SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho-McNeil Janssen Scientific Affairs, LLC NAME OF FINISHED PRODUCT: AXERT® NAME OF ACTIVE INGREDIENT(S): almotriptan malate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CAPSS-342

Title of Study: AXERT® 12.5 mg Time vs. Intensity - Migraine Study (AIMS): An Open-label Multicenter Trial to Evaluate the Efficacy of AXERT 12.5 mg Intervention at Onset of Migraine Pain

Investigators: Multicenter – Appendix 1.4.1

Publication (Reference):

Freitag FG, Finlayson G, Rapoport AM, Elkind AH, Diamond ML, Unger JR, Fisher AC, Armstrong RB, Hulihan JF, Greenberg SJ, on behalf of the AIMS Investigators. Effect of pain intensity and time to administration on responsiveness to almotriptan: results from AXERT® 12.5 mg time versus intensity migraine study (AIMS). Headache. 2007;47:519-530.

Study Initiation/Completion Dates: 11 June 2004 / 11 February 2005	**Phase of development:** 4

Objective:

The primary objective was to determine whether early intervention with AXERT was superior to treatment when pain reached at least moderate intensity in reducing the overall duration of migraine.

Methodology:

This was a multicenter, open-label, cluster-randomized study. Study centers were randomized to 1 of 2 treatment interventions: (1) Early Treatment (ET), ie, treatment at onset of migraine pain (within 1 hour), or (2) Conditional Treatment (CT), ie, treatment when migraine pain intensity was moderate or severe. Eligible subjects with International Headache Society (IHS)-defined migraine were instructed to treat 2 sequential migraine headaches with AXERT 12.5 mg using the treatment intervention randomly assigned to their study center. During the treatment phase, subjects were instructed to record data and dosing information using the Interactive Voice Response System (IVRS) phone call technology. Subjects used the Migraine Assessment Card as an aid in recording data. The 2 sequential migraine headaches were designated as first reported migraine headache attack (HA1) and as second reported migraine headache attack (HA2).

Number of Subjects (planned and analyzed):

Planned: 3800 subjects; 1900 subjects per treatment group

Analyzed (intent-to-treat): 1450 subjects; 757 ET subjects, 693 CT subjects

Diagnosis and Main Criteria for Inclusion:

Subjects had to be 18-65 years of age with at least a 1-year history of migraine headache with or without aura according to IHS classification criteria. Subjects had to have an average frequency of 1 to 6 headaches during the 3 months prior to screening and a history of migraine headaches of at least moderate pain intensity within the previous year.

Test Product, Dose and Mode of Administration, Batch No.:

AXERT® (almotriptan malate) 12.5 mg self-administered orally, Batch No.: not applicable

Reference Therapy, Dose and Mode of Administration, Batch No.:

No reference therapy was used.

SYNOPSIS (CONTINUED)

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Duration of Treatment:

Subjects self-administered AXERT 12.5 mg for 2 sequential migraine headaches within 60 days of study entry. If the subject did not treat 2 migraine headaches with study medication within 60 days, the final visit was scheduled.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was total headache duration of the first migraine headache attack, defined as the time from onset of migraine headache pain to no headache pain without the use of supplemental pain medication and/or antiemetic medication.

Secondary efficacy variables included:

- Pain free 2 hours after study medication administration, where pain free is defined as a decrease in baseline migraine pain intensity from severe, moderate, or mild to no pain without the use of supplemental pain medication and/or antiemetic medication
- Pain free sustained 24 hours after study medication administration, defined as pain free at 2 hours with no recurrence of pain of any intensity nor use of rescue headache medication between 2 to 24 hours posttreatment
- Use of rescue medication prior to achieving pain free

Safety:

Adverse events (AEs) were monitored throughout the study and collected at the final visit.

Statistical Methods:

The primary efficacy analysis was conducted on HA1 using the intent-to-treat (ITT) population. The ITT population is defined as all subjects who, for either study migraine headache (HA1 or HA2), took study medication and had postbaseline efficacy data.

Statistical analyses accounted for the cluster randomized study design. Total duration of migraine headache pain was analyzed utilizing the SURVIVAL procedure of the statistical program SUDAAN, which fits a proportional hazards model. Secondary efficacy variables, which each have a dichotomous outcome result, were analyzed using PROC GENMOD of SAS version 9.1. Separate statistical analyses were conducted for HA1 and HA2.

Comparative subgroup analyses were performed post hoc on 3 cohorts. Subgroups included the ET subjects who treated their mild, moderate, or severe migraine pain within 1 hour of pain onset (ET ≤1 hour), CT subjects who treated their moderate or severe migraine pain within 1 hour of pain onset (CT ≤1 hour), and CT subjects who treated their moderate or severe migraine pain greater than 1 hour from onset of pain (CT >1 hour). The ET subjects who treated their migraine after 1 hour of pain onset and the CT subjects who treated mild migraine pain were considered to be protocol violators and were not included in these analyses.

For each of the dichotomous variables, comparative results were summarized by the odds ratio. For total duration of migraine pain and time to medication from onset of pain, statistical analyses were also conducted with the Wilcoxon test.

The safety population is defined as all subjects who took study drug and had safety information postdosing. Adverse events were reported for the period of time from the initial visit to the return visit. Adverse events are summarized separately for the subjects in the ET and CT treatment groups.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

- Median headache duration (time from onset of headache pain until no pain) for HA1 for ITT subjects in the ET treatment group (3.18 hours) was significantly shorter than for ITT subjects in the CT treatment group (5.53 hours) ($P<0.001$).
- There were no significant differences between the 2 treatment groups in secondary efficacy parameters: number and percentage of subjects who were migraine pain free 2 hours after AXERT administration, the number and percentage of subjects who remained pain free 24 hours after AXERT administration (sustained pain relief), and the number of subjects who required rescue medication.
- The majority (55.4%) of subjects in the CT treatment group experienced moderate or severe pain at the onset of their headache making them eligible to receive their medication early, similar to subjects in the ET treatment group. Because of the substantial overlap between ET and CT subjects, with regard to time to treatment and intensity of pain at treatment, subgroup analyses were performed.
- The results of subgroup analyses at fixed time to treatment (≤1 hour vs. >1 hour) showed that subjects who treated mild or moderate pain had significantly better treatment outcomes, defined by shorter median headache duration and greater 2-hour pain free, sustained pain free, and use of rescue medication rates, compared to those who treated severe pain.
- The results of the subgroup analyses at comparable levels of pain intensity showed that early time to treatment (≤1 hour) was associated with shorter median headache duration and greater 2 hour pain free, sustained pain free, and use of rescue medication rates than later time to treatment (>1 hour)..

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SAFETY RESULTS:

- 94 (11.9%) subjects in the ET group and 77 (10.7%) subjects in the CT group reported at least 1 AE.
- 51 (6.5%) subjects in the ET treatment group and 43 (6.0%) subjects in the CT group had AEs that were considered by the investigator to be related to study medication (possible, probable or very likely).
- In 33 (4.2%) subjects in the ET group and 24 (3.3%) subjects in the CT group, study treatment was prematurely discontinued due to AEs.
- Adverse events with a subject incidence ≥1% in either group were nausea (2.5% and 1.7% in the ET and CT groups, respectively) and dizziness (1.1% and 0.7% in the ET and CT groups, respectively).
- Chest pain was reported by 6 (0.4%) subjects, throat tightness by 3 (0.2%) subjects, and chest tightness by 1 (0.1%) subject.
- There were 3 serious adverse events (SAEs) during the study (2 in the ET group and 1 in the CT group), including 1 death due to myocardial infarction in a subject who did not receive any study medication. The other 2 SAEs were breast cancer and right cerebellopontine angle tumor/aseptic chemical meningitis. All of the SAEs were considered by the investigator to be unrelated to study medication.

Subjects With Adverse Events

	ET Group (N=787) n	(%)	CT Group (N=721) n	(%)
One or more adverse events	94	(11.9)	77	(10.7)
Deaths[a]	1	(0.1)	0	
One or more serious adverse events[b]	2	(0.3)	1	(0.1)
Treatment stopped permanently due to adverse events	33	(4.2)	24	(3.3)

[a] Death occurred before any study medication was taken.
[b] Includes a serious AE with outcome of death.

CONCLUSION:

Early intervention resulted in shorter headache duration compared to intervention when headache reached moderate or severe intensity.

Date of the report: 01 November 2007

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