AstraZeneca

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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

International co-ordinating investigator

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A full list of the investigators and sites participating in this study is provided in Appendix 12.1.4 of this clinical study report (CSR).

Study centers

Patients were recruited for this study from approximately 40 centers in the United States, 10 centers in Canada, and 23 centers in India, Finland, Germany, and the United Kingdom. A full list of investigators and investigational sites is provided in Appendix 12.1.4.

Publications

None at the time of this report.

Study dates

First patient randomized (Phase I):	18 August 1999
First patient treated (Phase II):	06 September 1999
Last patient completed (Phase I):	16 February 2002
Last patient completed (Phase II):	21 August 2002

Phase of development

Therapeutic confirmatory (III)

Objectives

- Phase I: To evaluate the efficacy of oral zolmitriptan across a range of doses for the treatment of a single migraine headache in adolescent patients (aged 12 to 17 years, inclusive).

- Phase II: To evaluate the safety of the long-term use of oral 5.0 mg zolmitriptan for the acute treatment of multiple migraine headaches in the same adolescents (aged 12 to 17 years, inclusive).

Evaluation of tolerability was a secondary objective of Phase I and evaluation of long-term efficacy was a secondary objective of Phase II of the study.

Study design

This was a 2-phase, 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.

Target patient population and sample size

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.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

AstraZeneca supplied 2.5 mg and 5.0 mg zolmitriptan tablets (Formulation (F) number followed by lot number) F12092 and F12411, respectively; and 2.5 mg and 5.0 mg matching placebo tablets, F12134 and F12448, respectively. Lot numbers are provided within the clinical study report (Table 3); Batch numbers are provided in Appendix 12.1.6.

In Phase I, patients took a single oral dose of 2.5, 5.0, or 10.0 mg zolmitriptan or matching placebo (3 tablets in various combinations of study treatment and placebo were taken by each randomized patient regardless of the treatment assignment). Note that the 10.0 mg dose was achieved by taking two 5.0 mg zolmitriptan tablets and 1 placebo tablet.

In Phase II, patients took oral 5.0 mg zolmitriptan in an open-label fashion.

Duration of treatment

Phase I: A single migraine headache was to be treated within 12 weeks of randomization.

Phase II: Multiple migraine headaches were treated over a 12-month open-label period.

Criteria for evaluation (main variables)

Efficacy

Phase I

- Primary variable: 4-point scale headache response at 2 hours
- Secondary variables: Secondary variables included measurement of 4-point scale headache response at 30 minutes and 1 hour; visual analog scale (VAS) headache response; 4-point scale painfree migraine headache relief; VAS change from baseline in headache intensity and proportion of patients with migraine-associated symptoms at 30 minutes, 1 hour and 2 hours; use of escape medication and time to first use; migraine recurrence and time to migraine recurrence; and number and percent of patients who slept including time and duration.

Phase II

Efficacy was not a primary objective of Phase II; however, data was collected and summarized for the majority of the primary and secondary efficacy variables listed above for Phase I.

Safety (Phases I and II)

The primary objective of Phase II was safety. For both phases of the study, data was collected and recorded for all adverse events, specified clinical laboratory tests, electrocardiogram (ECG) and vital signs, and medical history and physical examination findings.

Statistical methods

Efficacy:

Phase I

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 is 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 0.050.

Phase II

Efficacy data for Phase II was summarized and listed; no formal analyses were done.

Safety (Phases I and II)

In Phases I and II, the numbers of, and crude incidence rates for, adverse events in each treatment group were summarized by body system according to an in-house dictionary based on the Food and Drug Administration's (FDA's) Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). Clinical laboratory, vital signs, ECG, medical history and physical examination findings were summarized and listed.

Results

After the completion of Phase I and an analysis of Phase I data, a decision was made by AstraZeneca to discontinue Phase II of the study. This decision was based on the fact that Phase I treatment of adolescent migraine with zolmitriptan tablets failed to differentiate from placebo treatment for the primary efficacy variable and also because considerable safety data had already been collected on Phase II patients. In discussions with the FDA (teleconference of 15 August 2002), the agency supported the decision to stop the study. In Phase II, 319 patients who had exposures up to 180 days treated a total of 1555 attacks, 239 patients who had exposures between 181 to 360 days treated a total of 4690 attacks up through 360 days, and 42 patients who had exposure times greater than 1 year (360 days) treated a total of 989 attacks over their total exposure time. (Note: Exposure was calculated from the time a patient took their first dose of study treatment to the time the last dose was taken).

Patient population

Phase I

The 850 patients who entered Phase I were equally distributed among treatment groups with evenly matched demographic and baseline migraine-related characteristics. Across all treatment groups there was a higher percentage of patients aged 12 to 14 years and of female adolescents. The majority of patients were White. The percentage of patients completing the study and who were withdrawn due to adverse events (less than 1.0% for all zolmitriptan groups and none for placebo) was similar.

Phase II

The demographic and baseline characteristics for the safety population in Phase II were very similar to those summarized for Phase I patients and are not reiterated here.

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.

Efficacy

Phase I

No statistically significant improvement in efficacy for 10.0 mg zolmitriptan over placebo was demonstrated for 2-hour headache response (primary variable) in Phase I.

Phase II

Efficacy data for Phase II was summarized and listed; no formal analyses were done.

Safety (Phases I and II)

No deaths occurred and no serious adverse events were considered treatment-related in either phase of the study. Serious adverse events occurred in only 1 (0.2%) five mg zolmitriptan patient) during Phase I and in 10 (1.7%) patients during Phase II. Only 2 (0.3%) patients had serious adverse events in Phase II within 24 hours of treatment. The number of patients withdrawn due to adverse events was also low; 5 (less than 1.0%) zolmitriptan patients and no placebo patients in Phase I and a total of 50 (8.3%) patients in Phase II.

The most common adverse events in Phase I 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. In Phase II, the most common adverse events at the patient level were dizziness (14.5%), nausea (14.3%), tightness (12.0%), and paresthesia (9.5%); at the attack level, the occurrence of these same events was lower (1.6%, 2.0%, 3.7%, and 2.8%, respectively). There appeared to be no association between the adverse events experience and the length of time exposed to study medication.

Shifts and mean changes from baseline in the clinical evaluations done in Phases I and II of the study were clinically insignificant and raised no safety concerns. Three patients in Phase I, and 6 patients in Phase II of the study had laboratory variables reported as adverse events. Two of the 3 patients in Phase I who had adverse events for laboratory results, were included in the 6 patients with laboratory adverse events in Phase II.

No mean changes from baseline for vital signs or ECG or physical examination findings in Phases I or II appeared to be clinically significant.

Conclusions:

Statistically significant efficacy for zolmitriptan over placebo in the treatment of adolescent migraine was not achieved for the primary efficacy variable or any secondary variable analyzed in Phase I of this study.

Efficacy data was not formally analyzed in Phase II.

Zolmitriptan tablets taken at a 10.0, 5.0, or 2.5 mg dose in Phase I (double-blind), and at a 5.0 mg dose during Phase II of this study were well tolerated by the adolescent population. No serious adverse events were considered by the investigators as treatment related. The most common adverse events seen were those typical of triptan use and were consistent with the current label for zolmitriptan use in adults.

Date of the report

11 September 2003