U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-768 / S012
Drug Name:	Zomig Tablet (zolmitriptan)
Indication(s):	Migraine (adolescent)
Applicant:	Astra Zeneca
Date(s):	Correspondence Date: September 30, 2003
	Date Review Completed: March 9, 2004
	PDUFA Date: March 31, 2004
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewer:	Yong-Cheng Wang, Ph.D. (HFD-710)
Concurring Reviewers:	Kun Jin, Ph.D. (HFD-710)
	Kooros Mahjoob, Ph.D. (HFD-710)
Medical Division:	Division of Neuropharmacological Drug Products (HFD-120)
Clinical Team:	Kevin Prohaska, D.O. (HFD-120)
Project Manager:	Ms. Lana Chen

Keywords: Response, Logistic Regression, Last Observation Carried Forward

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor, AstraZeneca submits a Pediatric Exclusivity Submission in accordance with Section 111 of title 1 of the Food and Drug Administration Act [Section 505A of the Federal Food, Drug, and Cosmetic Act]. The sponsor seeks Agency approval of their proposed labeling changes and requests a six-month pediatric exclusivity for completing all required studies as outlined in the original Pediatric Written request (March 26, 1999) and amended on May 29, 2002 (date extension only).

The purpose of this review is for the efficacy evaluation. This statistical reviewer provides statistical conclusions and recommendations. The format of this review will include the efficacy analyses, statistical findings, conclusions, and recommendations.

1.1 Conclusions and Recommendations

(b) (4)

1.2 Brief Overview of Clinical Studies

The clinical study selected for this statistical review is an acute efficacy Study 311CUS/0005 which was a phase II, multicenter, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in the acute treatment of migraine headache in adolescent patients.

In Phase I of the study, patients were randomized to treat a single migraine headache with either 2.5 mg, 5.0 mg, or 10.0 mg zolmitriptan, or placebo. In the Phase II, open-label portion of the study, patients treated multiple migraine headaches over a 12-month period with 5.0 mg zolmitriptan (tablet form). A second 5.0 mg tablet was allowed in Phase II, if necessary, between 2 hours and 24 hours after the 1st dose of study treatment.

Male and female patients aged between 12 and 17 years (inclusive), with a minimum of 2 migraines per month (according to International Headache Society [IHS]-defined criteria) and a maximum of 10 migraine headaches or nonmigraine headaches each month were eligible for inclusion in Phase I.

1.3 Statistical Findings

(b) (4)

[redacted]

2. INTRODUCTION

2.1 Overview

2.1.1 Background

Migraine is a debilitating and recurring disease affecting approximately 9% to 16% of the Western population (Goldstein and Chen 1982). Migraine is characterized by a throbbing headache that is usually unilateral, made worse by movement, and is often associated with nausea, vomiting, photophobia, and phonophobia. Attacks may be preceded by an aura in which transient focal neurological symptoms, usually visual disturbances, occur. Seventy-five percent of migraine sufferers are female.

Conventional therapy for migraine consists of acute treatments to abort attacks and, for patients who suffer from 2 or more attacks per month, prophylactic treatments to prevent attacks. Despite the large number of available therapies, both acute and prophylactic treatments are unsatisfactory for many people with migraine.

2.1.2 History of Drug Development

- November 25, 1997 Zomig Tablet (NDA 20-768) was approved.
- April 9, 1998 Sponsor submits results of adolescent PK Study (311CIL/0092) and a new protocol for study 311CUS/005 (adolescent efficacy study).
- 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. Also includes results from trial 311CUS/0007 and amendment to study 311CUS/0005.
- May 29, 2002 Pediatric Written Request Amendment issued.
- July 3, 2002 Pediatric Written Request Reissued.
- August 15, 2002 Teleconference between the sponsor and Agency.
- June 24, 2003 Sponsor submits new protocol to evaluate the efficacy of Zomig Nasal Spray in adolescents.

- September 3, 2003 Requested PK data summary submitted in serial N(PU); Biopharmacology Review pending.
- Pediatric Exclusivity Determination and labeling changes supplement submitted.

2.1.3 Specific Studies Reviewed

The study selected for the full statistical review and evaluation is only the controlled phase II Study 311CUS/0005: "A Multicenter, Double-blind, Placebo-controlled, Randomized Study and Open-label, Long-term, Tolerability Study with Zolmitriptan (Zomig™) for the Acute Treatment of Migraine Headaches in Adolescent Patients".

2.2 Data Sources

Data used for review is from the electronic submission received on September 30, 2003. The efficacy analysis data were submitted by the sponsor on September 30, 2003. All data sets analyzed are electronic documents and are located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "30-SEP-2003".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study 311CUS/0005 was a phase II, multicenter, outpatient study designed to evaluate the safety and efficacy of oral zolmitriptan in the acute treatment of migraine headache in adolescent patients. In Phase I of the study, patients were randomized to treat a single migraine headache with either 2.5 mg, 5.0 mg, or 10.0 mg zolmitriptan, or placebo. In the Phase II, open-label portion of the study, patients treated multiple migraine headaches over a 12-month period with 5.0 mg zolmitriptan (tablet form). A second 5.0 mg tablet was allowed in Phase II, if necessary, between 2 hours and 24 hours after the 1st dose of study treatment.

Male and female patients aged between 12 and 17 years (inclusive), with a minimum of 2 migraines per month (according to International Headache Society [IHS]-defined criteria) and a maximum of 10 migraine headaches or nonmigraine headaches each month were eligible for inclusion in Phase I.

Patients who completed Phase I of the study were eligible for inclusion in Phase II of the study. It was anticipated that a total of 800 patients would be randomized from approximately 40 centers in the United States, 10 centers in Canada, and 23 other centers throughout the in India, Finland, Germany, and the United Kingdom to obtain 736 evaluable patients for Phase I and 500 patients for Phase II.

The primary objective for Phase I of the study was to evaluate the efficacy of oral zolmitriptan across a range of doses for the treatment of a single migraine headache in adolescent patients (aged 12 to 17 years, inclusive). The primary objective for Phase II of the study was to evaluate the safety of the long-term use of oral 5.0 mg zolmitriptan for the acute treatment of multiple migraine headaches in the same adolescents (aged 12 to 17 years, inclusive). Evaluation of long-term efficacy was a secondary objective of the study.

The primary efficacy variable for Phase I of the study was headache response at 2 hours (4-point scale) in the zolmitriptan groups compared with placebo. The primary variable for Phase II of the study was the profile of treatment-emergent adverse events (safety). No primary efficacy variable was measured for Phase II.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Of the 680 patients who entered Phase II of the study, 603 were included in the safety population and 151 (25.0% of the safety population) completed Phase II of the study. The most common reason for withdrawal was cited as "Other" (176 patients, 29.2%); 50 (8.3%) patients were withdrawn for adverse events or concurrent illness. Note that approximately 110 (60%) patients in the withdrawal category classified as "Other" were patients terminated as a result of the AstraZeneca decision to discontinue Phase II of the study.

3.1.3 Statistical Methodologies

In Phase I, binary response data was analyzed using logistic regression for the primary and selected secondary efficacy variables; the model included terms for treatment, region, and baseline (either baseline severity 4-point scale or continuous baseline VAS as appropriate) was fitted irrespective of significance because intensity was known to influence efficacy. Analyses were done primarily on the intent-to-treat (ITT) population with some analyses being done on the per-protocol (PP) population. All formal statistical tests for treatment difference were performed using a 2-sided hypothesis test with a significance level of 0.05.

In Phase II, efficacy data for the study was summarized and listed; no formal analyses were done.

3.1.4 Efficacy Results

(b) (4)

(b) (4)

3.1.5 Reviewer's Conclusions and Comments

(b) (4)

3.2 Evaluation of Safety

There is no safety evaluation included in this review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

(b) (4)

there is no any special or subgroup analysis included in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical Issues:

- In the primary analysis, the endpoint was defined as 2 hours. If there was a missing data at the endpoint, the last observation would be carried forward (LOCF), i.e., the last post-treatment measurement was used in the analysis. The sponsor did not use LOCF algorithm for the primary efficacy analysis.
- There were multiple comparisons in the secondary analyses. The NDA submission did not adjust the overall significance level (α=0.05) for the comparisons of secondary endpoints.

5.2 Conclusions and Recommendations

(b) (4)

SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: Yong-Cheng Wang, Ph.D.
Date: March 9, 2004

Concurring Reviewer(s): Kun Jin, Ph.D.
Kooros Mahjoob, Ph.D.

Statistical Team Leader: Kun Jin, Ph.D.

Biometrics Acting Division Director: Kooros Mahjoob, Ph.D.

cc:

HFD-120/Ms. Chen
HFD-120/Dr. Prohaska
HFD-120/Dr. Oliva
HFD-120/Dr. Katz
HFD-710/Dr. Wang
HFD-710/Dr. Jin
HFD-710/Dr. Mahjoob
HFD-700/Dr. Anello
HFD-700/Dr. Dubey

C:\AAA\NDA\Zomig Peds (20-768)\REVIEW\Report\Zomig Peds.doc

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

/s/

Yong-Cheng Wang
3/9/04 11:08:34 AM
BIOMETRICS

Kun Jin
3/9/04 11:28:51 AM
BIOMETRICS

Kooros Mahjoob
3/11/04 01:03:18 PM
BIOMETRICS