	225 (95.3)	400 (99.8)	2603 (98.9)
Subjects withdrawn for any reason	31 (13.6)	14 (6.0)	19 (8.5)	21 (8.8)	11 (4.9)	11 (4.7)	1 (0.2)	30 (1.1)
Lack of efficacy	25 (11.0)	8 (3.4)	12 (5.4)	13 (5.5)	5 (2.2)	3 (1.3)	0	2 (<0.1)
Adverse event/concurrent illness[b]	1 (0.4)	3 (1.3)	1 (0.4)	3 (1.3)	1 (0.4)	4 (1.7)	0	0
Protocol non-compliance	3 (1.3)	2 (0.9)	3 (1.3)	0	1 (0.4)	0	1 (0.2)	27 (1.0)
Informed consent withdrawn	0	0	0	1 (0.4)	2 (0.9)	1 (0.4)	0	0
Subject lost to follow-up	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)	1 (0.4)	1 (0.4)	0	0
Administrative reasons	0	0	0	0	0	0	0	1 (<0.1)
Death	0	0	0	0	0	0	0	0
Other	1 (0.4)	0	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)	0	0

[a] Percentages are calculated using N, the total number of patients in the group, as the denominator.
[b] Includes 1 patient in each of the zolmitriptan nasal spray 5.0 mg, 2.5 mg and 1.0 mg groups that was withdrawn due to a non-serious adverse event that occurred outside 24 hours of treatment.
OT Conventional oral tablet.
PBO Placebo.
Data from Table T5.3 (nasal spray) and Data Summary 9 of original ISS (oral tablet).
Source: Sponsor Table 16, iss.pdf, page 70.

The following Sponsor table demonstrates the withdrawal rates seen in the long-term studies 078 and 0122. As demonstrated the most common reason for withdrawal in all cohorts was due to lack of efficacy. Again the same inverse dose relationship was seen as in Trial 077 with ZNS 0.5 mg having a higher withdrawal rate due to lack of efficacy (24.7%) compared to ZNS 5.0 mg (pre-crossover 4.0%, all other 5.0 mg dose 2.7%). Otherwise, there are no trends in withdrawals that would suggest a problem with ZNS.

Clinical Review Section

Table 36 Patient outcomes, Trial 0078 and 0122

Reason for withdrawal	Number (%) of subjects [a]						
	Trials 0078 and 0122					NDA 20-768	
	5.0 mg dose	Pre-crossover doses ≤ 5.0 mg (Trial 0078 only)				Conventional oral tablet	
	5.0 mg N=1319	0.5 mg N=275	1.0 mg N=272	2.5 mg N=271	5.0 mg N=275	2.5 mg	5.0 mg N=2058
Subjects who completed the trial or were ongoing in Trial 0122	1141 (86.5)	180 (65.5)	197 (72.4)	214 (79.0)	228 (82.9)	0	1303 (63.3)
Subjects withdrawn for any reason	178 (13.5)	95 (34.5)	75 (27.6)	57 (21.0)	47 (17.1)	0	755 (36.7)
Lack of efficacy	35 (2.7)	68 (24.7)	35 (12.9)	22 (8.1)	11 (4.0)	0	226 (11.0)
Adverse event/concurrent illness	46 (3.5)	7 (2.5)	15 (5.5)	8 (3.0)	11 (4.0)	0	167 (8.1)
Subject lost to follow-up	17 (1.3)	5 (1.8)	9 (3.3)	8 (3.0)	5 (1.8)	0	0
Informed consent withdrawn	19 (1.4)	3 (1.1)	9 (3.3)	8 (3.0)	5 (1.8)	0	0
Protocol non-compliance	20 (1.5)	4 (1.5)	2 (0.7)	6 (2.2)	8 (2.9)	0	138 (6.7)
Worsening condition	2 (0.2)	0	0	1 (0.4)	0	0	0
Administrative reasons	0	0	0	0	0	0	224 (10.9)
Pregnancy	3 (0.2)	0	0	0	0	NP	NP
Death	0	0	0	0	0	0	0
Other	36 (2.7)	8 (2.9)	5 (1.8)	4 (1.5)	7 (2.5)	0	0

[a] Percentages are calculated using N, the total number of patients in the group, as the denominator.
NP Not presented in original oral ISS.
Data from Tables T5.4 and T5.5 (nasal spray) and Data Summary 9 of original oral ISS (oral tablet).
Source: Sponsor Table 17, iss.pdf, page 71.

Ten patients in Trial 077 had adverse events within 24 hours of a dose that led to withdrawal. There were 3 additional withdrawals for nonserious AEs outside of the 24 hour period. Of the 10 patients, 6 (0.7% of 922 treated patients) were in ZNS treatment groups. There were 2 withdrawals from the ZNS 5.0 mg group because of unusual taste. No other individual event led to the withdrawal of more than 1 patient across all nasal spray dose groups. Cardiovascular adverse events (angina pectoris and palpitations) led to the withdrawal of 2 patients from the group receiving the conventional oral tablet.

Narratives describing each withdrawal due to an adverse event (a SAE at any time and nonserious AEs within 24 hours of a dose) are presented in Appendix B of the Sponsor's ISS (sections 1.5 & 1.6, pp. B27-B53). I have reviewed these narratives and most suggest no plausible relationship to the drug. The following table summarizes the narratives of patients who withdrew for AEs that were at least possibly associated with the drug in my opinion.

Table 37 Withdrawal from Trial 077 possibly related to study medication

Patient ID	Treatment	Reason for Withdrawal	Comments
0001/0024	ZNS 1.0 mg	Neck Pain	55 year old female developed severe neck pain 50 minutes after receiving first dose of trial medication. The pain resolved within 17 hours without treatment.
0001/0071	ZNS 0.5 mg	Nausea	48 year old female developed moderate nausea 210 minutes after receiving first dose of trial medication. the event resolved without treatment in about 7 hours.
0001/0073	ZNS 2.5 mg	Chest tightness	41 year old female developed severe palpitation, chest tightness, and sensation of throat closing 1 hour after receiving first dose of trial medication. All complaints resolved without treatment within 100 minutes.
0017/0015	ZNS 5.0 mg	Taste perversion	28 year old female developed severe "bad taste" 5 minutes after receiving trial medication. The event resolved within 30 minutes. A rechallenge 19 days later resulted in abnormal taste 5 days after taking trial medication
0018/0025	ZNS 5.0 mg	Taste perversion, throat tightness and headache	30 year old female developed a bitter taste, throat pressure and a bitemporal headache shortly after taking trial medication. Rechallenge several weeks later resulted in the same experience. Resolution of complaints occurred within 45 minutes.

As can be seen from these narratives none of these adverse events are unexpected with triptan products or nasal products in general.

Adverse events leading to withdrawal in the long-term, open-label trials (Trials 078 and 122) of ZNS 5.0 mg are summarized in the following Agency table by dose and type of adverse event. Of the 1319 patients who received long-term treatment with 5.0 mg doses, 37 (2.8%) had adverse events that led to withdrawal. The most frequently reported adverse events leading to withdrawal were unusual taste, aggravation reaction, and vomiting (no more than 0.4% of patients for each). Most adverse event withdrawal occurred in the first 90 days of treatment. Events leading to withdrawal were typical of adverse events reported acutely, and the majority were transient and resolved spontaneously. Despite the fact that 31.7% of patients experienced unusual taste when treating migraine headaches with ZNS 5.0 mg doses in these trials, only 0.4% (5 of 1319) of patients withdrew because of this event.

Table 38 Summary AE leading to withdrawal, Trial 078 and Trial 0122

Body System	Costart Term	EVENTS LEADING TO WITHDRAWAL IN LONG TERM TRIAL 078 AND TRIAL 122*			
		5 MG ZOMIG NASAL SPRAY			
		0-90 DAYS	91-180 DAYS	181-270 DAYS	TOTAL
		N = 1308	N = 971	N = 499	N = 1319
		n (%)	n (%)	n(%)	n (%)
	ANY ADVERSE EVENT LEADING TO WITHDRAWAL	26 (2.0)	5 (0.5)	2 (0.4)	37 (2.8)
Body General	ASTHENIA	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
	MALAISE	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	PAIN LOCAL SPECIFIC	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	PAIN THROAT	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	REACTION AGGRAVATION	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)
	TIGHTNESS JAW	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	TIGHTNESS OTHER	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	TIGHTNESS THROAT	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Body/Neck	TIGHTNESS NECK	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
Body/Thorax	TIGHTNESS CHEST	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiovascular	ANGINA PECTORIS	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	HYPERTENSION	1 (0.1)	0 (0.0)	1 (0.2)	2 (0.2)
	PALPITATION	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	SYNCOPE	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	THROMBOPHLEBITIS	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Digestive	DRY MOUTH	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)
	DYSPHAGIA	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
	EDEMA TONGUE	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	HEPATIC NEOPLASIA	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	NAUSEA	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)
	VOMIT	4 (0.3)	0 (0.0)	0 (0.0)	4 (0.3)
Nervous/CNS	DIZZINESS	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)
	SOMNOLENCE	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Nervous/General	HYPERESTHESIA	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
	HYPESTHESIA	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nervous/PNS	PARESTHESIA	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)
Respiratory	NASAL CAVITY DISCOMFORT	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Special Senses	UNUSUAL TASTE	4 (0.3)	0 (0.0)	1 (0.2)	5 (0.4)
Urogenital Female Genital	CARCINOMA BREAST	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	PREGNANCY UNINTENDED	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

*271-360 Days (N = 203) & >360 Days (N= 80) not shown; to date there have been no AEs leading to withdrawal.

The Sponsor's ISS Table 69 (iss.pdf, page 149) includes an additional summary of AEs leading to withdrawal in patients during the pre-crossover phase of Trial 0078 (i.e., 4 cohorts, dose range 0.5 to 5.0 mg ZNS). The frequency of adverse events leading to withdrawal (approximately 2%) and type of AEs is similar to the ZNS 5.0 mg groups described above. There was minimal difference between cohorts for withdrawal frequency and there was no adverse event reported more than once. One individual (patient 0078/0039/0004) had a myocardial infarction (MI) while in the ZNS 1 mg cohort, but this SAE was not plausibly related to the drug because of the many weeks that had passed between the MI and the last dose of the drug. This patient is further discussed in a section 7.4.10

In conclusion, there does not appear to be any clinically significant adverse events leading to withdrawal from these studies that would preclude the approval of ZNS [redacted] 5.0 mg for marketing in the United States.

7.4.5 Common Adverse Events

Table 39 outlines the common adverse events seen during the clinical trials for ZNS. The most common adverse events seen in the clinical development program for ZNS were unusual taste,

paresthesias, hypesthesia, local nose/throat pain, nausea, somnolence, asthenia, sensation of tightness or heaviness, and the category of disorder/discomfort of the nasal cavity. Many of these adverse events were seen during the clinical trials for Zomig Tablets and Zomig-ZMT and are typical for triptan products. However compared to the oral forms of zolmitriptan, the nasal spray formulation introduces several local effects not often seen with the tablet. These include disorder/discomfort of the nasal cavity, throat pain, dysphagia, epistaxis, throat discomfort, paresthesias, hypertonia, hyperesthesia, hypesthesia, pain local, pharyngitis, voice alteration, pruritis, and parosmia. Paresthesias in most situations referred to tingling in the nose after use of the spray. The sensation of tightness or heaviness affected the chest, neck, or throat was sometimes described as "pressure throat" or "tightness other." Fortunately, most of these common adverse events were of mild intensity and rarely resulted in withdrawal.

Unusual taste likewise can be thought of as a local effect and occurred in 3.1% of placebo treated patients in the Trial 077 compared to 4.9%, 9.7%, 17.4%, and 21.2% of those patients in the ZNS 0.5, 1.0, 2.5, and 5.0 mg cohorts respectively. A clear dose response is evident for this symptom. However the unusual taste sensation did not result in withdrawal in Trial 077. In the long-term safety studies (Trials 078 and 122), unusual taste was cited as the reason for withdrawal in only 0.4% of patients.

7.4.6 Adverse Events Incidence Table

The following Sponsor table summarizes the adverse events seen in at least 2% of the patients during the clinical development program for ZNS. This is the table proposed by the Sponsor for inclusion in the label.

events did not result in any significant patterns suggesting some underlying syndrome such as Steven Johnsons or unusual potential signals of concern.

Table 40 Common AEs Incidence (≥2%), Trial 077

COSTART Preferred Term	ZNS 0.5 mg N=224		ZNS 1.0 mg N=238		ZNS 2.5 mg N=224		ZNS 5.0 mg N=236		Zomig Tabs 2.5 mg N=233		Placebo N=228	
	n	%	n	%	n	%	n	%	n	%	n	%
TASTE PERVERSION	11	4.91	23	9.66	39	17.41	50	21.19	5	2.15	7	3.07
INTRANASAL PARESTHESIA	7	3.13	9	3.78	5	2.23	17	7.20	5	2.15	5	2.19
HYPERESTHESIA	0	0.00	3	1.26	3	1.34	12	5.08	7	3.00	0	0.00
PARESTHESIA	6	2.68	13	5.46	13	5.80	12	5.08	15	6.44	13	5.70
PHARYNGITIS	3	1.34	1	0.42	10	4.46	10	4.24	3	1.29	2	0.88
NAUSEA	2	0.89	4	1.68	3	1.34	9	3.81	9	3.86	3	1.32
PAIN	2	0.89	5	2.10	5	2.23	9	3.81	3	1.29	2	0.88
SOMNOLENCE	0	0.00	2	0.84	3	1.34	9	3.81	1	0.43	4	1.75
ASTHENIA	0	0.00	3	1.26	6	2.68	8	3.39	6	2.58	3	1.32
PRESSURE	1	0.45	4	1.68	1	0.45	8	3.39	9	3.86	0	0.00
TIGHTNESS	3	1.34	5	2.10	2	0.89	8	3.39	13	5.58	2	0.88
DIZZINESS	4	1.79	9	3.78	13	5.80	7	2.97	7	3.00	10	4.39
RHINITIS	3	1.34	6	2.52	3	1.34	7	2.97	3	1.29	4	1.75
AGGRAVATED REACTION	2	0.89	1	0.42	2	0.89	5	2.12	2	0.86	5	2.19

The following Sponsor table summarizes the proportion of patients (≥2%) reporting adverse events while taking ZNS 5mg in the long-term trials of 078 and 0122. For simplicity, subjects randomized to lower doses of ZNS in the first phase of study 078 are excluded. However a review of this low dose cohorts (0.5, 1.0, and 2.5 mg) safety data fails to demonstrate any unusual signals.

Clinical Review Section

Table 41 AEs occurring in ≥2% of patients, Trials 078 and 0122, ZNS 5 mg

COSTART body system / Adverse event	Number and % of patients with an adverse event						
	Zolmitriptan nasal spray (Trials 0078 and 0122)						Oral tablet (NDA 20-768)
	0-90 days (N=1308)	91-180 days (N=971)	181-270 days (N=499)	271-360 days (N=203)	>360 days (N=80)	Total[a] (N=1319)	Total (N=2058)
Body/General							
Asthenia	61 (4.7)	36 (3.7)	9 (1.8)	8 (3.9)	2 (2.5)	85 (6.4)	375 (18)
Heaviness other	26 (2.0)	12 (1.2)	4 (0.8)	0	0	31 (2.4)	178 (9)
Pain local specific	52 (4.0)	31 (3.2)	11 (2.2)	5 (2.5)	1 (1.3)	77 (5.8)	185 (9)
Pain throat	96 (7.3)	41 (4.2)	12 (2.4)	6 (3.0)	2 (2.5)	117 (8.9)	60 (3)
Reaction aggravation	21 (1.6)	8 (0.8)	6 (1.2)	0	0	40 (3.0)	49 (2)
Tightness throat	33 (2.5)	19 (2.0)	9 (1.8)	3 (1.5)	1 (1.3)	44 (3.3)	156 (8)
Body/Head							
Headache	18 (1.4)	10 (1.0)	3 (0.6)	1 (0.5)	0	26 (2.0)	31 (2)
Digestive							
Dry mouth	50 (3.8)	27 (2.8)	10 (2.0)	4 (2.0)	0	62 (4.7)	124 (6)
Dysphagia	23 (1.8)	12 (1.2)	1 (0.2)	4 (2.0)	1 (1.3)	32 (2.4)	85 (4)
Nausea	71 (5.4)	29 (3.0)	10 (2.0)	3 (1.5)	1 (1.3)	99 (7.5)	305 (15)
Musculo-skeletal							
Myasthenia	21 (1.6)	11 (1.1)	3 (0.6)	3 (1.5)	0	27 (2.0)	99 (5)
Nervous/CNS							
Dizziness	65 (5.0)	27 (2.8)	5 (1.0)	3 (1.5)	1 (1.3)	90 (6.8)	294 (14)
Somnolence	54 (4.1)	23 (2.4)	6 (1.2)	4 (2.0)	0	68 (5.2)	295 (14)
Nervous/General							
Hyperesthesia	73 (5.6)	44 (4.5)	22 (4.4)	8 (3.9)	2 (2.5)	88 (6.7)	114 (6)
Hypesthesia	24 (1.8)	13 (1.3)	1 (0.2)	1 (0.5)	0	34 (2.6)	97 (5)
Nervous/PNS							
Paresthesia	225 (17.2)	101 (10.4)	35 (7.0)	17 (8.4)	1 (1.3)	266 (20.2)	286 (14)
Respiratory							
Disorder/discom -fort, nasal cavity	79 (6.0)	42 (4.3)	9 (1.8)	6 (3.0)	2 (2.5)	112 (8.5)	0
Special senses							
Unusual taste	386 (29.5)	216 (22.2)	93 (18.6)	34 (16.7)	10 (12.5)	418 (31.7)	21 (1)

[a] Patients with an event in more than 1 time window are counted only once in the "Total" column. Adverse events that cannot be related to an attack are included in the "Total" column only.

N Number of patients.

Data from Summary Table T28.1 (nasal spray), Data Summary 23 of the clinical trial report for Trial 136-015 in NDA 20-768 (oral tablet).

Source: Sponsor Table 47, iss.pdf, page 121.

As was seen in the acute efficacy trial 077, most adverse events seen during the long-term trials are consistent with what is seen for triptan products in general. However there continues to be a fairly high incidence of patients complaining of local nasopharyngeal complaints consistent to what I would expect to see with a nasal triptan product. For example, "unusual taste" sensation continues to be a common complaint even after 1 year of treatment (1 year incidence, 12.5%). Despite this high incidence for unusual taste, few subjects withdrew from the study due to it. Otherwise, the adverse events reported in these long-term studies compare favorably to the reported incidences of adverse events seen in NDA 20-768 (Zomig Tablet). My own review of the long-term datasets resulted in similar adverse events incidence findings.

My review of the sponsor's translation of investigator's verbatim terms into COSTART terms found a few minor errors. For example, in Trial 077 the sponsor translated "slow thinking" to "amblyopia", "mild giddiness" to "dizziness", and "narrow throat" to "dysphagia". In Trial 078 the sponsor was inconsistent with translating "burning feeling (or smarting pain) in nose and throat", sometimes translating it to "intranasal paresthesia" and at other times translating it to

"paresthesia". Finally in Trial 0122 there were several times when it appears the sponsor translated multiple discrete adverse complaints contained under a single verbatim term entry into a single COSTART term. For example the verbatim term "burning in nose and throat, aching joints" was translated to arthralgia. Overall there were very few errors and it is unlikely they affect the actual incidence rates to any great extent.

7.4.7 Nose and Throat Examination

Nasopharyngeal examinations (NT) were done as part of the routine physical examination in all pharmacology trials. In Trial 077, and its open-label extension 0078, the NT examinations were done at screening and at the end of the trial on all patients at Centers 30 and 42. ENT specialists or investigators with prior ENT experience performed the examinations. In the long-term safety trial 0122, the investigator performed a standardized nasopharyngeal examinations at baseline, and after 6 and 12 months of treatment in all patients. If an abnormality was noted the patient was referred to an ENT specialist.

No abnormal findings were noted on NT examinations of the subjects in the pharmacology trials. In Trial 077, 2 (0.3%) patients had NT exam abnormalities, but these were not felt to be causally related to trial medication because they represented symptoms related to concurrent illness (e.g., influenza). In the long-term trials 078 and 0122, 4 (0.7% of 580 examined) patients had abnormalities on NT examination. Two were felt to be secondary to infections, one had a slightly swollen turbinate, and the fourth had minor nasal ulcerations and evidence of minimal bleeding.

Section 1.11 of Appendix B of the Integrated Summary of Safety (iss.pdf) provides the narrative reports of all significant nasopharyngeal examination findings. I examined these narratives as part of this safety review. In a small number of patients, slight swelling, minor ulcerations, and minimal bleeding were noted and felt by the examiner to be causally related to the nasal spray, but the patients were not withdrawn.

The narratives also include 37 subjects in long-term trials (0078 and 0122) who experienced epistaxis. In most cases the onset of the bleeding was typically soon after taking the nasal spray, but in some patients the bleeding occurred up to a week later (and in one patient, 51 days later). The duration of the bleeding was typically a few minutes. Most patients had used the nasal spray at least 7 times previously, and some had used it up to 42 times previously. These events subsided spontaneously, although one patient required silver nitrate cautery of a bleeding point. Most had no findings on their subsequent nasopharyngeal examinations. The investigator usually considered the epistaxis to be causally related to the study medication and judged the events to be mild in intensity.

With respect to the nasopharyngeal findings, the Sponsor concludes the following[15]: (1) few treatment emergent nasopharyngeal abnormalities were reported, (2) the incidence of nasopharyngeal abnormalities was not dose related and (3) there was no evidence that long-term use of ZNS resulted in nasopharyngeal abnormalities. I concur with the Sponsor's summary. From my review of the nasopharyngeal safety data, there does not appear to be any changes with

[15] Source: ISS (iss.pdf), section 12.5, page 179

long-term use of ZNS. Epistaxis with nasal inhalers is not unexpected and might reflect poor technique.

7.4.8 Laboratory Findings

All 5 clinical pharmacology trials and 3 patient treatment trials included a clinical chemistry panel (electrolytes plus renal and liver function tests) and a CBC to assess safety. In the pre-NDA meeting on February 18, 2000, it was agreed that data from clinical pharmacology trials need not be summarized in the ISS unless there were potentially significant clinical findings. No subjects in the clinical pharmacology trials had treatment-emergent hematology or clinical chemistry values outside the expanded reference ranges (See Appendix A for ranges) and no changes in laboratory values were reported as adverse events.

In Trial 077, 7 of the 9 CBC parameters remained within the reference range for all recorded values. Platelet values were above the reference range in 1 patient (0.4%) in each of the ZNS 1.0 mg and 5.0 mg groups, and below the reference range in 1 (0.4%) patient in the oral zolmitriptan 2.5 mg group. Eosinophil values increased to above the upper limit of the reference range for up to 3 patients (1.3%) in each of the ZNS and zolmitriptan tablet 2.5 mg groups and 2 patients (1.0%) in the placebo group. No adverse events were reported in association with any of these values.

In the long-term safety trials 078 and 0122 the number of patients with values outside the laboratory reference ranges was less than 2 (0.5%) for all hematology parameters except eosinophils. For eosinophils, 5 patients had counts exceeding the reference value, however no clinical adverse events were reported in association with these or any hematology value. There did not appear to be an increase in the incidence of values outside the reference ranges when patients were switched from lower doses of zolmitriptan (pre-crossover) to the 5.0 mg open-label (post-crossover) dose (see iss.pdf, page 741) in Trial 078.

In the efficacy trial 077, the values recorded for 3 of the 8 chemistry parameters (sodium, creatinine, albumin) remained within the respective expanded reference range. For 4 other parameters (potassium, alkaline phosphatase, ALT, and AST), the percentage of patients with a value outside the expanded reference range was <1%. Total bilirubin concentration was the most variable chemistry parameter. The proportion of patients with values outside of the reference range did not exceed 4% in any nasal spray dose group, compared with of 3% of patients on placebo. The total numbers of values above and below the expanded reference range were evenly distributed, with decreased total bilirubin levels being slightly more common than increased levels; this was also the case for the placebo group. No adverse events of jaundice were reported during the trial, and no adverse events were reported in association with any threshold value. There was no apparent increase in the incidence of chemistry values outside the reference ranges with increasing doses of zolmitriptan (see iss.pdf, page 731).

For patients who received ZNS 5.0 mg during long-term treatment in the open-label trials 078 and 122, the numbers of patients with treatment-emergent clinical chemistry values outside the expanded reference ranges did not exceed 3 patients (0.4%) for any parameter except bilirubin. For total bilirubin, 37 patients (2.8%, 37/1319) had a value outside the expanded reference range; 8 (0.7%, 8/1319) had increased values and 29 (2.2%, 29/1319) had decreased values. One

adverse event of jaundice was recorded; this was a SAE occurring more than 24 hours after treatment in one patient (patient ID 311CIL/0122/0554/0014) and was related to cholecystic pathology. The patient recovered after cholecystectomy and continued in the study. The event was not considered drug-related by the investigator.

Other clinical chemistry values were reported as adverse events in 3 patients in Trial 122 (elevated creatinine in 1 patient, elevated ALT and g-glutamyl transferase in 1 patient, and elevated g-glutamyl transferase in 1 patient). The nature, pattern, and incidence of these events appeared to be random from my review.

Based on the laboratory testing results, the Sponsor concludes[16] the following: (1) ZNS does not have any clinically significant effects on standard measures of hematology or clinical chemistry, (2) the incidence of treatment-emergent abnormalities was low and comparable to placebo, (3) there were no apparent dose-related trends for lab abnormalities, (4) laboratory findings in the nasal spray trials were consistent with those for the oral tablet in NDA 20-768 and (5) there were no differences in the incidence of abnormalities between trials where zolmitriptan was administered for the treatment of up to 3 attacks and where it was administered long-term for the treatment of multiple attacks. I concur with the Sponsor's conclusions.

7.4.9 Vital Signs

The cardiovascular effects of oral zolmitriptan seen during clinical trials are summarized in Dr. Armando Oliva's safety review of NDA 20-768 (Zomig Tablet, page 51, dated 5/1/97). He notes that zolmitriptan tablet 5 mg was associated with a mean increase in diastolic blood pressure of 5 mm, a mean increase in systolic blood pressure of 1 mm, and no changes in heart rate. My own analysis of vital signs findings from Trial 077 and 078 demonstrated that ZNS 5mg was associated with a mean drop in systolic blood pressure of 0.75 mm, a mean increase in diastolic blood pressure of 0.04 mm, and a mean increase in pulse of 1.68 beats per minute. Results from other cohorts failed to demonstrate any consistent dose effect for any of these vital signs.

The thresholds used by the Sponsor for potentially clinically significant changes in VS are outlined in the following Sponsor table. Based on a pre-NDA agreement (February 18, 2000) the vital sign (VS) data from the pharmacokinetic studies are not summarized in the ISS unless there were clinically significant changes. There were no clinically significant changes in VS seen during the PK Trial 032 and Trial 041. In Trial 079, 3 volunteers experienced changes in their vital signs that met the threshold for potentially clinically significant changes. Two subjects had a decrease in their heart rate and 1 subject had a decrease in their diastolic blood pressure that all occurred with no consistent temporal relationship to dosing (2 hours, 21.5 hours and 15 minutes after dosing respectively). All findings resolved within 2 hours of observation and were clinically asymptotic. None of the findings in any clinical pharmacology trial was reported as an adverse event by the investigator, and none were considered to be of clinical significance.

[16] Source:iss.pdf, page 163

Table 42 Threshold criteria for potentially clinically significant changes in vital signs

Variable	Threshold criteria for potentially clinically significant change
Systolic blood pressure (SBP)	≤90 mmHg and ≥20 mmHg decrease
	≥180 mmHg and ≥20 mmHg increase
Diastolic blood pressure (DBP)	≤50 mmHg and ≥15 mmHg decrease
	≥105 mmHg and ≥15 mmHg increase
Heart rate (HR)	≤50 beats per minute (bpm) and ≥15 bpm decrease
	≥120 bpm and ≥15 bpm increase

Source: Sponsor Table 75, ISS (iss.pdf), page 164.

In the efficacy trial 077, VS were collected at screening, randomization, and at the post treatment follow up visit. The proportion of subjects with a change in a vital sign exceeding the threshold value for systolic blood pressure, diastolic blood pressure, or heart rate was ≤2.5% of patients across all cohorts. Unlike the slight increase in diastolic blood pressure and systolic blood pressure seen during the clinical development program for Zomig Tablets, the potentially clinically significant changes in vital signs seen during Trial 077 were predominately decreases in systolic blood pressure, diastolic blood pressure and heart rate. Only 2 subjects (1 who received zolmitriptan 5.0 mg and 1 who received placebo) had increases in their vital signs that exceeded the threshold for potentially clinically significant changes in vital signs. This pattern suggests there is no consistent finding in changes of VS associated with the use of zolmitriptan.

In Trial 077 no adverse events associated with blood pressure changes were reported. Seven patients reported tachycardia after treatment with study medication, 2 (0.8%) patients treated with ZNS 1.0 mg, 1 (0.4%) patient treated with ZNS 5.0 mg, 1 (0.4%) patient treated with placebo, and 2 (0.9%) patients treated with oral zolmitriptan 2.5 mg. The ZNS 1 mg patient reporting tachycardia required treatment and was considered severe. This event occurred more than 9 hours after dosing and was associated with anxiety and insomnia. All events of tachycardia were considered drug-related by the investigator, including those on placebo. These findings are similar to the findings seen in the original NDA for Zomig Tablet where tachycardia was reported in approximately 0.8% of patients at doses of either 2.5 or 5.0 mg.

In the long-term safety trial 078, vital signs were recorded only at the start and end of treatment (after 12 months). In Trial 0122 vital signs were assessed at screening, 6 weeks, 14 weeks, 22 weeks, 6 months, 9 months and 12 months. For patients who received ZNS 5.0 mg in the long term studies, the proportion of patients exceeding threshold values for systolic blood pressure, diastolic blood pressure, or heart rate was ≤2.3% (25/1101) during any time period. The proportion of patients exceeding threshold values did not change with increasing duration of treatment. The reported findings were below and above the threshold ranges for each vital sign. These findings are slightly better than the findings seen in the original NDA for Zomig Tablet where the overall percentage of patients exceeding threshold values for vital signs in Trial 136-015 (long term safety trial) was 5% (98/2058).

In the long-term safety studies 5 patients (0.4%, 5/1319) reported tachycardia, and 3 (0.2%, 3/1319) patients reported hypertension. The three patients reporting hypertension in the long-term studies were withdrawn. These findings are similar to the findings seen in the original NDA

for Zomig Tablet where the overall percentage of patients that withdrew due to hypertension in the long term study was 0.2% (5/2058).

Overall there does to appear to be any consistent clinically significant changes in systolic blood pressure, diastolic blood pressure, or heart rate associated with the use of ZNS up to 5. 0 mg during acute and long terms studies.

7.4.10 Electrocardiogram Findings

In the five pharmacokinetic trials involving healthy volunteers, 12-lead ECGs were recorded at baseline and at frequent intervals for 24 hours after dosing. Eighty-one healthy subjects received a total of 303 exposures to ZNS (0.5 to 10 mg), some receiving two doses in a single day separated by 2 hours others receiving consecutive doses over three days. No abnormalities were noted in ECGs during these trials.

In all clinical trials the enrollment criteria excluded migraine patients with cardiovascular risk factors. ECGs were recorded at baseline and follow up (end of treatment) for Trial 077 and 078. In Trial 0122, ECGs were performed at baseline, 26 to 28 weeks, and at 12 months. All ECGs were read by both the center investigator and by a central cardiologist who was blinded to history. The central cardiologist was encouraged to assume the worst-case scenario and to ask that patients with even equivocal abnormal ECG findings be withdrawn if warranted by the findings.

In the efficacy trial 077, 10 patients (0.7%) had a treatment-emergent ECG abnormality as defined by the central cardiologist. The abnormalities occurred across all zolmitriptan and placebo groups. The following table outlines the abnormal electrocardiographic findings from study 077. As can be seen, there does not appear to be any consistent ECG findings associated with zolmitriptan use and no apparent dose effect.

Table 43 Treatment-emergent ECG abnormalities, Trial 077

Treatment	Center/ patient	Details of abnormality (clinically significant change from baseline)	Time from last dose (d)	Ischemic event	Abnormality reported as an adverse event
Zolmitriptan nasal spray					
2.5 mg	0038/0029	Atrial tachycardia	24	No	Yes
	0043/0003	Multiple premature ventricular beats	11	No	No
	0043/0037	Sinus tachycardia with increased P-wave amplitude	3	No	No
5.0 mg	0042/0012	Markedly decreased voltage in limb leads	11	No	No
	0043/0035	T-wave inversion leads V2 and V3	1	Possibly	No
	0045/0014	T-wave inversion leads V2 to V6	90	Possibly	No
Oral zolmitriptan					
2.5 mg	0029/0003	New right bundle branch block and left atrial enlargement	5	No	Yes
	0043/0046	T-wave inversion leads V1 to V5	49	Possibly	No
Placebo					
	0024/0003	Multiple premature ventricular beats	6	No	Yes
	0034/0016	ST depression leads V4 to V6	16	Possibly	No

Data from the clinical trial report for Trial 0077. Number of abnormalities is summarized in Table T61.2 of this ISS.

Source: Sponsor Table 76, ISS (iss.pdf), page 169.

As can be seen in the above table, 6 patients (0.7% of 907) who were treated with ZNS in Trial 077 had a treatment-emergent ECG abnormality. These ECGs were obtained at the end of treatment visits, were scheduled, and were not done because of symptoms and therefore may be incidental findings. These finding are higher than that seen in the original Zomig Tablet NDA (20-768) where 0.2% (6/2512) of patients across all doses of zolmitriptan had a treatment emergent ECG in placebo-controlled studies.

Only one patient (patient 0043/0034, receiving ZNS 5.0 mg) with an abnormal ECG in Trial 077, had it performed relatively soon after the last dose. In this case it was recorded 1 day later and showed possible ischemia. The clinical narrative for this patient is as follows:

> *"This 44-year-old female Caucasian patient, who had a normal ECG at Visit 1, was observed to have T-wave inversion in leads V2 and V3 on her ECG taken at Visit 3 , ——— after receiving treatment with zolmitriptan nasal spray 5.0 mg. The central cardiologist commented that this inversion may represent ischemia or could be due to an increase in heart rate. Her heart rate decreased from Visit 1 to Visit 3 from 90 to 70 bpm. Her past medical history included a mitral valve prolapse. Blood pressure remained reasonably constant with only a slight fall in diastolic blood pressure; values were 110/80 mmHG at Visit 1 and 110/70 mmHG at Visit 3. Adverse events reported in association with trial medication included dizziness on —— ——— ' when treating her second migraine headache."*

In the remaining patients the recordings were done days or weeks after the last dose of the drug and are probably unrelated to study medication.

In the long-term safety studies, 9 patients (0.8% out of 1074) had an ECG with a clinically significant change from baseline. Six patients were from Trial 0122 and 3 patients were from Trial 078. None of the abnormal ECGs were associated with symptoms. A description of each of the 9 abnormalities is given in the following Sponsor table. As can be seen from the table all but 1 abnormal ECG was done several days to weeks after the last dose of study medication and therefore probably incidental. These findings are slightly higher than the results seen in the long-term study done in support of the original Zomig Tablet NDA (20-768) where 11 patients (0.5% out of 2029) had abnormal ECG changes. However in the current NDA the reviewing cardiologists were encouraged to prospectively identify all potentially ischemic changes whereas in the original Zomig Tablet NDA cardiologists reviewed post-treatment ECG retrospectively and received no prompting to report potentially ischemic changes. This difference in methodology might account for the slight reporting difference.

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Table 44 Treatment-emergent ECG abnormalities, Trials 0078 and 0122

	5.0 mg zolmitriptan nasal spray				
Centre/ Patient	Details of abnormalities (clinically significant change from baseline)	Time from most recent dose (d) [a]	N of attacks / doses up to date of abnormality	Possibility of ischemic event	Abnormality reported as an AE (within 24 h or serious)
Trial 0078					
0019/0045 [b]	T wave inversion: not diagnostic in isolation	40	7 / 7	No	Yes
0036/0006 [c]	Loss of R wave in V2: not diagnostic in isolation	145	2 / 2	No	No
0041/0025 [d]	Multiple premature ventricular beats	104	1 / 1	No	Yes
Trial 0122					
0677/0011	T-wave inversion	1	27 / 31	Yes	No
0677/0027	T-wave inversion; subtle ST segment depression	4	14 / 17	Yes	No
0950/0012	Poor R-wave regression with associated repolarisation abnormalities consisting of biphasic T waves	25	22 / 35	Yes	No
0951/0027	R-wave regression with associated T-wave flattening	11	21 / 29	Yes	No
0952/0005 [e]	Progression of pre-existing T-wave inversion	18	2 / 4	Yes	No
0952/0008	Development of Q-waves	26	16 / 18	Yes	No

[a] For Trial 0122, this value is based on data at time of interim database lock.
[b] Patient was receiving 5.0 mg post-crossover, and had received a pre-crossover dose of 1 mg.
[c] Patient was receiving 5.0 mg post-crossover, and had received a pre-crossover dose of 0.5 mg. The abnormality was reported as an adverse event but outside 24 hours of treatment, and thus this event is not included in summary tables.
[d] This patient had treated a single migraine attack in the trial during the pre-crossover portion of the trial, 104 days previously.
[e] ECG at unscheduled Visit (Visit 3).
Data from Table 89 in clinical trial report for Trial 0078, and Table 48 in clinical trial report for Trial 0122.
Source: Sponsor Table 77, ISS (iss.pdf) page 171

In Trial 078, one patient (patient 0039/0004), not included in the above tabulation, had a myocardial infarction 2 weeks after administering ZNS 2.5 mg. The event was not felt to be drug-related by the investigator and from my review of the narrative[17], I concur.

In summary, there were no consistent significant ECG changes seen during clinical development program for ZNS. The few ECG abnormalities seen during the clinical trials were rarely temporally associated with study medication and none were associated with symptoms.

7.4.11 Drug-Drug Interaction

This NDA does not include any investigations into potential drug interactions between ZNS and orally administered drugs. Since nasal formulation and tablet formulation of zolmitriptan have the same metabolic fate, the labeling for drug interactions for the nasal spray should be the same as for the tablet.

The interaction of ZNS and the nasal decongestant Otrivine Sinus Spray (xylometazoline) was studied in clinical pharmacokinetic trial 0102. This trial involved 18 healthy men, in a crossover design, each receiving a single ZNS 5.0 mg dose spray, with and without pre-treatment with nasal xylometazoline (140 µg). The incidence, type and frequency of adverse events were similar

[17] Source: Sponsor Appendix B, iss.pdf, page 1183.

after both dosing regimens. The most common adverse event was unusual taste (11 subjects receiving ZNS alone, 7 subjects receiving combination treatment). Overall there was no evidence of any clinically relevant interaction between ZNS and xylometazoline.

7.4.12 Drug Disease Interaction

The incidence of adverse events while using ZNS in the presence of rhinitis was assessed by the Sponsor in long-term safety trial 0122. The presence of rhinitis was inferred from any complaints of blocked, congested, or runny nose at the time of nasal spray dosing and the previous 24 hours. There was no evidence to suggest that the presence of rhinitis affected the nature or frequency of adverse events reported. The most common adverse events were similar to those reported in the overall safety population and included unusual taste, paresthesia, and disorder or discomfort of nasal cavity.

7.4.13 Drug-Demographic Interactions

Since the trials submitted under this NDA involved 96-98% Caucasian individuals, there is little experience using ZNS in non-Caucasians. Therefore I am unable to draw any conclusions about the potential impact of race on the incidence of adverse events. With respect to gender, weight, and age there appears to be no significant differences in the incidence of adverse events when these subgroups were analyzed[18]. This pattern of findings is consistent with what was seen for the zolmitriptan tablet NDA (20-768).

7.4.14 Class Effect of $5HT_{1D}$ Agonists—"Atypical Sensations"

As pointed out in the safety review of zolmitriptan tablets[19], atypical sensations are reported AEs with zolmitriptan just as they are with other $5HT_{1D}$ agonists. These atypical sensations include vague feelings of tightness, pressure sensations, warmth, and tingling in the chest, neck, and jaw. With sumatriptan tablets 100 mg and zolmitriptan tablets 5 mg, these sensations occurred at an incidence of approximately 3-7% in clinical trials.

The following Agency table outlines the proportion of patients reporting various atypical sensations during the clinical development program for ZNS. As would be expected, ZNS is associated with similar types of atypical sensations at a frequency similar to what was seen for zolmitriptan tablets.

[18] See Sponsor Table 31 (AEs by gender), Table 32 (AEs by age), and Table 33 (AEs by weight), iss.pdf, pages 94 through 100.

[19] NDA 20-768, Review by Dr. Armando Oliva, dated 5/1/97, page 63.

Table 45 AE: "Atypical sensations" seen during the clinical development of ZNS

Clinical Pharmacology Studies[1]							
Adverse Event	**PB (N=60)**	**OT[2] (N=0)**	**Zolmitriptan Nasal Spray**				
			0.5 mg (N=48)	**1.0 mg (N=48)**	**2.5 mg (N=95)**	**5.0 mg (N=74)**	**10 mg (N=20)**
Tightness jaw	0 (0.0)	na	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tightness chest	0 (0.0)	na	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tightness throat	0 (0.0)	na	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	2 (10.0)
Tightness neck	0 (0.0)	na	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Sensation warm	0 (0.0)	na	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Trial 077, Controlled Efficacy Trial[3]							
Adverse Events	**PB (N=228)**	**OT (N=233)**	**Zolmitriptan Nasal Spray**				
			0.5 mg (N=224)	**1.0 mg (N=238)**	**2.5 mg (N+238)**	**5.0 mg (N=224)**	**10 mg (N=0)**
Tightness Throat	2 (0.9)	7 (3.0)	0 (0.0)	3 (1.3)	1 (0.4)	5 (2.1)	na
Paresthesia	13 (5.7)	14 (6.0)	11 (4.9)	16 (6.7)	12 (5.4)	23 (9.7)	na
Sensation warmth	5 (2.2)	8 (3.4)	0 (0.0)	1 (0.4)	8 (3.6)	0 (0.0)	na
Disorder/discomfort of nasal cavity	4 (1.8)	3 (1.3)	2 (0.9)	6 (2.5)	3 (1.3)	7 (3.0)	na
Long-Term Uncontrolled Trials, Pre-Cross-Over[4]							
Adverse Event	**PB (N=0)**	**OT (N=0)**	**Zolmitriptan Nasal Spray**				
			0.5 mg (N=275)	**1.0 mg (N=272)**	**2.5 mg (N=271)**	**5.0 mg (N=275)**	**10 mg (N=0)**
Tightness Throat	na	na	4 (1.5)	2 (0.7)	5 (1.8)	12 (4.4)	na
Tightness Chest	na	na	4 (1.5)	0 (0.0)	2 (0.7)	9 (3.3)	na
Paresthesia[5]	na	na	12 (4.4)	12 (4.4)	21 (7.7)	25 (9.1)	na
Disorder/discomfort of nasal cavity	na	na	5 (1.8)	5 (1.8)	4 (1.5)	11 (4.0)	na

1 Source: Adapted from Sponsor Table 19, iss.pdf, page 75.
2 OT = zolmitriptan tablet 2.5 mg, PB= placebo.
3 Source: Adapted from Sponsor Table 24, iss.pdf, page 86.
4 Source: Adapted from Sponsor Table 59, iss.pdf, page 136.
5 Included local nasal sensations such as tingling and burning

7.4.15 Withdrawal Phenomena, Abuse Potential, and Overdose

No adverse events of drug abuse or overdose with ZNS were reported in any of the clinical trials. Zolmitriptan is not known to be addictive and has no known chemical similarities with any known abused or addictive drug. The Sponsor recommends since the elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, the rare patient overdosed with zolmitriptan should be monitored for at least 15 hours. The effect of hemodialysis or peritoneal dialysis on the serum concentration of zolmitriptan is not known.

7.4.16 Human Reproduction Data

The following Sponsor table outlines the 18 pregnancies that occurred in subjects participating in the clinical development program for ZNS. Three pregnancies occurred in Trial 077, 12 in Trial 078, and 3 in Trial 0122. Of the 18 pregnancies, there were 10 uncomplicated healthy live births, 5 elective terminations, and 3 where the outcome is unknown. In 1 terminated pregnancy an ultrasound examination during the late first trimester revealed no fetal heart activity. In this case, microscopic examination revealed hybrid deposits of degeneration, no hydatidiform mole and no malignancies. As demonstrated in the table less than 50% of the pregnancies were associated with ZNS exposure after their last menstrual period and only a single pregnancy was associated with multiple doses (PID 0038/0018) hence little can be said about ZNS use and pregnancy outcome.

Table 46 Pregnancy during clinical development program for ZNS

Trial	Center/ subject	Age (y)	Date of LMP	N of doses after LMP	Outcome	Abnormalities
0077	0019/0053	29	08 Sep 98	1 x 5.0 mg	Normal pregnancy	None
	0024/0029	27	27 Aug 98	1 x 2.5 mg	Normal pregnancy	None
	0031/0004	24	03 Oct 98	1 x 0.5 mg	Normal pregnancy	None
0078	0001/0071	38	13 Dec 98	0	Elective termination	None
	0005/0010	32	10 Jan 99	0	Normal pregnancy	None
	0016/0014	26	24 Mar 99	0	Elective termination	No fetal heart activity
	0019/0026	38	27 Jun 99	1 x 5.0 mg	Elective termination	None
	0033/0010	31	3 Jan 99	0	Normal pregnancy	None
	0033/0026	28	13 Mar 99	0	Normal pregnancy	None
	0034/0027	35	13 Oct 99	0	Normal	None
	0038/0018	28	26 Nov 98	4 x 0.5 mg	Elective termination	None
	0041/0008	34	3 Nov 98	1x 1.0 mg	Elective termination	None
	0041/0033	34	5 Sep 98	1 x 5.0 mg	Normal pregnancy	None
	0048/0004	27	21 Jun 99	0	Normal pregnancy	None
	0049/0002	29	Unknown	0	Normal pregnancy	None
0122	0256/0004	34	4 April 2001	0	Unknown	Not applicable
	0602/0002	21	Unknown	0	Unknown	Not applicable
	0678/0004	23	27 Mar 2001	0	Unknown	Not applicable

LMP Last menstrual period.

Source: Sponsor Table 83, iss.pdf, page 182.

7.4.17 Long-term Safety Update Trial 311CIL/0122

On June 27, 2002 the sponsor submitted a 4 month safety update for the ZNS clinical program. This update includes safety information from the long-term, open-label trial 311CIL/0122 up to the cut off date of May 20, 2002. Although Trial 0122 is now complete this safety update does not include data entered between May 21, 2002 and June 6, 2002 the final database entry lock date. A final document including all data will be submitted to the Agency once it is complete. In this section I will briefly summarize the new safety information and provide details if the information is substantially different from what was previously reported.

The design of Trail 0122 has been previously described and will not be discussed here. Instead of presenting only data collected during the update period the sponsor presents the new data in an integrated manner with the previously reported safety data from Trial 0122. No new patients enrolled in Trial 0122 since the cut off date of the ISS. In Trial 0122 a total of 538 migraine patients treated 20,719 migraines with ZNS 5.0 mg. The breakdown of the monthly frequency of attacks treated in subjects remaining in the study for 180 and 350 days is summarized below. As previously described the majority of patients were female, white and around 40 years of age.

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Table 47 Frequency of attacks for patients with at least 180 and 350 days in Trial 0122.

Number of days in study		Zolmitriptan nasal spray – 5.0 mg dose (N=538)	
	Mean number of attacks per 30 days	n	%
≥180	<1	52	9.7
	≥1 to <2	94	17.5
	≥2 to <3	78	14.5
	≥3	237	44.1
≥350	<1	39	7.2
	≥1 to <2	89	16.5
	≥2 to <3	72	13.4
	≥3	230	42.8

N, n Number of attacks.

Source: Sponsor table 5, Study report 4MSU.pdf, page 29.

No deaths occurred during this study. No new serious drug-related adverse events were reported during the 4 month safety update period of data collection.

The all-adverse-events-reported profile is nearly identical to what has been previously described and will not be repeated in detail here. As before the most common adverse events included unusual taste, local paresthesia, disorder and discomfort of the nasal cavity, throat pain and nausea. The majority (97%) of adverse events reported were of mild or moderate intensity and few resulted in subject withdrawal. Essentially the report is consistent with the previous summary that long-term use of ZNS does not appear to result in an increase incidence of side effects and the pattern of adverse events are similar to what is expected for the nasal route of administration (e.g., unusual taste, and local effects in the nasopharynx) and triptan products in general (e.g., paresthesias).

The additional nasopharyngeal examinations done during the safety update period failed to demonstrate any safety concerns. As previously discussed a few subjects experienced mild epistaxis. Of interest, two subjects (0.4%) were classified as having laryngeal edema (0250/0008 and 0950/0010) however the complaints were subjective, rated mild, resolved spontaneously, and were without any objective findings on physical examination according to the sponsor.

A total of 24 patients (4.5%) withdrew consent for treatment due to adverse events during Trial 0122. Adverse events resulting in withdrawal that occurred in more than one patient included vomiting (4), nausea (3), paresthesia (3), dysphagia (2), unusual taste (2), and unintended pregnancy (2). This profile is consistent with what has already been described. There is no evidence of an adverse event leading to withdrawal becoming more frequent with prolonged use of ZNS.

New safety laboratories and ECGs done during this safety update period failed to demonstrate any clinically significant changes. Several ECGs had equivocal changes however all ECGs were

done well outside the period in which it would be reasonable to expect zolmitriptan to be in circulation. A single patient (0952/0028) had an upward trend in their blood pressure over the period of 7 visits (maximum 153/105). A second patient (0675/0025) was withdrawn from the study due to increase blood pressure noted by her primary care physician. Otherwise there were no clinically relevant changes in vital signs during this study. Repeated nasopharyngeal examinations continued to not find any clinically significant changes with prolonged use of ZNS.

The sponsor includes 2 abstracts from articles recently published on ZNS [both Shakra S et al, Neurology 200;58(7)(Suppl 3) A414 and A91-2]. Neither article presents any new concerns not already characterized in my review.

In summary, the new safety data collected from Trial 0122 raises no new safety concerns. The safety data presented in this 4 month safety update is similar to the safety information previously summarized in the ISS. Most patients (85.3%) reported at least 1 adverse event during this trial however relatively few individual attacks were associated with an adverse event (32.8%). Few adverse events resulted in withdrawal (4.5%). The nature of the adverse events seen during the safety update period was similar to what has already been described in the ISS. There is no evidence that any particular adverse events becomes more frequent with prolonged therapy. Clinical laboratories, vital signs measurement and ECGs results revealed no treatment related clinically significant abnormalities.

7.5 Adequacy of Safety Testing

The amount and duration of ZNS exposure during the clinical development program is in excess of what is generally required for short and long-term studies in migraine. In Trial 077, 922 patients were given 2311 individual exposures to ZNS. In Trial 078, 1097 patients administered 20114 doses of ZNS. In Trial 0122, 538 subjects have administered 20719 doses of ZNS 5 mg as of the date of the 4 month safety update. Trial 0122 permitted repeat dosing of ZNS 5.0 mg at 2 hours if needed. In the long-term trials, subjects taking ZNS 5mg treated approximately 2.7 migraines per month. The pharmacokinetic studies adequately evaluated acute safety with close monitoring of vital signs, serial ECGs, and basic laboratories. Since a great deal of safety information is already known about zolmitriptan there was little expectation for unusual findings during the clinical studies of ZNS. Appropriately the Sponsor included close monitoring of nasopharyngeal symptoms and examinations in a large number of patients during these trials.

In summary the safety population and safety monitoring was adequate for this NDA. I do not have any recommendations for additional post-marketing surveillance other than what is generally required by regulation.

7.6 Summary of Critical Safety Findings

The overall incidence of adverse events for ZNS increase in dose-related manner, as is seen with the zolmitriptan tablets. The adverse events of the nasal spray seen in the clinical development program for ZNS are for the most part similar to those seen in the clinical development program for zolmitriptan tablets. The most common adverse events seen with zolmitriptan tablet in the original NDA (dizziness, somnolence, nausea, paresthesia, asthenia) occur at approximately the same frequency with ZNS.

A significant difference between ZNS and zolmitriptan tablets is the adverse event "unusual taste", which is uncommon with the tablet (<1% of patients in the original NDA) but very common in the ZNS product (PB 3.1%, zolmitriptan tablet 2.5 mg 2.1%, ZNS 0.5 mg 2.1%, ZNS 1.0 mg 4.9%, ZNS 2.5 mg 17.4% and ZNS 5.0 mg 21.2%[20]). This most likely represents a formulation-specific local effect of the nasal spray. Other relatively common local effects seen with ZNS include paresthesia, throat pain, and local irritation/soreness. These local effects in most individuals were mild, transient and did not result in withdrawal. Physical examination of the nasopharyngeal system failed to demonstrate any significant changes with acute and long-term use of ZNS.

In two long-term studies ZNS 5.0 mg has been well tolerated. The rate of withdrawal due to adverse events was 2.8% of patients. There was no change in the frequency, type, seriousness, intensity or duration of adverse events with increasing duration of treatment.

At all ZNS doses, all adverse events were typically mild and transient. Zolmitriptan nasal spray at the dose range studied (up to 10 mg in Study 136-032) did not reveal any clinically significant cardiac effects, changes in clinical laboratories, or changes in ECGs. The incidence of adverse events was not affected by gender, age, weight, or the presence of rhinitis. There was insufficient experience in non-Caucasian populations to assess the impact of race on the incidence of adverse events.

In conclusion ZNS has a similar safety profile to that of oral zolmitriptan, except for local effects, in the acute treatment of migraine with or without aura in adult patients. Apart from adverse effects related to the intranasal route of administration (nasopharyngeal discomfort, unusual taste, etc.), labeling for the nasal spray should be similar to that of zolmitriptan oral tablet.

8. Dosing, Regimen, and Administration Issues

In the proposed package insert the Sponsor states that ZNS ——— 5.0 mg may be administered in a single nostril for the acute treatment of a migraine. Additionally, the Sponsor states that if the headache returns the dose may be repeated after two hours, but not to exceed 10 mg zolmitriptan (administered orally and/or nasally) in 24 hours.

This proposed regimen is similar to the regimen for Zomig Tablets and Zomig-ZMT and is supported by the clinical program for Zomig Nasal Spray. The pharmacokinetics of ZNS 10 mg was evaluated in Trial 136-032 and the safety of repeated dosing at 2 hours (maximum zolmitriptan 10 mg in 24 hours) was evaluated in the long-term trial 0122. The single placebo-controlled efficacy trial 077 demonstrated a clear dose response for efficacy and many safety concerns however the study did not evaluate repeat dosing.

No study evaluated the effect of food on absorption of ZNS however since ZNS is primarily absorbed via the nasal mucosa than food effect should be negligible. Previous studies with zolmitriptan tablets failed to demonstrate any affect on absorption due to food. Since the clinical

[20] Source: Sponsor Table 24, iss.pdf, page 86.

development plan for ZNS excluded patients with renal or hepatic insufficiency there is inadequate information to provide dosing recommendations in these special populations other than to say caution is warranted.

9. Use in Special Populations

The efficacy of ZNS in the various subgroup analyses (age, gender, weight) is summarized in Table 14. Since approximately 98% of the participants in the ZNS trials are Caucasian, no conclusions can be drawn about efficacy or safety among different ethnic or racial groups. Over 80% of the participants were women, reflecting the natural predilection for migraine in women. When the 234 men are analyzed separately for the same primary endpoints for efficacy, the result was the same as that obtained for women. Likewise, when men are analyzed separately for AEs, the nature and frequency of AEs is the same as for women. Since elderly (>65 years of age) and pediatric patients (<18 years of age) were not enrolled in the clinical trials for ZNS no conclusion can be drawn about safety and efficacy of ZNS for these populations. There were no apparent difference in efficacy when the data was analyzed by age in groups between the ages of 18 thorough 65 (18-39, 40-65). The incidence of adverse events was not adversely affected by gender, age, weight, a second dose of trial medication, or the presence of rhinitis. Since pregnant patients and patients with hepatic or renal insufficiency were not enrolled in the clinical trials for ZNS no conclusion can be drawn about safety efficacy and use of ZNS for these populations.

The clinical development plan for ZNS use in adolescents with migraine is presently deferred as per our agreement with the Sponsor.

10. Conclusions and Recommendations

10.1 Conclusions

My conclusions about efficacy can be found in section 6.4 of the Clinical Review. My conclusions about safety can be found in section 7.6 of the Clinical Review.

The benefits of ZNS are clear. Trial 077 demonstrates convincingly that ZNS is effective for the pain of migraine and its associated symptoms of photophobia and phonophobia at 2 hours. For each of these symptoms there was a dose effect with the highest dose of ZNS demonstrating the highest efficacy and the lowest dose demonstrating the lowest efficacy. For many of these symptoms ZNS was more effective than placebo at earlier times than 2 hours, especially ZNS 5 mg. Efficacy against nausea was demonstrated at 2 hours for subjects receiving ZNS 5.0 mg but not until 4 hours for all other ZNS cohorts.

ZNS was developed to provide an alternative treatment options to zolmitriptan oral

or other triptan injection formulations. The efficacy results from ZNS 5 mg [redacted] suggests that it may provide more rapid relief (at 15 minutes) than placebo or zolmitriptan tablets 2.5 mg however additional studies are warranted.

The risks associated with the use of ZNS are similar to zolmitriptan tablets except for the additional concerns for local effects such as nasal paresthesia, abnormal taste sensation and local irritation. In general, none of these local effects were bothersome enough for patients to withdraw from treatment. The most common systemic adverse events seen the clinical trials for zolmitriptan tablets (dizziness, somnolence, nausea, paresthesia, and asthenia) occurred at approximately the same frequency with the nasal formulation and oral tablet when compared dose for dose. Otherwise ZNS was well tolerated without any clinically significant changes in vital signs, laboratories, ECGs or nasopharyngeal examinations. Long-term studies fail to demonstrate any change in adverse event frequency, type, seriousness or duration with increasing use of ZNS.

Migraine can be a debilitating condition and warrants a reasonable level of risk when choosing therapy. ZNS offers no additional risk, outside the local effects, than already approved triptan products. The local effects were relatively minor and self limiting in all cases and rarely resulted in withdrawal. In summary the risk benefit equation favors the approval of ZNS for the acute treatment of migraine

10.2 Recommendations

From a clinical perspective I recommend the approval of zolmitriptan nasal spray 5.0 [redacted] for the acute treatment of migraine with and without aura. My review of the proposed label can be found in Appendix B.

Appendix

A. Expanded Reference Range for Laboratory Values

Table C1 Normal and expanded reference ranges for hematology and clinical chemistry

Laboratory test	normal range	normal range	Expanded reference range
Hematology			
Hemoglobin (HgB)			
Female	12.1 to 15.6 g/dL	11.6 to 16.4 g/dL	9.5 to 20.0 g/dL
Male	14.0 to 17.6 g/dL	12.7 to 18.1 g/dL	11.5 to 20.0 g/dL
Mean cell volume (MCV)	87 to 98 fl	79 to 98 fl	70 to 110 fl
Platelets	160 to 375 x 10^9/L	130 to 394 x 10^9/L	100 to 600 x 10^9/L
White blood cells (WBC)	4.0 to 11.0 x 10^9/L	4.36 to 10.74 x 10^9/L	2.5 to 17.0 x 10^9/L
Neutrophils	40 to 75%	40.5 to 75%	≥15%
Lymphocytes	16 to 50%	15.4 to 48.5%	2.0 to 70.0%
Monocytes	2.8 to 8.3%	2.6 to 10.1%	≤20%
Eosinophils	0.6 to 6.5%	0.0 to 6.8%	≤10%
Basophils	0.3 to 1.5%	0.0 to 2.0%	≤10%
Clinical chemistry			

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Appendices

B. Label Review

1. Draft Retail Carton

The sponsor provides a copy of the Draft Retail Carton and immediate product label for each dose of Zomig Nasal Spray under "labeling" of the original submission. The proposed Retail Carton and immediate product label appear adequate.

2. Draft Professional Package Insert

The sponsor used the Zomig Tablet package insert as the template for the ZNS package insert and this is acceptable. An annotated version of the differences, with referenced explanations of the changes between the two labels can be found at the beginning of summary.pdf. I found this version very helpful during my label review.

All page numbers referenced in the following sections refer to the final non-annotated clean version of the package insert which can be found in "current clean.pdf" (November 5, 2002).

2.1 Description

This section contains modifications to the description appropriate for the nasal formulation. I have no comments and defer to the chemistry reviewer for any recommended changes to this section.

2.2 Clinical Pharmacology

The sponsor maintains the ADME format used in the approved Zomig Tablet Label with changes appropriate for the nasal formulation. The format is acceptable and the changes are appropriately referenced.

- Under special populations, Renal Impairment, I recommend the following clarification:

  To: "...($Cl_{cr} \geq 5 \leq 25$ mL/min) compared to the normal group ($Cl_{cr} \geq 70$ ml/min); no significant change in renal clearance was observed in the moderately renally impaired group ($Cl_{cr} \geq 26 \leq 50$ mL/min)."

This is data taken directly from the original Zomig Tablet Label.

- Under Hepatic Impairment, I recommend the following clarification:

  From:

  To: "...the mean C_{max}, T_{max}, and $AUC_{0-\infty}$ of zolmitriptan..."

This is data taken directly from the original Zomig Tablet Label.

- Under special populations, Hypertensive Patients, I recommend the following clarification:

Appendices

From: [redacted]

To: "No differences in the pharmacokinetics of oral zolmitriptan or its effects on blood pressure were seen in mild to moderate hypertensive volunteers compared to normotensive controls."

This information is derived from clinical pharmacology study 013 in which oral doses of zolmitriptan up to 20 mg were given to volunteers with mild to moderate hypertension[21].

I have no other comments and defer to the biopharmaceutics review for any additional recommended changes to this section.

2.3 Clinical Studies

This section has been extensively rewritten to reflect the information derived from Study 077. All data is well referenced by the sponsor. However I have the following recommendations:

- In the first paragraph the following change is recommended:
  From: [redacted]
  To: "...placebo-controlled trial."
- The following minor editorial change should be done:
  The spacing between the first and second paragraph and the second and third paragraph should be corrected. Presently there is not spacing between paragraphs. The content of the third paragraph could be incorporated into the second paragraph.
- The legends, titles, and abscissa-ordinate labels in Figure 1 and Figure 2 are incomplete and should be corrected. The notes under each figure should be in smaller case and properly positioned so that it is apparent that they belong to the figure.
- [redacted]

[21] Source: Dr. Armando Oliva's NDA 20768 (Zomig Tablet) review, page 16.

Appendices

- To provide consistency across triptan labels and to provide clinicians with relevant information I recommend the sponsor add the following statement prior to the statement

  Add: "For patients with migraine associated photophobia, phonophobia and nausea at baseline, there was a decreased incidence of these symptoms following the administration of Zomig Nasal Spray as compared to placebo

2.4 Indications and Usage

This section contains a modification to the product name appropriate for the nasal formulation and is acceptable.

2.5 Contraindications

The sponsor proposes no changes from the Zomig Tablet Label for this section. The proposed wording is acceptable.

2.6 Warnings

This section contains few modifications to the original Zomig Tablet label.

- Under "Cardiac Events and Fatalities" (page 11) the spacing between the first and second paragraph needs to be corrected.
- Under the subsection "*Premarketing experience with zolmitriptan*" the sponsor adds information that there were no deaths or serious cardiac events reported in Trial 077. This change is acceptable.
- Under the Warning Section the sponsor adds a new section entitled "Local Adverse Reactions" to describe the nasopharyngeal effects seen during Trial 077. The content of the information is acceptable however I would recommend the following statement be added after the sentence ending "...approximately 60% resolved in 1 hour".

  "Nasopharyngeal examinations, in a subset of patients participating in 2 long term trials up to 1 year duration, failed to demonstrate any clinically significant changes with repeated use of Zomig Nasal Spray."
- On page 13, second paragraph the statement should be changed to "All nasopharyngeal adverse events with an incidence of ≥ 2% of patients...".

Appendices

[redacted]

2.7 Precaution

This section contains modifications appropriate for the nasal formulation. The content changes are acceptable. The subsection "Carcinogenicity, Mutagenicity, Impaired Fertility" include new information derived from the preclinical studies using zolmitriptan nasal spray. The additional information appears acceptable however I defer to the pharmacotoxicology reviewer for additional comments. As with other sections the recently revised label (November 5 submission) has multiple problems with spacing between paragraphs. For example on page 14 there is no space between the 2nd and 3rd paragraph, the 3rd and 4th paragraph and so on. This lack of spacing may seem minor but can cause problems with busy clinicians trying to scan the label for specific information. The spacing in the label included in the original NDA submission is acceptable and should be followed.

2.8 Adverse Reactions

This section was extensively rewritten by the sponsor to reflect the data obtained from the clinical development program for Zomig Nasal Spray.

- As with other section the sponsor did not maintain spacing between paragraph. This should be addressed.
- On page 18 the statement [redacted] should be changed to " [redacted]
- On page 19 the title of Table 2 should changed from ' [redacted] to "Adverse events with an incidence of ≥2%...". Also on the table the column header "*Percentage of patients*" should be properly positioned closer to the actual data. The parenthesis surrounding "COSTART defined" should be completed.
- On page 19 the statement [redacted] should be changed to "The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age (18 – 39 vs. 40 – 65 years of age) [redacted] or presence of aura".
- On page 19 the sentence " [redacted] ." should be changed to "Adverse clinical events occurring in ≥ 1% and...".
- Under the subsection "Other Events" there is inconsistency in the use of bolding for subsection titles. For example Hemic is bolded whereas no other subsection is. The use of bolding should be consistent throughout.
- Under "Urogenital" (page 21) change ' [redacted] to the more common abbreviation, "PAP smear", for a Papanicolaou smear.

2.9 Dosage and Administration

This section has been extensively rewritten from the oral Zomig label to reflect prescribing information for Zomig Nasal Spray. The changes are acceptable.

Appendices

3. Draft Patient Information Sheet

The sponsor provides a revised copy of the proposed Patient Information Sheet for Zomig Nasal Spray electronically under "current clean.pdf" (page 25 November 5, 2002 submission). The sponsor used the Zomig Tablet Patient Information sheet as the template for the ZNS Patient Information sheet and this is acceptable. An annotated version, with referenced explanations of the changes between the two labels can be found in summary.pdf (page 37).

Most of the changes involve appropriate modifications needed for the ZNS formulation and are acceptable. However I recommend the following:

- There are multiple editorial problems with the Patient Information label. As with the professional package insert the recently submitted (November 5, 2002) revised Patient Information label fails to include appropriate spacing between paragraphs and/or sections. For example the sponsor does not provide a spacing between the sections "Information for the Consumer on Zomig Nasal Spray" and "Information About Your Medication". Also the sponsor is inconsistent with bolding (example heading "1" is bolded but "2" is not). On the 6th bulleted item the spacing between "containing " is excessive (this may be due to the block construction the sponsor employed for this label). These editorial problems should be corrected.
- [redacted]
- The figures (page 27 through 28) are not properly labeled resulting in an abnormal floating of the titles. The position of the first figure results in an awkward fracturing of the sentence "*Do not press the plunger until you have put the nozzle into your nostril or you will lose the dose*"

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Appendices

C. List of Table and Figures

Tables

Appendices

Figures

Appendices

D. Demographic Worksheet

Application Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-450 **Submission Type:** _____ **Serial Number:** 000

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	323	All Females	1596	Females >50	356

Age:	0-1 Mo.	0	>1 Mo.- 2Year	0	>2-12	0
	12-16	0	17-65	1919	>65	0

Race:	White	1883	Black	5	Asian	Not specified
	Other	31				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?				Was gender-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	√ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	√	☐
Safety	√ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	√

Is a dosing modification based on gender recommended in the label? ☐ Yes √ No

If the analysis was completed, who performed the analysis √ Sponsor ☐ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was age-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☐ Yes	√ No	√ Inadequate #'s	☐ Disease Absent	☐	☐
Safety	☐ Yes	√ No	√ Inadequate #'s	☐ Disease Absent	☐	☐

Is a dosing modification based on age recommended in the label? √ Yes ☐ No

If the analysis was completed, who performed the analysis √ Sponsor ☐ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was race-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☐ Yes	√ No	√ Inadequate #'s	☐ Disease Absent	☐	√
Safety	☐ Yes	√ No	√ Inadequate #'s	☐ Disease Absent	☐	√

Is a dosing modification based on race recommended in the label? ☐ Yes √ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

Appendices

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

- Demographic numbers excludes subjects participating in the pharmacokinetics trials (N=81) and Trial 078 (an open-label extension of Trial 077).
- There are insufficient numbers of non-Caucasian subjects to perform a subset analysis of safety and efficacy.
- There are no subjects less than 18 or greater than 65 years of age therefore subset analysis of safety and efficacy based on age not possible. The sponsor did perform an age based analysis using the age groups 18 to 39 and 40 to 65 years of age.
- The proposed label includes the standard recommended language for describing use in pediatric and geriatric patients when there is insufficient clinical experience.

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

/s/

Kevin Prohaska
12/9/02 06:12:00 PM
MEDICAL OFFICER

Armando Oliva
12/10/02 11:51:56 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

IND (Serial Number)	**21450(BB)**
Sponsor:	**AstraZeneca**
Drug:	**Zomig Nasal Spray**
Proposed Indication:	**Migraine**
Material Submitted:	**Response to 10/9/02 teleconference**
Correspondence Date:	**11/11/02**
Date Received / Agency:	**11/12/02**
Date Review Completed	**12/5/02**
Reviewer:	**Kevin Prohaska, D.O.**

1. Introduction

This submission is in response to our teleconference with the sponsor on October 9, 2002. At that time we informed the sponsor that their in-vitro bioequivalence study comparing the spray pattern of the clinical device and the proposed commercial device did not meet regulatory specification for equivalence. The sponsor responds by providing a two tiered argument supporting the position that the differences are inconsequential. The first argument is biopharmaceutical in nature. Essentially they argue that the Agency standards are not consistent with Industry standards or are due to chance. I refer the reader to the biopharm review of this submission for additional details. The second approach to their argument is clinical in nature and is the primary topic of this review.

To support the clinical argument the sponsor performed a subset analysis comparing the efficacy results from Part 1 of Trial 078 (ZNS 5.0 mg cohort using the clinical device) to Part 2 of Trial 078 (ZNS 5.0 mg cohort using the commercial device). The comparison they provide demonstrates comparable results using the two formulations. Likewise the sponsor compares the results of their analysis of Part 2 of Trial 078 (ZNS 5.0 mg using commercial device) to the results of Trial 077 (ZNS 5.0 mg cohort using the clinical device). The response rates were similar. Finally the sponsor provides 3 expert opinion that support their position.

In the following section I briefly summarize the design of Trail 077 and 078. It is important to keep the trial design in mind when assessing the strength of the sponsor's argument. Following that I itemize my thought on the sponsor's clinical argument.

2. Discussion

2.1 Trial Design 077

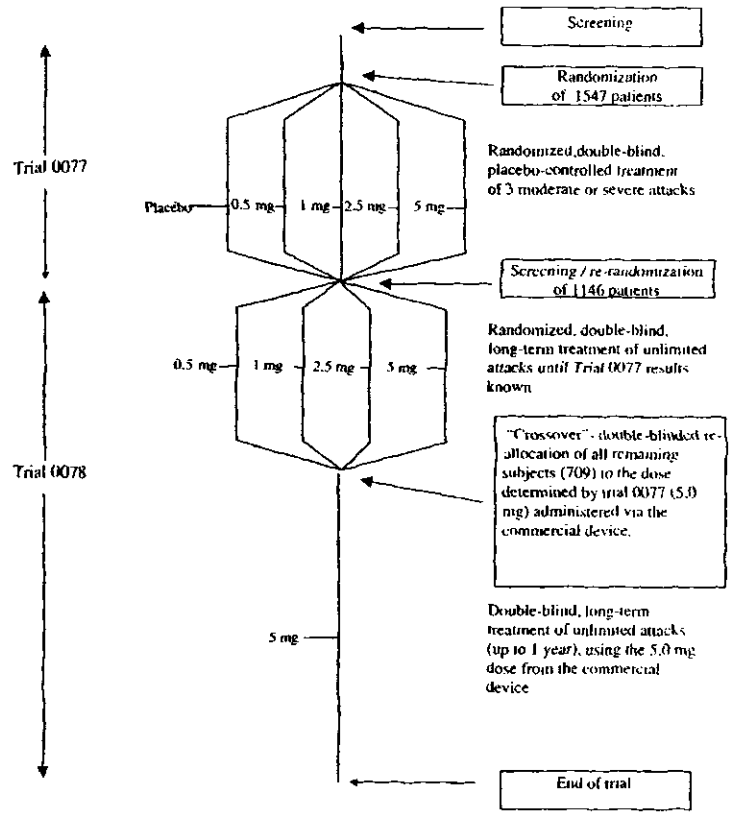
This was a double blind, placebo controlled, parallel, dose finding study to assess the safety and efficacy of Zomig Nasal Spray (0.5, 1.0, 2.5, and 5.0 mg) in 3 migraines. Due to an imbalance in withdrawals, with more placebo patients withdrawing for lack of efficacy, the sponsor only analyzed the first 2 migraines treated. At our request they also analyzed the first treated migraine. Trial 077 used the clinical device exclusively.

2.2 Trial design 078

This was a long-term extension of Trial 077. As previously discussed the patient population at entry included a disproportionally less people from the original placebo cohort due to an imbalance in withdrawal. In Part 1 of the Trial subjects were randomized to ZNS 0.5, 1.0, 2.5 or 5.0 mg in a double blinded manner. However subjects and investigator were all aware they would receive active compound but not at which dose. The clinical device was used for the majority of time in this period. In the submission the sponsor is vague as to when the devices were changed however they state it was about the time of the crossover. In Part 2 all subjects were switched to ZNS 5.0 mg using the new proposed commercial device. Again this was done in a blinded manner however according to the study report subjects and investigators where aware they would be switched to the most effective dose from Trial 077. From my review I was not able to determine if patients knew when the switch occurred however since the two devices appear differently it is likely to affect blinding.

In all, the sponsor states that 202 identical subjects participated in Part 1, receiving ZNS 5.0 mg clinical device, and Part 2 (ZNS 5.0 mg commercial device). An additional 507 subjects were switched to ZNS 5.0 mg during Part 2 crossover.

Figure 1 **Flow chart of events in the clinical efficacy dose-response study (Trial 0077) and its long-term extension (Trial 0078)**



2.3 Sponsor's argument:

⇒ A subset analysis of Study 078 comparing efficacy results (Part 1 ZNS 5.0-mg clinical device vs. Part 2 ZNS 5.0 mg commercial device) in 200 subject using the two devices shows no difference in efficacy at any timepoint (see figure 4, page 19).

⇒ Part 1 of Study 078 demonstrated a dose effect and all lower dose cohorts had a higher response rate once switched to ZNS 5.0mg.

⇒ A comparison of results from Study 077 (ZNS 5.0 mg, clinical device) and Study 078 (Part 2 commercial device) shows no difference in efficacy.

⇒ A comparison of tolerability between the two devices demonstrates no difference.

⇒ The lack of placebo control in 078 is inconsequential since both Part 1 and Part 2 where double blind to dose. The sensitivity and robustness of Trial 078 in terms of clinical efficacy is demonstrated by the incremental effect of increasing the dose of ZNS in a blinded manner at crossover in patients switching to the 5.0 mg commercial device (see figure 2, page 17).

⇒ The sponsor provides 3 expert opinion supporting their position.

- [redacted]
- Professor Frans Merkus[3]
- Professor Lisbeth Illum[4]

2.4 Issues

In this section I itemize several concerns I have about the sponsor's clinical argument.

The comparison of study results from Trial 077 to Part 2 of Trial 078 is not valid for the following reasons:

1. The two studies were designed differently. During Trial 078 subjects were permitted to treat a migraine of mild intensity and in 077 they were instructed to treat moderate to severe migraines. In Trial 078 subjects treated up to 8 migraines per months whereas in Study 077 subjects treated up to 3 migraines.
2. The population of migraineurs from Trial 078 were comprised of subjects from Trial 077. However subjects originally randomized to placebo in Trial 077 tended to withdraw more often that subjects on active therapy. This resulted in a treatment bias favoring active therapy in subjects randomized in Trial 078. This would confound any comparisons between studies.

The comparison of Part 2 and Part 1 of Trial 078 is problematic for the following reasons:

1. Despite the double blind in Part 1 of 078, subjects and patients were aware that they were on active therapy.
2. Despite the double blind in Part 2 of 078, subjects and investigators were aware that the dose selected would be the most effective dose seen in Study 077.
3. On page 16 of submission the sponsor states that the histogram (Figure 2) represent a comparison of HA response between Part 1 and Part 2 of Study 078

[1] [redacted]
[2] Vice Chair and Associate Professor, Department of Pharmaceutical Sciences, University of Maryland
[3] Director ID$_{IDENTITY}$ and Special Professor University of Nottingham, United Kingdom
[4] Innoscience Technology, Belgium

and defines HA response as moderate to severe pain going to mild or no pain. However in Study 078 subjects were permitted to treat a migraine of mild intensity. I am uncertain if the data represented by the histogram is a subset of patients with moderate to severe headache at baseline or whether the sponsor incorrectly defined headache response.

4. The histogram demonstrates a dose response for the clinical device in Part 1 of Study 078 (this was also seen in Study 077), and it shows that the two devices are comparable in efficacy for the 5.0 mg dose. This does not mean that this comparison would hold for the lower doses. This is especially a concern for ZNS 0.5 mg, which barely met the 0.05 level for significance using the clinical device.
5. The original study report for Trial 078 does not discuss efficacy results comparing the two devices or when the new formulation was introduced. [redacted] However in this submission the sponsor restricts their discussion to only the 5 mg dose.
6. The sponsor states (page 14) that the switch to the commercial device occurred "about the same time as the time they switched all subjects to ZNS 5.0 mg [redacted]
7. Only 709 subjects were remaining at the time of crossover in study 078 (compares to 1547 that started study 077 and 1146 that started part 1 of 078). A more detailed review of the drop outs would be necessary to determine whether this confounds the comparisons between studies and between parts of Trial 078.
8. Trial 078 started 3/98 and ended 2/00. The protocol amendment for the new formulation is dated May 17, 1999 (p 1005/32683). The sponsor states the new commercial device was introduced in 12/99. I was not able to determine when all subjects were switched to ZNS 5.0 mg (Part 2). I was not able to determine if subjects were actually dispensed the lower dose new commercial product in Part 1.
9. The two devices are not identical. This may affect the blind. This is especially a concern since subjects were informed that sometime during Trial 078 they would be switched to the most efficacious dose as determined by the analysis of Trial 077.
10. I performed a line by line review of define.pdf for Trial 078 and I could not find any simple variable that indicates which device was used to treat which migraine. An automatic search using the terms commercial, device, spray, formulation and clinical found no relevant variables. The term batch resulted in the variable IDCODE01 and IDCODE02, which apparently represents the batch number for the 1st and 2nd dose of treatment taken. However the summary of these variables resulted in numbers that did not correspond to the batch numbers identified in Table I (page 20/32683 IL0078.pdf). The formulation numbers for the commercial device are F12438 (0.5 mg), F12439 (1.0 mg), F12440 (2.5 mg) and

F12441 (5.0 mg)[5]. Table I does not indicate which batch goes to which formulation. One possible manner of determining which migraine was treated with which device would be to go back to the original case report form which required the patient to affix the label of the product used to it. The sponsor states they were able to determine treatment for the vast majority (i.e. not all) of each migraine event by tracking batch numbers and manufacturing dates. The methodology is not apparent from my review of the datasets.

Table 1 Batch numbers used in the trial

Preparation	Zolmitriptan dose (mg)	Formulation number	Batch number
Zolmitriptan intranasal solution	0.5	F12234, F12438	37501A97, 38381E97, 37501A9701, 00157E98, 01400B98, 02353D98
Zolmitriptan intranasal solution	1.0	F12215, F12439	37805G97, 38380H97, 00277C98, 01733J98, 02128K98, 60160G99
Zolmitriptan intranasal solution	2.5	F12235, F12440	37900F97, 38911C97, 00321C98, 00795I98, 01803F98, 02379K98, 60161D99
Zolmitriptan intranasal solution	5.0	F12216, F12441	37981D97, 39082J97, 00464F98, 01249B98, 01892F98, 60162A99, 05078H98, 61333D99, 61944K99, 62522E99, 62268H99

3. Comments

1. In my opinion the clinical argument does not appear compelling enough to warrant ignoring the failed bioequivalence study however a detailed review of the data is required. There appears to be multiple design issues that make a comparison of efficacy results from Trial 077 and 078 not valid. Additionally, there appears to be several design issues that make a comparison between Part 1 and Part 2 of Trial 078 difficult.
2. For Trial 078, the sponsor needs to clarify when exactly subjects switched to the commercial device. If it occurred precisely at the time subjects were entering Part 2 of the study, and they were aware they were entering Part 2 of the study, this may be a critical design flaw making a comparison between Part 1 and Part 2 confounded by blinding concerns. The study report for Trial 078 states that subjects and investigators were aware that Part 2 of the study would involve a crossover to the most effective dose from Trial 077. The study report does not state whether subjects were told when the crossover occurred. However even if patients were not told that the crossover was occurring it is reasonable to assume most patients would believe the crossover occurred at the time of the new device was distributed.
3. [redacted]
4. If the sponsor intends to pursue the clinical argument outlined in this review to refute the findings from the failed in-vitro bioequivalence study then additional time will be needed to review the data in detail. The sponsor will need to inform us how they were able to determine which device was used for which migraine given the database submitted to the NDA. If they, as I expect, went back the original Case Report Forms then a new database will be needed for my review.

[5] Source Study Report 078, page 1005, IL0078.pdf

5. The review of this submission by the biopharm reviewer states *"the arguments presented by the firm provide no compelling new evidence to support the in-vitro equivalence of the commercial device to the clinical device."*
6. On December 2, 2002 the following comments were forwarded to the sponsor via e-mail:

   1. "We understand that subjects and investigators in study 0078 knew that, at some point during the study, subjects would be switched to the best optimal dose (based on the results of 0077). Did subjects and investigators know when the change in dose took place?"

   2. " We also understand that the change in device from the clinical to commercial spray occurred "around the same time" as the change to the best optimal dose. Can you be more specific? Are there subjects that received a randomized dose using the commercial device? If so, how many?"

Kevin Prohaska, D.O.
Medical Reviewer

A. Oliva, M.D. _____

HFD-120
IND 21450(BB)

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/s/

Kevin Prohaska
12/12/02 04:55:47 PM
MEDICAL OFFICER