Clinical Review Cover Sheet
Pediatric Supplement Review

NDA:	**20-768 (Sequence 012)**
Sponsor:	**Astra Zeneca**
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Proposed Indication:	**Migraine (adolescent)**
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Division:	**Division of Neuropharmacological Drug Products (HFD-120)**
Reviewer:	**Kevin Prohaska, D.O.**

Table of Contents

Table of Contents 2

1. Introduction and Background 4

1.1 Regulatory History and Significant Previous Reviews 4

2. Clinical Review Methods 5

2.1 How the Review was Conducted 5

2.2 Were Trials Conducted in Accordance with Accepted Ethical Standards 5

2.3 Evaluation of Financial Disclosure 5

3. Review of Trial 311 CUS/0007 (non-migraineur adolescent safety study) **..... 5**

3.1 Design and Schedule of Events 5

3.2 Patient population and demographics 6

3.3 Safety Results 7

3.4 Conclusions/Comments 10

4. Review of Trial 311 CUS/0005 (acute adolescent efficacy and long term safety study) **..... 10**

4.1 Design and Schedule of Events 10

4.2 Patient population and demographics 11

4.3 Patient Disposition and Treatment Exposure 12

4.4 Efficacy Results 14

4.5 Safety Results 15

4.6 Pregnancy 19

4.7 Adverse events by gender, race and age 20

4.8 Safety Conclusions 20

5. Brief Review of trial 311CIL/0092 (PK trial adolescents vs. adults**) 21**

5.1 Design, Patient Population 21

5.2 Pharmacokinetic Results 21

5.3 Safety Findings 24

5.4 Conclusions 25

6. Conclusion/Recommendation 26

7. Appendix 1: Tables and Figures 28

8. Appendix 2: Labeling Review 29

Clinical Review for NDA 20-768, Supplement 8

1. Introduction and Background

In this document I will review the studies submitted by the sponsor in support of their pediatric supplemental NDA submitted on September 30, 2003. This review will supplement the review I conducted for the Pediatric Exclusivity Determination (see DFS). The Exclusivity Determination Board met on December 8, 2003. Pediatric Exclusivity was granted on December 18, 2003.

The original Pediatric Written Request letter outlined 4 clinical trials to be completed; an acute adolescent efficacy study (study 3), a long term adolescent safety study (study 4), an adolescent migraineur PK study (study 2), and an adolescent inpatient safety study (study 1, if doses greater than 5 mg are proposed). In support of the Exclusivity request the sponsor submits the results of 5 studies (trial 311CUS/007, 311CUS/005, 311CIL/092, 136-007, and D1221C0004). Trial 311CUS/0007 evaluated the safety of Zomig Tablets 2.5, 5.0 and 10.0 mg in adolescents (to address the requirements of Pediatric WR study 1). Trial 311CUS/0005 evaluated the safety and efficacy of Zomig 5mg in adolescent in a two-phase trial. Phase 1 was an acute efficacy trial (study 3 of Pediatric WR) and phase 2 was a long-term safety trial (study 4 of Pediatric WR). In order to meet the requirements of the PK trial (study 2 of Pediatric WR) the sponsor submits the results of 3 PK studies (trials 311CIL/092, 136-007, and D1221C0004). Trial 311CIL/092 evaluated the PK of Zomig 5 mg in healthy adolescents and adults and included non-migrainous subjects. Trial 136-007 evaluated the PK of Zomig 10 mg in adult migraineurs during and between an attack. Trial D1221C0004 evaluated the PK of Zomig Nasal Spray 5 mg in adolescents and adults with a history of migraine.

A review of the relevance of each trial in meeting the requirements of the pediatric written request was the topic of my original Exclusivity review and will not be repeated here. The nature of the submission relative to the Pediatric Supplement is a bit unusual since the sponsor readily admits the single acute efficacy study (trial 311CUS/0005) conducted in adolescents did not demonstrate efficacy (b) (4) and does not seek an adolescent indication. Despite the lack of efficacy the sponsor still proposes to describe the study in the product label. I address this issue in my label review (Appendix 2: Labeling Review).

For the purposes of this review I will focus my attentions on the results from trial 311CUS/0005 (acute efficacy and long term safety study), trial 311CUS/0007 (adolescent safety study), and trial 311CIL/092 (adolescent/adult PK study) since they all included adolescent subjects and used the tablet formulation of zolmitriptan. All PK studies submitted in support of the Pediatric Exclusivity Determination Request were old studies previously submitted to the Agency and resubmitted with this submission. (b) (4) Since the sponsor does not provide an integrated summary of efficacy or safety I will review each trial independently. Following the review of each trial I will provide my summary comments about safety and efficacy.

1.1 Regulatory History and Significant Previous Reviews

- November 25, 1997 Zomig Tablet (NDA 20-768) approved.

- April 9, 1998 — Sponsor submits results of adolescent PK Study (311CIL/0092) and a new protocol for study 311CUS/0005 (adolescent efficacy study, Dr. Oliva's review of serial 079 can be found in the Division file).
- September 2, 1998 — Proposed pediatric clinical development plan submitted.
- March 26, 1999 — Original Pediatric Written Request issued.
- April 16, 1999 — Sponsor's reply to Written Request submitted (Dr. Oliva's review of serial 100 can be found in the Division file). Also includes results from trial 311CUS/0007 and amendment to study 311CUS/0005.
- May 29, 2002 — Pediatric Written Request Amendment issued (amended date only).
- August 15, 2002 — Teleconference to discuss pediatric development program.
- September 30, 2003 — Pediatric Exclusivity Determination and labeling changes supplement submitted.
- December 8, 2003 — Pediatric Exclusivity Determination Board meets.
- December 18, 2003 — Pediatric Exclusivity granted.

2. Clinical Review Methods

2.1 How the Review was Conducted

All data submitted by the sponsor for this review is contained in the electronic submission dated September 30, 2003 and can be found at \\CDSESUB1\N20768\S_012\2003-09-30.

2.2 Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor asserts that all studies conducted in support of this supplement were conducted according to the procedures and principals of Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki.

2.3 Evaluation of Financial Disclosure

1. Study 311CUS/00005 (Adolescent acute efficacy and long term safety study)
   The sponsor has submitted a completed Form FDA 3454 certifying that they have not entered into any prohibited financial agreements with investigators. A single investigator (b) (6) responded positively to receiving sums greater than $25,000 from AstraZeneca. (b) (6) The sponsor does not give any details about the nature or complete amount of moneys provided (b) (6) In the final analysis the study failed so I do not believe this resulted in any significant bias.
2. Study 311CUS/00007 (Adolescent inpatient safety study)
   The sponsor has submitted a completed Form FDA 3454 certifying that they have not entered into any prohibited financial agreements with investigators.
3. Study 311CIL/092 (Adolescent/Adult PK study).
   The sponsor does not provide a Form FDA 3454 for study 311CIL/092.

3. Review of Trial 311 CUS/0007 (non-migraineur adolescent safety study)

3.1 Design and Schedule of Events

This was a multicenter, double-blind, randomized, placebo-controlled, 4 parallel group, single dose trial in healthy adolescent subjects. A past medical history of migraine was not required for entry. The primary objective of this trial was to evaluate the safety and tolerability of a single tablet of zolmitriptan 2.5, 5.0 and 10.0 mg in adolescents between the ages of 12 to 17 years. This is an older

study previously submitted (draft version) and briefly reviewed by Dr. Oliva on April 16, 1999 (serial 100). The final study report is submitted with this supplement.

Potential subjects were screened at visit 1 to determine eligibility. Visit 1 assessments included a complete physical examination, vital signs assessment, ECG, a comprehensive metabolic panel, CBC, urinalysis and a urine pregnancy test (if appropriate). Additionally entry criteria and the informed consent were reviewed. Eligible subjects were invited to return to the center for randomized treatment (visit 2) within 7 days of screening. During visit 2 subjects received a single dose of randomized treatment and followed inpatient for at least 4 hours. Safety evaluations included a continuous 24 hour holter monitor (started 30 minutes prior to dosing), serial vital signs assessments (0.5, 1.0, 2.0 and 4.0 hours), and hour 4 laboratories (Chemistry panel, CBC, and urinalysis). Vital signs included respiratory rate, temperature, and standing/seated blood pressure and pulse. Additional ECGs were done if there were any signs of ischemia during the first 4 hours of monitoring. If subjects reported feeling well they were released to their guardians with a 24-hour adverse event diary (event, duration, intensity, action taken, and outcome collected). All subjects were contacted by telephone at hour 24 to determine status. A final safety visit (visit 3) occurred within 10 days of randomized treatment and included a physical examination and a review of adverse events. There were no protocol amendments. The level of safety monitoring is acceptable to this reviewer.

3.2 Patient population and demographics

Key entry criteria included all adolescents between the age of 12 to 17 years (inclusive) without any significant past medical history. Specifically excluded were adolescents with abnormal screening assessments or history or findings of ischemic heart disease, any vascular disorders, cardiac accessory conduction pathway arrhythmias (e.g.. WPW), hypertension, orthostatic hypotension, epilepsy or convulsive disorder, basilar, hemiplegic or ophthalmoplegic migraine, renal or hepatic impairment, pregnancy or lactation. Subjects were not specifically required to have a history of migraine however if they did the entry criteria specifically excluded subjects who should not receive triptans (e.g. cardiovascular conditions or unusual migraines such as basilar migraines). Prophylactic migraine medication was prohibited. Concomitant use of SSRIs or cimetidine was prohibited within 24 hours of treatment.

A total of 84 healthy adolescent subjects (with or without a migraine history) were equally randomized to Zomig 2.5, 5.0 10 mg or placebo in 6 centers. The sample size was chosen based on practical consideration. The following table summarizes the demographic characteristics of subjects participating in the trial. As demonstrated in the table the mean age was 14.8 years (range 12 to 17 years), 22.6% of subjects were between the age of 12 to 13 years, 35.7% were between the ages 14 to 15 years, and 41.7% were between the ages of 16 to 17 years. The majority of subjects were male (64%) and Caucasian (66%). All subjects completed the trial. There were no significant differences between cohorts for baseline demographics.

Table 1 Demographic Trial 0007

Characteristic	Placebo	Zolmitriptan			All
		2.5 mg	5 mg	10 mg	subjects
	(N=21)	(N=21)	(N=21)	(N=21)	(N=84)
Sex, n (%)					
Male	14 (66.7)	12 (57.1)	13 (61.9)	15 (71.4)	54 (64.3)
Female	7 (33.3)	9 (42.9)	8 (38.1)	6 (28.6)	30 (35.7)
Ethnic origin, n (%)					
White	16 (76.2)	11 (52.4)	14 (66.7)	14 (66.7)	55 (65.5)
Black	3 (14.3)	8 (38.1)	4 (19.0)	5 (23.8)	20 (23.8)
Hispanic	2 (9.5)	2 (9.5)	2 (9.5)	2 (9.5)	8 (9.5)
Asian	0	0	1 (4.8)	0	1 (1.2)
Age (y)					
Mean (SD)	15.2 (1.3)	14.7 (1.6)	14.7 (1.9)	14.8 (1.6)	14.8 (1.6)
Range	13-17	12-17	12-17	12-17	12-17
Age group, n (%)					
12 to 13 y	3 (14.3)	5 (23.8)	6 (28.6)	5 (23.8)	19 (22.6)
14 to 15 y	9 (42.9)	8 (38.1)	6 (28.6)	7 (33.3)	30 (35.7)
16 to 17 y	9 (42.9)	8 (38.1)	9 (42.9)	9 (42.9)	35 (41.7)

N Total number of subjects.
n Number of subjects in this group.
Source: Sponsor table 2, study report 007, page 21

3.3 Safety Results

Trial 007 was strictly a safety trial. The primary endpoint was the incidence, nature and severity of treatment emergent adverse events. Descriptive statistics were used to describe trial results. Verbatim terms were translated to COSTART terms.

3.3.1 Death, Serious Adverse events, and Withdrawals

There were no deaths, serious adverse events or withdrawal during this trial.

3.3.2 Common Adverse Events

The following table briefly summarizes the incidence and nature of adverse events experienced in each cohort. All adverse events included in summary tables are those that occurred within 24 hours after treatment with trial medication. Overall 43 (51.2%) subjects reported an adverse event. There was some evidence of a dose effect in the incidence of subjects reporting at least 1 adverse event as evidenced by the fact that 38.1% of subject randomized to Zomig 2.5 mg reported at least 1 adverse events compared to 71.4% of subjects randomized to Zomig 5.0 mg. However this trend was not evidenced in the comparison between Zomig 5.0 mg to Zomig 10 mg (71.4% vs. 66.7% respectively). As demonstrated in the following table the most common adverse events were headache, nausea, tightness (head, neck, jaw, throat or shoulder), somnolence, and dizziness. Nearly all adverse events were rated a mild or moderate in severity. Only 5 (5%) adverse events were rated as severe; thirst (placebo), tightness (2.5 mg), somnolence (2.5 mg), and headache (2.5 and 10 mg).

Table 2 Adverse Events seen during Trial 311 CUS/0007

	Placebo (n=21)	Zomig 2.5 mg (N=21)	Zomig 5.0 mg (n=21)	Zomig 10.0 mg (n=21)
Incidence of subjects reporting ≥ 1 AE	6 (28.6%)	8 (38.1%)	15 (71.4%)	14 (66.7%)
Serious Adverse Events	0	0	0	0
Withdrawals	0	0	0	0
Deaths	0	0	0	0
AEs reported by more than 1 subject in any treatment group				
Abdominal Pain	0	0	0	2 (9.5%)
Asthenia	0	1 (4.8%)	2 (9.5%)	0
Chest Pain	1 (4.8%)	0	0	2 (9.5%)
Headache	2 (9.5%)	6 (28.6%)	4 (19.0%)	5 (23.8%)
Tightness	0	1 (4.8%)	5 (23.8%)	1 (4.8%)
Nausea	2 (9.5%)	1 (4.8%)	2 (9.5%)	3 (14.3%)
Dizziness	0	0	3 (14.3%)	3 (14.3%)
Hypertonia	0	0	1 (4.8%)	2 (9.5%)
Somnolence	1 (4.8%)	1 (4.8%)	2 (9.5%)	3 (14.3%)
Dyspnea	1 (4.8%)	0	0	2 (9.5%)

Source: Sponsor table 3 and 4 Trial 311 CUS/0007 study report.

3.3.3 Clinical Laboratories

A comprehensive metabolic panel (creatinine, bilirubin, alkaline phosphatase, albumin, ALT, AST, sodium, potassium, glucose and cholesterol), urinalysis, and complete blood count were collected at baseline and 4 hours after treatment. The following table summarizes the mean changes from baseline in each of these tests. No individual subject on zolmitriptan had a clinically significant change in any laboratory assessment. A single patient on placebo had a drop in platelet count from $134X10^3/mm^3$ at baseline to $114x10^3/mm^3$ at 4 hours. There was a slight trend in increased hemoglobin, hematocrit, alkaline phosphatase, ALT and cholesterol with increasing dose of zolmitriptan however the rise was not clinically significant. No subject had a clinically significant change in his or her urinalysis at 4 hours post dose.

Table 3 Change (SD) from baseline in clinical laboratories

Variable	Placebo	Zolmitriptan		
		2.5 mg	5.0 mg	10.0 mg
Hemoglobin	0.1 (0.4)	0.4 (0.5)	0.5 (1.0)	0.6 (0.4)
Hematocrit	-0.2 (1.5)	1.3 (2.0)	1.3 (2.6)	1.6 (1.6)
MCV	-0.5 (1.5)	0.1 (1.2)	0.0 (1.1)	-0.2 (1.1)
Platelets	-0.7 (10.4)	5.0 (17.2)	13.1 (38.5)	6.0 (11.5)
WBC	0.2 (1.3)	0.5 (0.9)	0.4 (1.4)	0.7 (1.2)
Neutrophils	-2.8 (6.6)	0.2 (6.1)	0.4 (7.7)	-0.2 (8.4)
Lymphocytes	2.5 (6.0)	0.9 (4.4)	0.5 (5.6)	1.1 (6.2)
Monocytes	0.3 (2.0)	-1.0 (2.8)	-0.3 (2.3)	-0.4 (3.1)
Eosinophils	0.1 (1.3)	-0.1 (2.0)	-0.6 (1.8)	-0.5 (2.5)
Basophils	0.4 (0.4)	0.4 (0.3)	0.4 (0.3)	0.5 (0.5)
Creatinine	-0.02 (0.1)	0.02 (0.1)	0.01 (0.1)	-0.02 (0.1)
Total bilirubin	0.02 (0.2)	0.06 (0.1)	0.05 (0.1)	0.08 (0.1)
Alkaline phosphatase	1.7 (6.7)	4.7 (8.9)	7.5 (51.3)	8.6 (9.2)
Albumin	0.1 (0.1)	0.1 (0.3)	0.1 (0.3)	0.2 (0.1)
ALT	0.4 (1.6)	0.5 (1.6)	0.6 (1.7)	1.2 (2.6)
AST	-0.5 (2.6)	-0.3 (1.7)	0.4 (1.9)	0.3 (2.6)
Sodium	0.6 (1.4)	1.7 (1.7)	0.9 (2.0)	0.7 (2.1)
Potassium	-0.3 (0.4)	-0.2 (0.4)	-0.2 (0.4)	-0.3 (0.5)
Glucose	5.7 (25.7)	35 (18.3)	6.4 (17.7)	11.5 (19.4)
Cholesterol	1.0 (6.7)	7.1 (9.0)	8.4 (7.6)	10.3 (7.5)

Adapted from sponsor table 5 and 6, study report 007

3.3.4 Electrocardiograms and 24-hour Holters

All subjects had a 12-lead ECG performed at screening and a 24-hour cardiac holter applied at baseline. Additional ECGs were performed if clinically necessary. All ECGs were considered normal. Thirteen subjects had ST segment depression recorded during Holter monitoring. The sponsor states evaluation of the Holter monitoring results by 2 independent cardiologists indicated that the findings were compatible with tachycardia in 11 of the 13 subjects. In the remaining 2 subjects, the findings were considered to be of undetermined significance by 1 cardiologist; the 2nd cardiologist considered the findings to be of undetermined significance, not ischemic in nature, and probably related to early repolarization. None of the 13 subjects had symptoms suggestive of an ischemic heart event.

3.3.5 Vital signs

Vital signs were assessed at time 0, 0.5, 1, 2 and 4 hours after treatment. Overall there were no clinically relevant changes in vital signs. There was a trend for a slight increase in standing systolic pressure and diastolic pressure at 0.5 and 1.0 hours after dosing administration in subjects given zolmitriptan 10 mg compared to the other cohorts. This trend was not evident at 2 and 4 hours. None of the changes were considered clinically relevant. No subject had a change in vital signs that meet the threshold for an adverse event.

3.3.6 Physical Examination

There were no clinically relevant changes in physical examination between baseline and hour 4. Two subjects had mild erythema at the site of the holter electrode patch but otherwise were healthy.

3.4 Conclusions/Comments

Overall single oral doses of Zomig 2.5, 5, and 10 mg were well tolerated in adolescent subjects during this study. The nature of adverse events seen during this trial were similar to those seen during adult migraine studies using Zomig tablets except for the higher incidence of headache. There were no clinically significant changes in clinical laboratories, vital signs, or physical examination. No adolescent had any evidence of ischemic heart changes on 24-hour holter recordings. There does not appear to be any clinically significant differences in the nature and type of adverse events experienced by adolescents or adults exposed to zolmitriptan. Efficacy was not assessed in this study.

4. Review of Trial 311 CUS/0005 (acute adolescent efficacy and long term safety study)

4.1 Design and Schedule of Events

This was a 2-phase, multicenter, international, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in the acute treatment of migraine attacks in adolescent patients. Patients were recruited from approximately 40 centers in the United States, 10 centers in Canada, and 23 centers in India, Finland, Germany and the United Kingdom. In phase 1 of the study, patients were randomized in a double blind fashion to treat a single migraine headache with either 2.5 mg, 5.0 mg, or 10.0 mg zolmitriptan, or placebo. In the phase 2, open-label portion of the study, patients treated multiple migraine attacks (up to 8 migraines in any 2.5 month period) over a 12-month period with 5.0 mg zolmitriptan (tablet form). In phase 1 subjects were permitted to use approved escape medication (NSAIDs, sedatives, or analgesics) at 2 hours if required; a second dose of study medication was not permitted. A second 5.0 mg tablet was allowed in phase 2, if necessary, between 2 hours and 24 hours after the 1st dose of study treatment.

The primary objective of the first phase of the study is to evaluate the efficacy of Zomig Tablet (2.5, 5, and 10 mg) in the treatment of an acute migraine of moderate to severe intensity in adolescent patients. The objective of the second phase of the study is to evaluate the safety of Zomig 5 mg in the treatment of multiple migraine events over a period of 1 year. In phase 2 of the trial subjects were permitted to treat migraines at any time including when the pain intensity was mild (1). In Phase 1 the onset of the treated migraine attack had to be less than 1 hour prior to administration of study medication. In Phase 2 the onset of the migraine attack had to be less than 12 hours prior to the administration of Zomig 5 mg. Subjects were also not permitted to treat with study medication if they had experienced a migraine attack within the previous 24 hour (both phases), used a triptan product within 24 hours (both phases), planned to sleep within 2 hours of treatment (phase 1 only) or had used an MAOI within 2 weeks (both phases).

The following sponsor tables briefly outlines the schedule of events for each phase of the study. As can be seen visit 1 of phase 1 included the usual review of entry criteria, complete physical examination, 12-lead ECG, clinical chemistry, hematology, and pregnancy test. Eligible subjects returned to the clinical site (visit 2) for randomization, instructions, and dispensing of study materials. Thereafter subjects were instructed to treat their next migraine of moderate to severe intensity with randomized medication. A final follow up visit for phase 1 (visit 3, within 7 days of treatment) included a physical examination, 12-lead ECG, clinical chemistry, hematology and a pregnancy test. Subjects who continued to meet the original entry criteria were invited to participate in phase 2 of the study. In phase 2 of the study subjects were seen in the clinic and called on alternating months for the duration of their participation. Safety monitoring was adequate.

Table 4 Schedule of events, phase 1

Assessment	Visit 1 Screening	Visit 2 Training	When headache occurs	Visit 3 Follow-up/ completion[a]
Informed consent	√			
Medical history	√			
Inclusion/exclusion	√			
Physical exam	√			√
Elelctrocardiogram	√			√
Clinical chemistry/hematology	√			√
Pregnancy test	√			
Randomization		√		
Dosing and diary instructions		√		
Study drug dispensed		√		
Diary card dispensed		√		
Study drug used			√	
Diary card completed			√	
Diary card returned and reviewed				√[b]
Unused study drug returned				√[b]
Review of adverse experiences				√[b]
End-of-study form completed				√[b]

[a] The follow-up visit for Phase I occurred within 7 days following the treatment of the migraine attack.
[b] End of study or at withdrawal from the study.
Data source: Study protocol.

Table 5 Schedule of events; phase 2

Assessment	Visit 3 Phase II (training)[a]	5-week telephone contact	Visit 4 After HA	5-week telephone contact	Visit 5 After HA	5-week telephone contact	Visit 6 After HA	5-week telephone contact	Visit 7 Post-HA	5-week telephone contact	Visit 8
Physical exam											√[b]
Electrocardiogram					√						√[b]
Clinical chemistry/hematology					√						√[b]
Pregnancy test											
Dosing, diary card instructions	√	√	√	√	√	√	√	√	√	√	
Study drug dispensed	√		√		√		√		√		
Diary card dispensed	√		√		√		√		√		
Diary card returned			√		√		√		√		√[b]
Unused study drug returned			√		√		√		√		√[b]
Review of diary card			√		√		√		√		√[b]
Quality-of-life questionnaire	√		√		√		√		√		√[b]
Review of adverse experiences		√	√	√	√	√	√	√	√	√	√[b]
End-of-study form completed											√[b]

[a] Visit 3 Phase I is the same visit as Visit 3 Phase II.
[b] End of study or when withdrawal from the study occurs
HA Headache
Data source: Study protocol

4.2 Patient population and demographics

Subjects were eligible to participate in the study if they were between 12 to 17 years of age (inclusive) and experienced a minimum of 2 migraines per month meeting the IHS definition for migraine with and without an aura and a maximum of 10 headaches (migraine or non-migraine headaches) per month. Other significant criteria included a history of untreated migraine duration of at least 4 hours, and the typical exclusions for triptan products (e.g., cardiovascular risk factors, abnormal ECG etc.). Patients who completed phase 1 of the trial were eligible for entry into phase 2

of the trial. No pregnant or lactating females were permitted to participate in the study. In phase 1, prophylactic (non-ergotamine) migraine medications were permitted however the regimen used had to be stable for at least 2 months prior to treatment.

The following table summarizes the baseline characteristics of subjects participating in phase 1 of trial 0005. For simplicity I do not describe the subjects continuing through phase 2 since there were no significant differences in populations. As demonstrated each cohort was well balanced for all baseline characteristics. A total of 850 subjects enrolled in phase 1 of the trial and 696 subjects took study medication. Treated subjects were equally randomized to placebo (n=175), Zomig 2.5 mg (n=171), Zomig 5 mg (n=171) or Zomig 10 mg (n=179). The mean age of all subjects treated was 14.2 years with 54.3% being between 12 to 14 years of age and 45.7% being between 15 to 17 years of age. As is typical for migraine studies the majority of patients were female (58.6%) and Caucasian (78.7%). The mean number of migraines per month historically experienced by subjects was 4.3 (SD 2.1) and the vast majority of subjects historically experienced nausea (79.9 to 90.1%), photophobia (92.2 to 97.1%) and phonophobia (89.4 to 93.7%) with their migraines.

Table 6 Baseline Demographic, Trial 0005, Phase 1

	Zomig 10 mg N=179	Zomig 5 mg N=171	Zomig 2.5 mg N=171	Placebo N=175	All subjects N=696
Age (years)					
Mean (SD)	14.2 (1.7)	14.3 (1.7)	14.3 (1.7)	14.2 (1.7)	14.2 (1.7)
Range	12-17	12-17	12-17	12-17	12-17
Age Cohorts (years)					
12 to 14 n (%)	101 (56.4)	91 (53.2)	93 (54.4)	93 (53.1)	378 (54.3)
15 to 17 n (%)	78 (43.6)	80 (46.8)	78 (45.6)	82 (46.9)	318 (45.7)
Gender n (%)					
Male	77 (43.0)	66 (38.6)	69 (40.4)	76 (43.4)	288 (41.4)
Female	102 (57.0)	105 (61.4)	102 (59.7)	99 (56.6)	408 (58.6)
Race n (%)					
White	141 (78.8)	136 (79.5)	141 (82.5)	130 (74.3)	548 (78.7)
Black	17 (9.5)	223 (13.5)	18 (10.5)	23 (13.1)	81 (11.6)
Other	21 (11.7)	12 (7.0)	12 (7.1)	22 (12.6)	67 (9.6)
Type of Migraine					
With aura n (%)	23 (12.9)	17 (9.9)	17 (9.9)	17 (9.7)	74 (10.6)
Without aura n (%)	110 (61.5)	118 (69.0)	115 (67.3)	116 (66.3)	459 (66.0)
Both n (%)	46 (25.7)	36 (21.1)	39 (21.1)	42 (24.0)	163 (23.4)
Duration of typical migraine					
4-12 hour	106 (59.2)	87 (50.9)	80 (46.8)	96 (54.9)	369 (53.0)
12 to 24 hours	43 (24.0)	41 (24.0)	53 (31.0)	42 (24.0)	179 (25.7)
>24 hours	30 (16.8)	43 (25.2)	38 (22.2)	37 (21.1)	148 (21.4)

Source: Adapted from sponsor table 12 and 13, study report 0005.pdf

In conclusion, in trial 0005 patient demographics and baseline migraine characteristics were generally well balanced between cohorts.

4.3 Patient Disposition and Treatment Exposure

The following table briefly summarizes patient disposition during trial 0005. A total of 850 subjects enrolled in phase 1 of the trial and 696 subjects took study medication. As demonstrated in the table each cohort was well balanced for the proportion of subjects completing the study. I discuss withdrawals due to adverse events in the safety section of this review.

In phase 2 of the study a total of 680 subjects entered and 603 subjects took study medication (safety population) and 151 completed the study (defined as >326 days by the sponsor). Overall 452 subjects (75%) discontinued from phase 2 of the study however many of these withdrawals were due to early termination of the study (110 patients). Fifty subjects (8.3%) withdrew due to an adverse event and 54 (9.0%) subjects withdrew due to ineffectiveness of the trial medication. In phase 2 of the study only 25% of the subjects completed the study however this number was significantly affected by the sponsor's decision to stop the trial early due to the lack of efficacy demonstrated in phase 1.

Table 7 Subject disposition trial 0005

Phase 1				
	Zomig 10 mg	**Zomig 5 mg**	**Zomig 2.5 mg**	**Placebo**
Randomized	214	212	210	214
Completed	176 (82.2%)	172 (81.1%)	168 (80.0%)	174 (81.3%)
Lost to follow up	7 (3.3%)	9 (4.3%)	13 (6.2%)	14 (6.5%)
Adverse event	4 (1.9%)	0	2 (1.0%)	0
Protocol noncompliance	10 (4.7%)	12 (5.7%)	10 (4.8%)	11 (5.1%)
Withdrew consent	5 (2.3%)	4 (1.9%)	2 (1.0%)	1 (0.5%)
Other	12 (5.6%)	15 (7.1%)	15 (7.1%)	14 (6.5%)
Phase 2; All Zomig 5 mg				
Entered	680			
Took study medication	603			
Completed	151 (25.0%)			
Discontinued	452 (75.0%)			
Lost to follow up	47 (7.8%)			
Adverse Event	50 (8.3%)			
Protocol noncompliance	81 (13.4%)			
Withdrew consent	44 (7.3%)			
Other[1]	176 (29.2%)			
Medication ineffective	54 (9.0%)			

1 Includes 110 subjects who were discontinued due to decision to stop study early.
Source: Adapted from sponsor table 6 and 7, study report 0005.

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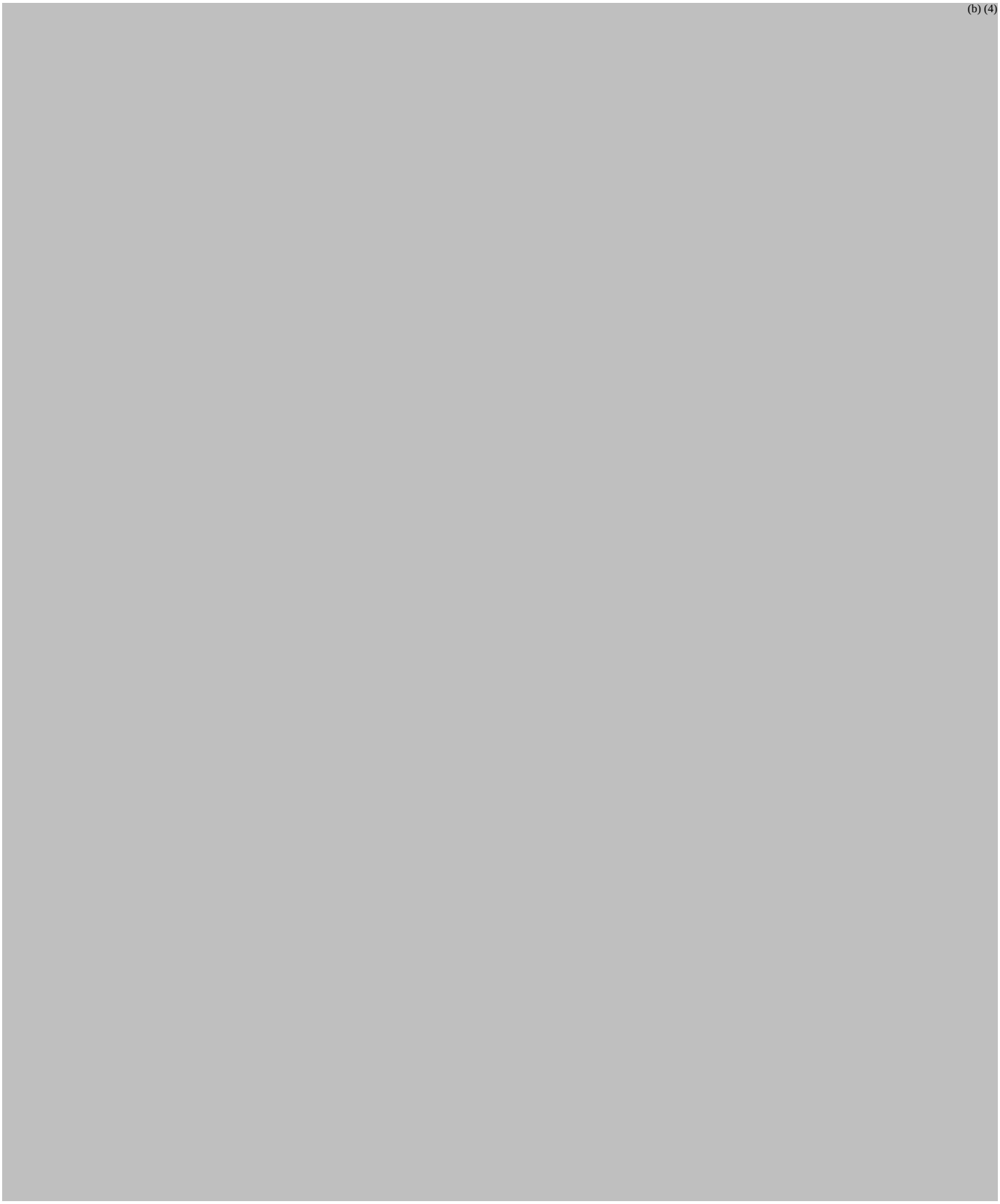
Despite the early termination of this trial the sponsor reports that 319 subjects with exposures up to 180 days treated a total of 1555 attacks and 239 patients with exposures "between 181 to 360 days" treated a total of 4690 attacks. Forty-two subjects had exposure times greater than 1 year and treated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

4.4 Efficacy Results

(b) (4)



(b) (4)

4.5 Safety Results

The primary objective of phase 2 of the study was to evaluate safety over a 1-year period. The safety population in both phases of the study included all subjects that took study medication. Safety information was presented using descriptive statistics. No formal analysis of safety was performed.

Safety monitoring is described in *Table 4* and *Table 5* above. Briefly serial clinical chemistries and CBC were done at visit 1, 3, 5, and 8 (end of study). Adverse assessments were done on each visit and telephone contact during phase 2. All chemistries and CBC were done in a designated central laboratory and reported back to the investigation site within 48 hours. Pregnancy tests were done at visit 1, 3, 6, 7, 8 and 10 and were completed at the local investigator site. Each patient had a 12-lead ECG done at visits 1, 3, 5, 8 and as needed. A central cardiologist independently interpreted all ECGs. Physical examinations were done at visit 1, 3 (end of phase 1), and visit 8 (end of phase 2). The amount of safety assessments is adequate in this reviewer's opinion.

4.5.1 Deaths, Serious Adverse Events and Withdrawals

There were no deaths or treatment related serious adverse events in either phase of the trial.

In phase 1 of the trial 6 patients randomized to Zomig withdrew due to an adverse event [4 in Zomig 10 mg (1.9%), 2 in Zomig 2.5 mg (1.0%)] compared to no patients randomized to placebo. The cited reasons for discontinuation are listed in the following table.

Table 10 Adverse Events resulting in Discontinuation, Phase 1

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

*subject did not use study medication.

There was a single serious adverse event in phase 1; a subject randomized to Zomig 5 mg (PID 0038/2014) reported "prolonged migraine headache" after taking Zomig 5 mg. This event ultimately resulted in hospitalization. He was released several days later with a final diagnosis of labyrinthitis and sinusitis.

In phase 2 of the trial 50 (8.3%) subject withdrew from the study due to an adverse event. Common reasons for withdrawing included continued migraine/headache, parasthesias, tightness, nausea, asthenia, pharyngitis and dizziness. The following table summarizes the 10 (1.7%) subjects that reported a serious adverse events during phase 2 of the trial. According to the sponsor only 2 of these events occurred within 24 hours of treatment however from the narratives I am only able to ascertain that the malaise case occurred within several hours of taking study medication. No serious adverse events were considered by the investigators to be related to study medication. I reviewed each narrative and agree with the investigator's assessment.

Table 11 Serious AE, Phase 2

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

*Occurred within 24 hours of treatment

In summary there were few serious adverse events associated with the use of zolmitriptan in adolescents. A review of each case report failed to demonstrate any significant trends.

4.5.2 Common Adverse Events

During phase 1 of the study, the percentage of patients with at least 1 adverse event over the course of the study was higher in all zolmitriptan groups (183 patients, 35.0%) compared with placebo (27 patients, 15.3%).

Table 12 Number of patients (%) with an adverse event, Trial 0005

	Zomig 10 mg	Zomig 5 mg	Zomig 2.5 mg	Placebo
Reporting at least 1 AE	81 (45.5%)	47 (27.0%)	55 (32.2%)	27 (15.3%)
Serious Adverse Event	0	1 (0.6%)	0	0
Withdrawal due to an AE	4 (2.3%)	0	1 (0.6%)	0

Source: Adapted from sponsor table 18 study report 0005

The following table briefly summarizes the adverse events occurring in at least 5% of patients in any treatment group seen during phase 1 of this trial. In general the occurrence of adverse events were generally higher with active treatment compared to placebo. Likewise there was a fairly consistent dose effect with zolmitriptan 10 mg demonstrating the highest incidence rate for any given adverse event. The most common adverse events in phase 1 across all zolmitriptan groups were tightness (6.7%), dizziness (6.1%), nausea (5.5%), and paresthesia (4.2%) compared with 1.1%, 2.3%, 1.1%, and 0 for these same events, respectively, in the placebo group. Seventy four percent of all adverse events reported by subjects randomized to Zomig (all doses) were rated as mild to moderate compared to 90% for placebo.

Table 13 **AEs occurring in ≥ 5% of patients in any cohort, Safety population, Phase 1**

COSTART term	Treatment group number (%) of patients					
	Zolmitriptan 10.0 mg N=178	Zolmitriptan 5.0 mg N=174	Zolmitriptan 2.5 mg N=171	All zolmitriptan N=523	Placebo N=176	All treatments N=699
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All patients with adverse events (AEs)	79 (44.4)	45 (25.9)	49 (28.7)	173 (33.1)	22 (12.5)	195 (27.9)
Tightness	20 (11.2)	10 (5.8)	5 (2.9)	35 (6.7)	2 (1.1)	37 (5.3)
Dizziness	16 (9.0)	8 (4.6)	8 (4.7)	32 (6.1)	4 (2.3)	36 (5.2)
Nausea	14 (7.9)	5 (2.9)	10 (5.9)	29 (5.5)	2 (1.1)	31 (4.4)
Paresthesia	11 (6.2)	8 (4.6)	3 (1.8)	22 (4.2)	0	22 (3.2)
Asthenia	9 (5.1)	2 (1.2)	3 (1.8)	14 (2.7)	2 (1.1)	16 (2.3)
Pain	9 (5.1)	3 (1.7)	3 (1.8)	15 (2.9)	0	15 (2.2)

[a] This table includes the number of patients reporting an adverse event at least once; patients reporting nonserious adverse events outside of the 24-hour time window are not included in the table.

[b] The decreasing order of frequency is based on the 10.0 mg zolmitriptan group.

N Number of patients; n number of patients with adverse events.

Data derived from Table T26.3, Section 11.1.

The following table summarizes the most common adverse events seen during the long-term phase of trial 005 by duration of study. Overall 351 (58.2%) patients in the safety population (603) reported at least 1 adverse event and 279 (46.3%) patients reported at least 1 adverse event within the 24-hour time window at the patient level. Across 7253 individual attacks, adverse events were associated with 1209 (16.7%) attacks. The most common adverse events reported during phase 2 of the trial were tightness sensation (3.7%), paresthesia (2.8%), nausea (2.0%), dizziness (1.6%) and pain (1.2%) at the attack level. There appeared to be no association between the adverse events experience and the length of time exposed to study medication. At the attack level, 974 (80.8%) of all adverse events were rated as mild or moderate.

Table 14 Common AEs, Zomig 5 mg Safety Population, Phase 2

	Patient level					
	30 days N=109	**90 days N=44**	**180 days N=30**	**270 days N=24**	**360 N=59**	**Total N=603**
Dizziness	16 (14.7%)	6 (13.6%)	4 (10.8%)	4 (16.7%)	8 (13.6%)	87 (14.5%)
Nausea	15 (13.8%)	7 (15.9%)	3 (8.1%)	7 (29.2%)	11 (18.6%)	86 (14.3%)
Tightness	14 (12.8%)	5 (11.4%)	2 (5.4%)	3 (12.5%)	6 (10.2%)	72 (12.0%)
Paresthesia	13 (11.9%)	8 (18.2%)	2 (5.4%)	3 (12.5%)	8 (13.6%)	57 (9.5%)
Pharyngitis	9 (8.3%)	7 (15.9%)	3 (8.1%)	3 (12.5%)	7 (11.9%)	48 (8.0%)
Pain	9 (8.3%)	1 (2.3%)	0	1 (4.2%)	8 (13.6%)	44 (7.3%)
Asthenia	8 (7.4%)	2 (4.6%)	1 (2.7%)	2 (8.3%)	3 (5.1%)	38 (6.3%)
	Attack Level					
	30 days N=209	**90 days N=242**	**180 days N=280**	**270 days N=420**	**360 N=1598**	**Total N=7253**
Dizziness	13 (6.2)	8 (3.3)	3 (1.1)	10 (2.4)	8 (0.5)	118 (1.6)
Nausea	12 (5.7)	8 (3.3)	6 (2.1)	18 (4.3)	10 (0.6)	147 (2.0)
Tightness	14 (6.7)	7 (2.9)	22 (7.9)	17 (4.1)	61 (3.8)	267 (3.7)
Paresthesia	14 (6.7)	12 (5.0)	11 (3.9)	11 (2.6)	46 (2.9)	204 (2.8)
Pharyngitis	10 (4.8)	7 (2.9)	3 (1.1)	8 (1.9)	4 (0.3)	60 (0.8)
Pain	9 (4.3)	0	9 (3.2)	3 (0.7)	13 (0.8)	84 (1.2)

Source: Adapted from sponsor tables 25 and 26 study report 0005

4.5.3 Clinical Laboratories

Hematology, Complete Blood Counts (CBC)

The following table summarizes the mean change from baseline for each hematology variable during the acute phase of the study. As demonstrated there were no clinically significant mean changes from baseline for any hematological assessments. A review of individual changes revealed no significant patterns to suggest an underlying problem. Shifts from normal to high or normal to low were few in each cohort and generally similar in all cohorts including placebo. Similar findings were seen during the long-term phase of the study.

Table 15 Mean Change in hematology results from baseline

	Zomig 10 mg (n=178)	**Zomig 5 mg (n=174)**	**Zomig 2.5 mg (n=171)**	**Placebo (n=176)**
Hemoglobin (g/dl)	-0.13 (0.59)	-0.13 (0.63)	-0.09 (0.56)	-0.15 (0.64)
Hematocrit (volume)	-0.01 (0.02)	-0.00 (0.02)	-0.00 (0.02)	-0.01 (0.02)
Basophils (%)	-0.01 (0.37)	0.02 (0.37)	-0.03 (0.38)	0.01 (0.31)
Eosinophils (%)	-0.24 (2.14)	0.58 (4.35)	-0.32 (1.82)	0.002 (2.01)
Lymphocytes (%)	-0.43 (7.79)	-0.25 (9.42)	-0.70 (8.11)	0.03 (7.54)
MCV (fl)	-0.28 (1.73)	-0.14 (1.92)	-0.08 (1.86)	-0.52 (1.70)
Monocytes (%)	0.24 (3.45)	-0.21 (2.71)	0.07 (2.51)	0.18 (2.81)
Neutrophil (%)	1.42 (18.36)	2.25 (21.73)	1.13 (24.50)	0.32 (21.30)
Platelets (X 10^9/L)	-0.12 (1.40)	0.03 (1.55)	-0.23 (1.75)	-0.07 (1.47)

Source: Adapted from sponsor table T25.3.1.2

Clinical Chemistry Profile

The following table summarizes the mean change from baseline for each clinical chemistry variable during the acute phase of the study. As demonstrated in the table there were no clinically significant changes from baseline for any chemistry study. A review of individual changes failed to demonstrate

any significant patterns to suggest an underlying problem. Shifts from normal to high or normal to low were few in each cohort and generally similar in all cohorts including placebo. Similar findings were seen during the long-term phase of the study although there was a single patient with moderately elevated liver enzymes on several post-treatment visits. Patient 0926 had moderately elevated AST and ALT reported as an adverse event and was considered possible related to study medication. During the study the highest AST level was < 2 times the ULN for ALT and < 3 times ULN for AST. These elevation improved by the final study visit (visit 8) and was < 1.2 times ULN for ALT and < 2 times ULN for AST.

Table 16 Mean Change in Chemistry results from baseline

	Zomig 10 mg (n=178)	Zomig 5 mg (n=174)	Zomig 2.5 mg (n=171)	Placebo (n=176)
Albumin (g/l)	-0.28 (3.09)	-0.46 (3.02)	-0.64 (2.72)	-0.46 (3.13)
Alkaline Phosphatase (U/L)	-4.06 (16.92)	-4.32 (24.83)	-3.67 (21.95)	-5.44 (23.32)
Alanine Aminotransferase (U/L)	1.19 (9.24)	-0.05 (5.28)	-0.07 (8.03)	-0.22 (4.79)
Aspartate Aminotransferase (U/L)	1.39 (9.75)	0.31 (7.10)	-0.14 (6.89)	-0.35 (5.15)
Cholesterol (mmol/L)	0.00 (0.53)	-0.08 (0.56)	-0.00 (0.41)	-0.09 (0.42)
Creatinine (UMOL/L)	0.60 (7.56)	-1.55 (15.62)	1.02 (7.67)	0.24 (10.47)
Glucose (MMOL/L)	0.04 (0.86)	0.00 (0.88)	0.07 (0.97)	0.04 (0.86)
Potassium (MMOL/L)	-0.01 (0.39)	-0.06 (0.36)	-0.01 (0.38)	-0.04 (0.33)
Sodium (MMOL/L)	0.10 (2.32)	-0.18 (2.76)	-0.09 (2.33)	0.39 (2.15)
Total Bilirubin (UMOL/L)	-0.20 (2.89)	-0.03 (3.66)	0.63 (3.74)	-0.35 (3.52)

Source: Adapted from sponsor table T25.4.1.2, study report 0005

In summary there were no clinically significant changes in mean safety laboratory values or shifts from baseline.

4.5.4 Vital signs and Electrocardiograms

In both phases of trial 005 there were no clinically significant changes in mean vital signs from baseline to visit 3. In the phase 1 four subjects (0.4%) on zolmitriptan with normal ECGs at baseline had abnormal findings on follow up ECG (visit 3). Three patients had sinus bradycardia and one subject had sinus tachycardia. Of the three with bradycardia, one was taking Inderal (PID 0009/0365) and the other was noted to be in superb athletic condition (PID 0009/364). By comparison three subjects (1.9%) on placebo with normal ECG at baseline had an abnormal ECG on follow up visit. Similar ECG findings were seen in phase 2 of the trial where less than 1.6% of patients with normal baseline ECGs shifted to abnormal ECGS at visits 5 and 8. None of the abnormal ECGs were considered adverse events.

4.5.5 Physical Examination

There were no clinically significant changes in physical findings in either phase of the study.

4.6 Pregnancy

There were 3 pregnancy during trial 0005. All three pregnancies went to term and resulted in healthy newborns.

Table 17 Pregnancies during trial 0005

Subject	Phase/Treatment	Comment
0003/0316	Phase 1/ Zomig 10 mg	Negative pregnancy test (b) (6), randomized 1/11/00 and found to be pregnant (b) (6) Patient treated migraine (b) (6) Withdrawn from the study on follow up visit (b) (6) Delivered healthy bay (b) (6)
0008/0082	Phase 2/ Zomig 5 mg	Negative pregnancy test (b) (6) randomized on 9/3/99. Found to be pregnant (b) (6) Patient took 17 doses of study medication during trial. Withdrawn form study on follow up visit (b) (6) Delivered healthy baby (b) (6)
0013/0373	Phase 2/ Zomig 5 mg	Negative pregnancy test (b) (6) and randomized on 12/15/99. Withdrawn from the study (b) (6) due to pregnancy. Patient took 7 doses of study medication. Delivered healthy baby (b) (6)

4.7 Adverse events by gender, race and age

In general women taking zolmitriptan (all doses) reported more adverse events then men in both phases of the study (acute phase, 20.7% vs. 12.4%; long term phase, 37.0% vs. 21.2%). In the placebo group of phase 1 slightly more men reported an adverse event than women (acute phase, 5.7% female vs. 6.8% male). There were no significant differences between genders for the type and nature of adverse event reported. There were too few non-Caucasians in this study to make a meaningful comparison of adverse events by race. The percentage of adverse events reported in phase 1 for all zolmitriptan patients aged 12 to 14 years (18.0%) was slightly higher but generally similar to the percentage of adverse events reported for all zolmitriptan patients aged 15 to 17 years (15.1%). A similar pattern occurred during the long term phase of the study (aged 12 to 14, 30.7% compared to aged 15 to 17, 27.5%).

4.8 Safety Conclusions

In phase 1, the number of patients with serious adverse events was low (1 [0.2%] zolmitriptan patient, none placebo). The number of patients withdrawn due to adverse events was also low [5 (<1%) zolmitriptan patients and no placebo patients]. Overall, the occurrence of adverse events and potentially treatment-related adverse events was higher in the zolmitriptan group compared with placebo. For the zolmitriptan group 128 (74.0%) patients had adverse events that were mild or moderate in intensity compared with 20 (90.9%) placebo patients. The most common adverse events (tightness, dizziness, nausea, and paresthesia) were consistent with those noted in the label for zolmitriptan and consistent with those seen in adult zolmitriptan studies. Mean changes from baseline for clinical laboratory, ECG, vital signs, and physical findings results raised no safety concerns.

In phase 2, the number of patients with serious adverse events was also low [10 (1.7%)] with only 2 occurring within 24 hours of treatment. Fifty (8.3%) patients had adverse events leading to withdrawal. At the attack level, across 7253 attacks, adverse events were associated with 1209 (16.7%) attacks. The most common adverse events in phase 2 were dizziness, nausea, tightness, and paresthesia with the majority (62.4%) being graded as mild or moderate in intensity. Mean changes from baseline for clinical laboratory, ECG, vital signs, and physical findings results raised no safety concerns. As previously discussed the amount of long term exposure was significant although slightly short of the minimum requirements of 300 subjects for 6 months and 100 subjects for 1 year. Overall 281 subjects took Zomig Tablet 5 mg for at least 6 months (180 days) and treated 3408 attacks (approximately 2 attacks/month) and 42 subjects took Zomig tablet 5 mg for at least 1 year (360 days) and treated 989 attacks (approximately 2 attacks/month). However 151 subjects took

Zomig tablet 5 mg for at least 326 days and treated approximately 2 attacks per month. Depending upon how one defines 6 months and 1 year the amount of long term exposure may be adequate. We may need to discuss internally whether additional long term exposure will be required.

In conclusion Zomig tablets up to 10 mg were well tolerated in the acute, single migraine phase of the trial. Zomig 5 mg was well tolerated in the long-term, open label phase 2 of trial 0005. In both phases the most common adverse events seen were typical of triptan products in adults and are consistent with the current label for Zomig.

5. Brief Review of trial 311CIL/0092 (PK trial adolescents vs. adults)

5.1 Design, Patient Population

Trial 311CIL/0092 was a single dose trial to compare the pharmacokinetics of Zomig 5 mg in adolescents to adults. This is an old trial submitted to IND (b) (4) (serial 079) on April 9, 1998. I include a brief review here (b) (4) This was a single center, open-label, single dose, parallel group study. A total of 39 subjects were enrolled [21 adolescents (13 females/8 males) and 18 adults (12 females/6 males)]. The mean age of for adolescents was 14.5 years (range 12 to 17) and for adults 39.1 years (range 18 to 65). Serial plasma samples were collected for 15 hours. Enrolled subjects did not necessarily have a history of a migraine. The study report does not state whether any subjects had a history of migraine. In an e-mail dated December 4, 2003 the sponsor states they did not capture information about migraine history for this study.

Table 18 Baseline Demographics, Trial 311CIL/0092

Demographic characteristic	Age group			
	Adolescents		Adults	
Number of subjects exposed	21		18	
Mean age (range) (y)	14.5	(12-17)	39.1	(18-65)
Sex				
Female (%)	13	(62)	12	(67)
Male (%)	8	(38)	6	(33)
Mean weight (range) (kg)	61.2	(37.3-92.3)	73.9	(51.7-103.0)
Race				
White (%)	20	(95)	15	(83)
Black (%)	0		2	(11)
Other[a] (%)	1	(5)	1	(6)

[a] Other includes Asian, Hispanic.

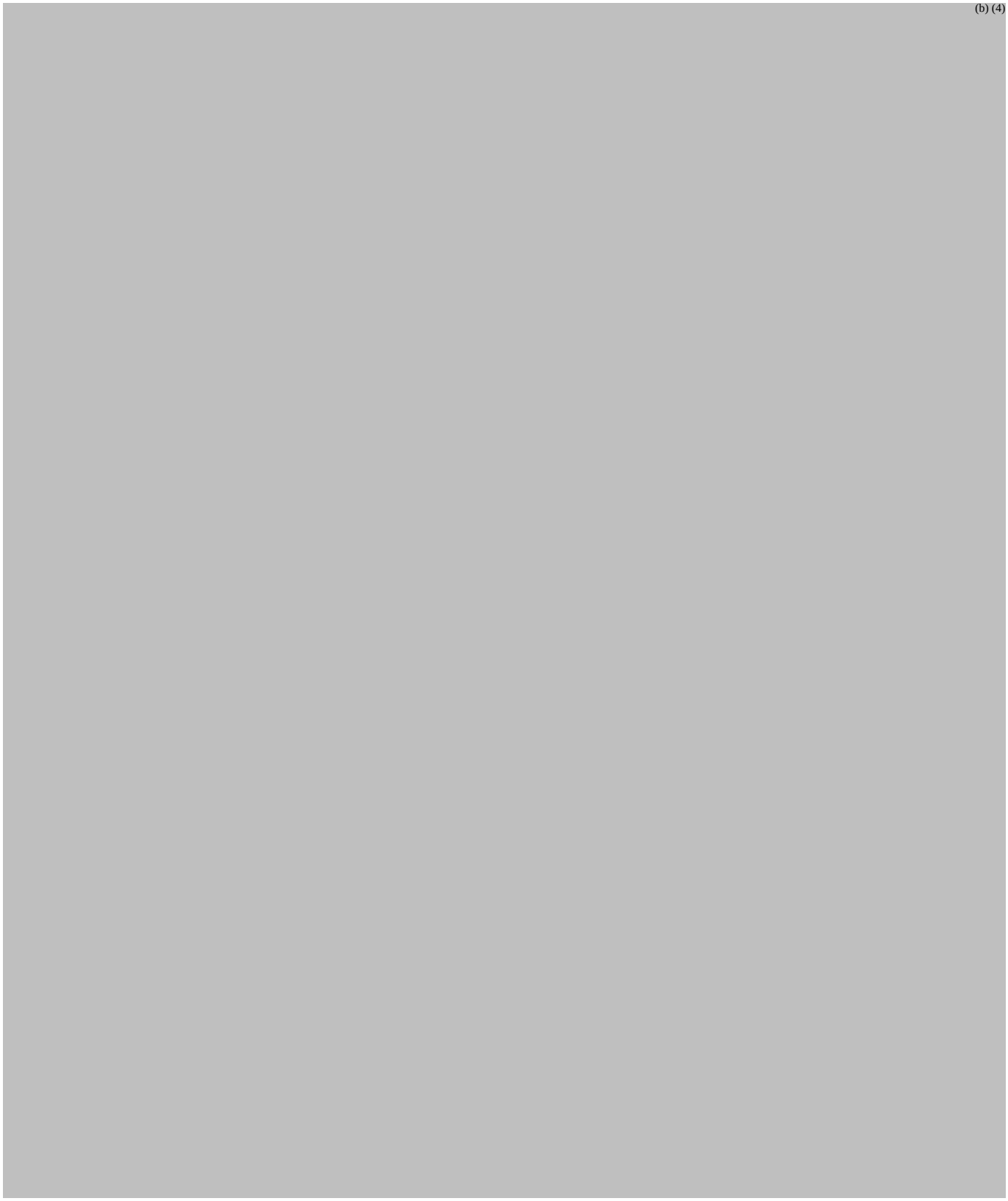
Source: Sponsor table 1, study report 0092, page 9

Subject selection required all subjects to be in good health with no contraindication for triptan products. All screened subjects were admitted to the study site the night before treatment. The following morning (Day 2) subjects were given Zomig Tablet 5 mg (two 2.5 mg tablets) and followed for the next 24 hours. Stable subjects were discharged from the study site the morning of Day 3.

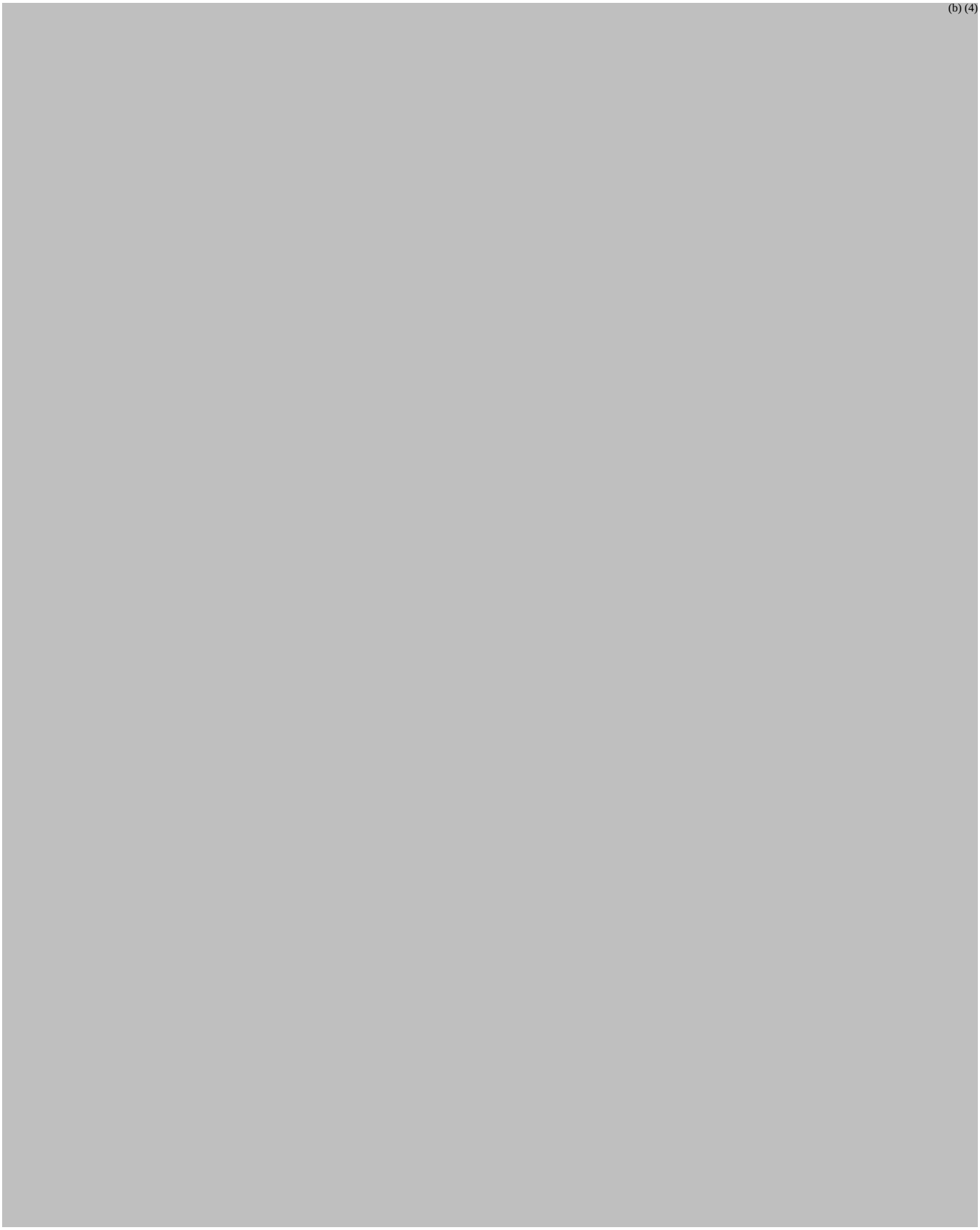
5.2 Pharmacokinetic Results

The following two tables demonstrate the pharmacokinetic parameters of zolmitriptan in adults and adolescents following the administration of Zomig 5 mg. (b) (4)

(b) (4)



(b) (4)



(b) (4)

5.3 Safety Findings

The following table briefly summarizes the safety monitoring during the trial.

Table 23 Safety Assessment, Trial 311CIL/0092

	Screening	Day 1	Day 2 (treatment)	Day 3
Physical exam	√			
HIV, HB_sAg	√	√		√
Clinical Laboratories	√	√		√
Urine drug screen	√			
Vital Signs	√	√	√ (serial)	√
12-lead ECG	√	√	√ (hour 4)	√
24-hour Holter	√			

Source: Adapted from sponsor table 1, trial report 0092, page 16

There were no deaths, withdrawals or serious adverse events during this trial. All adverse events were transient and rated as mild in intensity. Approximately 52% (11/21) adolescents reported at least 1 adverse event. This compares to 56% of adults (10/18).

The following table summarizes all adverse events seen during the study. As demonstrated in the table the most common adverse event was headache reported in 8 adolescents (38%) and 6 adults (33%). All adverse events were rated as mild and resolved without treatment.

Table 24 Adverse Events, Trial 0092

Body system and adverse event[a]	Adolescents (n = 21)	Adults (n = 18)
	Total number (%) of subjects with adverse event	Total number (%) of subjects with adverse event
Body as a whole		
Headache	8 (38)	6[b] (33)
Neck pain	1 (5)	0
Cardiovascular		
Vasodilatation	1 (5)	4 (22)
Digestive		
Nausea	2 (10)	2 (11)
Nervous system		
Depression	0	1 (6)
Dizziness	2 (10)	0

[a] A subject may have had more than 1 adverse event.
[b] A 7th subject reported a headache before trial drug was administered.

Source: Sponsor table 11, study report 0092, page 39.

For all clinical chemistries, CBC and urinalysis there was no clinically significant abnormalities. There were no trends in mean systolic and diastolic blood pressure, heart rate, respiratory rate or oral temperature following treatment with Zomig 5 mg in either cohort. However a few individuals from each cohort had a relatively large drop in their systolic and diastolic blood pressure after receiving treatment (see following table). None of these isolated changes were associated with symptoms and were not considered clinically significant by the investigator.

Table 25 Subjects with clinically relevant changes in vital signs during the trial.

Subject	Age group	Parameter	Baseline (mmHg)[a]	Change from baseline (mmHg)	Time after dose
123	Adolescent	DBP	62	-22	3 h
124		SBP	106	-24	1 h
125		SBP	108	-20	1 h
125		DBP	68	-18	1 h
128		SBP	100	-20	1 h
138		DBP	64	-22	8 h
108	Adults	DBP	80	-40	3 h
114		DBP	72	-22	6 h
118		SBP	118	-28	6 h
118		SBP	118	-36	24 h
118		DBP	74	-26	24 h

[a] Day 2 value before dose administration.
DBP Diastolic blood pressure.
SBP Systolic blood pressure.

Source: Sponsor table 14, study report 009, page 42

All except a single ECG were assessed as normal. A thin 16 year old male (PID 131) was noted to have high-voltage QRS patterns on baseline and hour 4 and 24 ECGs. It has been my experience high voltage findings are not unusual in thin subjects.

5.4 Conclusions

(b) (4)

(b) (4)

Safety findings in adolescents suggest no areas of clinical concern and are similar to those reported in adults in this and other trials. All adverse events were mild and transient. There were no consistent and clinically significant changes in hematology, clinical chemistry, ECG, or urinalysis. In a few subjects (both adolescents and adults) there was a transient asymptomatic drop in systolic and diastolic blood pressure.

6. Conclusion/Recommendation

Trial 311CUS/0007 demonstrated that a single dose of zolmitriptan as high as 10 mg was well tolerated in adolescents. The nature of adverse events seen during this trial were similar to those seen in adult migraine studies using Zomig tablets except for the higher incidence of headache. There were no clinically significant changes in clinical laboratories, vital signs, or physical examination. No adolescent had any evidence of ischemic heart changes on 24-hour holter recordings. There does not appear to be any clinically significant differences in the nature and type of adverse events experienced by adolescents or adults exposed to zolmitriptan. Efficacy was not assessed in this study.

(b) (4)

(b) (4) the long term multiple attack phase of the study shows zolmitriptan 5 mg to be well tolerated in the adolescent population. Although the sponsor terminated the study early there is still a considerable amount of long term safety with 281 subjects treating for at least 6 months and 42 patients treating for 1 year (360 days).

(b) (4)

In conclusion Zomig tablets up to 10 mg were well tolerated in adolescents. Reported adverse events in adolescents were similar in nature and incidence to adverse events reported in adults. Unfortunately efficacy of Zomig Tablet (b) (4) has not been demonstrated. (b) (4)

(b) (4) My review of the proposed labeling changes can be found in section 8 (Appendix 2) of this review.

Appendices

7. Appendix 1: Tables and Figures

Table 1 Demographic Trial 0007 7
Table 2 Adverse Events seen during Trial 311 CUS/0007 8
Table 3 Change (SD) from baseline in clinical laboratories 9
Table 4 Schedule of events, phase 1 11
Table 5 Schedule of events; phase 2 11
Table 6 Baseline Demographic, Trial 0005, Phase 1 12
Table 7 Subject disposition trial 0005 13
Table 8 Two-Hour Headache Response, Acute Phase Trial 0005 14
Table 9 Efficacy results from Phase 1 of Trial 311CUS/0005 15
Table 10 Adverse Events resulting in Discontinuation, Phase 1 16
Table 11 Serious AE, Phase 2 16
Table 12 Number of patients (%) with an adverse event, Trial 0005 17
Table 13 AEs occurring in ≥ 5% of patients in any cohort, Safety population, Phase 1 17
Table 14 Common AEs, Zomig 5 mg Safety Population, Phase 2 18
Table 15 Mean Change in hematology results from baseline 18
Table 16 Mean Change in Chemistry results from baseline 19
Table 17 Pregnancies during trial 0005 20
Table 18 Baseline Demographics, Trial 311CIL/0092 21
Table 19 PK parameters of zolmitriptan; ratio of geometric means[a] for adolescents 22
Table 20 Mean PK Parameters for zolmitriptan and ranges by age and gender 22
Table 21 PK parameters of 183C91; ratio of geometric means[a] for adolescents 24
Table 22 Mean PK Parameters for 183C91 and ranges by age cohorts and gender 24
Table 23 Safety Assessment, Trial 311CIL/0092 24
Table 24 Adverse Events, Trial 0092 25
Table 25 Subjects with clinically relevant changes in vital signs during the trial. 25

Figure 1: Plasma zolmitriptan concentrations (ng/ml) 23
Figure 2: Plasma 183C91 concentration (ng/ml) 23

8. Appendix 2: Labeling Review

The sponsor proposes the following underlined and strike-out changes to the present label for Zomig tablets:

Pediatric Use

~~Safety and e~~ Effectiveness of ZOMIG Tablets in pediatric patients has~~ve~~ not been established therefore, ZOMIG is not recommended for use in patients under 18 years of age.

Clinical Trial Report 311CUS/0005

(b) (4)

Adverse events observed were similar in nature and frequency to those reported in clinical trials in adults. (b) (4)

Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

I do not agree with the proposed changes for several reasons. (b) (4) For these reasons I believe none of the proposed changes should be accepted and the original language should be retained. Additionally, the sponsor should be requested to provide updated post marketing safety information on any serious adverse events in the pediatric population. I provide this recommendation so that the final statement about serious adverse events in pediatric patients using "other triptans" can be updated to reflect any serious adverse events using Zomig (if there have been any). The label for Imitrex includes a specific discussion of serious adverse events seen with Imitrex (e.g. 14 year old with myocardial infarction). An ODS consult to review the AERS database for serious adverse events in children using Zomig should also be requested.

Present and Suggested labeling:

Pediatric Use: Safety and effectiveness of ZOMIG in pediatric patients have not been established therefore, ZOMIG is not recommended for use in patients under 18 years of age. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

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/s/

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3/22/04 11:18:09 AM
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Includes labeling

Eric Bastings
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