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-316 **Title of Study:** AXERT® Early miGraine Intervention Study (AEGIS): Efficacy and Safety of AXERT® (Almotriptan Malate) versus Placebo for the Acute Treatment of Migraine Headache		
Principal Investigator: Multicenter		
Publication (Reference): Mathew NT, Finlayson G, Smith TR, Mao L, Wright P, Greenberg S. Early Intervention With Almotriptan: Results of the AEGIS Trial (AXERT® Early miGraine Intervention Study). *Headache* Abstract 2006; 46:857.		
Study Initiation/Completion Dates: 06 Dec 2004 / 29 Jun 2005		**Phase of development:** IV
Objective: To evaluate the efficacy and safety of AXERT (almotriptan malate) 12.5 mg tablets compared with placebo for the acute treatment of migraine headache (HA) at the earliest onset of HA pain.		
Methodology: A multi-center, randomized, double-blind, placebo-controlled, parallel group study of subjects with a diagnosis of migraine HA. The study consisted of 2 phases: screening and double-blind. Subjects were randomized in a 1:1 ratio to one of two treatment groups. Subjects in each group treated a total of 3 consecutive qualifying migraine HA attacks at the earliest onset of HA pain. One treatment group received almotriptan 12.5 mg for each attack; the other treatment group received matching placebo tablets for each attack.		
Number of Subjects (planned and enrolled): Planned: 316 subjects; 158 subjects per treatment group. Enrolled: 378; 189 randomized to almotriptan; 189 randomized to placebo.		
Diagnosis and Main Criteria for Inclusion: Individuals 18-65 years of age with a history of migraine HA with or without aura, according to the International Headache Society (IHS) classification criteria, were eligible to participate. Each subject successfully completed the screening procedures and met all inclusion and exclusion criteria (see Section 3.2.2 and Section 3.2.3).		
Test Product, Dose and Mode of Administration: AXERT (12.5 mg almotriptan malate) self-administered orally. **Batch No.:** D04LC1195		
Reference Therapy, Dose and Mode of Administration: Placebo, as an identically appearing tablet, self-administered orally. **Batch No.:** D04LD1245		
Duration of Treatment: Treatment with the first dose of double-blind study medication took place within 30 days of randomization. All 3 acute doses of study medication were to be taken within 60 days of Visit 2 (Randomization). If the subject did not treat 3 migraine HA attacks with study medication within 60 days of Visit 2, Visit 4 (Final Visit) was scheduled.		
Criteria for Evaluation: Pharmacokinetics: No pharmacokinetic measurements were made in this study.		

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Efficacy:

The primary efficacy variable was HA pain free, defined as a decrease in baseline pain intensity from severe, moderate, or mild, to no pain, without the use of supplemental pain medication and/or anti-emetic medication, at 2 hours post-dosing of the first migraine HA attack.

Secondary efficacy variables are:

- Cumulative pain free post-dosing over the 2-hour incremental post-dosing assessment, defined as achieved pain free at any time within 2 hours post-dosing.
- Pain relief 2 hours post-dosing, defined as a decrease in baseline HA pain intensity from severe or moderate to mild or no pain, without the use of supplemental pain medication and/or anti-emetic medication up to the 2-hour incremental post-dosing assessment, at 2 hours post-dosing (observed) and at anytime within 2 hours post-dosing (cumulative).
- Modified pain relief 2 hours post-dosing, defined as a decrease in baseline HA pain intensity from severe or moderate to mild or no pain, or from mild to no pain, without the use of supplemental pain medication and/or anti-emetic medication up to the 2-hour incremental post-dosing assessment (observed and cumulative).
- HA pain free at 0.5, 1, 4, and 24 hours post-dosing (cumulative and observed).
- Median time to HA pain free post-dosing.
- HA pain relief at 0.5, 1, 4, and 24 hours post-dosing (cumulative and observed).
- Modified HA pain relief at 0.5, 1, 4, and 24 hours post-dosing (cumulative and observed).
- Median time to HA pain relief post-dosing.
- Median time to modified HA pain relief post-dosing.
- Pain intensity differences (PID) from baseline at 0.5, 1, 2, 4, and 24 hours post-dosing.
- Consistency of response: Percentage of attacks in which a subject achieved HA pain free at 2 hours; percentage of attacks in which a subject achieved pain relief at 2 hours; percentage of attacks in which a subject achieved modified pain relief at 2 hours.
- Occurrence and severity of migraine-associated symptoms, including phonophobia, photophobia, or nausea from baseline at 0.5, 1, 2, 4, and 24 hours post-dosing.
- Presence or absence of migraine-associated vomiting at baseline, 0.5, 1, 2, 4, and 24 hours post-dosing and at the time of no pain.
- Change in functional disability from baseline at 0.5, 1, 2, 4, and 24 hours post-dosing and at the time of no pain.
- Assessments of development of symptoms of peripheral sensitization and cutaneous allodynia at baseline, 0.5, 1, 2, 4, and 24 hours post-dosing using the Central Sensitization Questionnaire (CSQ-4).
- Sustained pain free, which was defined as pain free at 2 hours post-dosing with no recurrence of moderate or severe HA pain over the ensuing 2 to 24 hours, with no use of supplemental pain medication and/or no use of anti-emetic medication through 24 hours post-dosing. In addition, the subject must have had both a 2-hour and 24-hour pain intensity assessment.
- Health-Related Quality of Life Measures: 24-hour Migraine Quality of Life Questionnaire (MQOL); Migraine-Specific Quality of Life Questionnaire (MSQ); Migraine Assessment of Current Therapy Questionnaire (Migraine-ACT); and Migraine Disability Assessment (MIDAS).

Safety: Safety evaluations included: Adverse events (AEs), brief physical exam, clinical laboratory tests, electrocardiogram (ECG), and vital signs. A urine drug screen for specified substances (see Section 3.9.5) was performed at screening, and a urine pregnancy test was performed on women of childbearing potential at each visit.

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Statistical Methods:

The primary efficacy analysis was conducted on the first migraine HA using the modified Intent-to-Treat (mITT) population. Additional sensitivity analyses were conducted using the Intent-to-Treat (ITT) population, and the Per Protocol (PP) population. Safety information data were summarized using the Safety Evaluable Subject (SES) population. The analysis populations (Section 3.11) are:

- Randomized – All subjects enrolled and randomized to treatment.
- ITT – All randomized subjects who, for the first study migraine HA, took study medication, and had post-dose HA pain intensity data.
- mITT – All ITT subjects who for the first study migraine HA, took study medication, and had evaluable baseline and 2 hour post-dosing HA pain intensity data.
- PP – mITT subjects who had PDA-documented treatment of 3 migraine HAs and for whom there was no major protocol violation.

The primary efficacy analysis was a comparison of the percentage of subjects who responded (i.e., were HA pain free at 2 hours post-dosing of the first migraine HA) in the two treatment groups, using a Cochran-Mantel-Haenszel (CMH) general association test, stratified by pre-dosing pain intensity and pooled centers.

Secondary efficacy outcome variables were analyzed as follows:

- Cumulative percentage of subjects who were pain free at 2 hours post-dosing, percentage of subjects with pain relief at 2 hours post-dosing; percentage of subjects pain free at 0.5, 1, 4, and 24 hours post-dosing, percentage of subjects with pain relief at 0.5, 1, 4, and 24 hours post-dosing; and percentage of subjects achieving sustained pain free at 24 hours post-dosing of the first attack, were compared between the two treatment groups using a CMH general association test, stratified by pre-dosing pain intensity and pooled center.
- The occurrence of migraine-associated vomiting assessed at pre-dosing, 0.5, 1, 2, 4, and 24 hours post-dosing of the first attack was analyzed by a CMH general association test, stratified by pooled center.
- The occurrence of peripheral sensitization and cutaneous allodynia, as measured by the CSQ-4, at pre-dosing, 0.5, 1, 2, 4, and 24 hours post-dosing of the first attack, was analyzed by a CMH general association test, stratified by pooled center.
- A CMH row mean scores test stratified by pooled center was used to analyze the following secondary efficacy variables: the occurrence and severity of migraine-associated symptoms (including phonophobia, photophobia, and nausea) assessed at pre-dosing, 0.5, 1, 2, 4, and 24 hours post-dosing, and the level of functional disability at pre-dosing at 0.5, 1, 2, 4, and 24 hours post-dosing of the first attack and at the time of no pain.
- The variables time to achieve pain free and time to achieve pain relief post-dosing, were analyzed by the log rank test.
- An analysis of covariance (ANCOVA) model with treatment, pre-dosing pain, and pooled center as covariates was used to analyze the following variables: pain intensity differences from pre-dosing at 0.5, 1, 2, 4, and 24 hours post-dosing of the first attack, consistency of response as evaluated by the percentage of attacks out of 3 in which pain free, pain relief, and modified pain relief were achieved 2 hours post-dosing.
- MQOL, MSQ and Migraine-ACT data were analyzed with ANCOVA; the MIDAS was used to derive meaningful subgroup stratifications in the evaluation of these measures.

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Data imputation and last observation carried forward (LOCF) rules for pain intensity, pain free, and migraine symptoms (phonophobia, photophobia, and nausea) are described in Section 3.11 and also in the SAP (Appendix 2.2, see Section 4.11.1.2).

All statistical tests were two-tailed and employ a Type I error of 0.05. No corrections for multiplicity were made.

A summary is provided of AEs by treatment group, categorized by system/organ/class (SOC) and preferred term, coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 7.0, and an overall summary of AEs, by treatment group, includes the number and percentage of subjects with 1 or more of the following: any AE regardless of relationship to study drug, a treatment-related AE, a serious AE (SAE), a treatment-related SAE, discontinuations due to an AE, and the number and percent of subjects who died. Separate summaries are presented for AEs by relationship to study drug, by maximum severity, for treatment-emergent AEs, and for AEs resulting in discontinuation of treatment, and also for SAEs. All AEs occurring during the double-blind phase are listed.

Changes in vital signs from baseline, incidence of abnormal vital sign values by treatment group at the Final Visit, and brief physical examination data are summarized.

No inferential statistics were performed on the safety data; no imputation rule was applied to missing safety data.

SUMMARY

EFFICACY RESULTS:

- The primary efficacy outcome based on the first HA attack revealed that significantly more almotriptan treated subjects than placebo treated subjects (37.0% vs 23.9%) reported being HA pain free at 2 hours post-dosing without the use of supplemental medication and/or anti-emetic medication in the mITT population (p=0.0099). A significant difference was also observed in the PP population (p=0.0056), and in the ITT population (p=0.0204).

The following secondary efficacy outcomes were based on analysis of the mITT population:

- Significantly more almotriptan treated subjects than placebo treated subjects treated subjects (72.3 % vs. 48.4%) reported HA pain relief at 2 hours post-dosing of the first attack (p=0.0005).
- Significantly more almotriptan treated subjects than placebo treated subjects (59.9% vs. 42.6%) reported modified HA pain relief at 2 hours post-dosing of the first attack (p=0.0007).
- At 1, 2, 4, and 24 hours post-dosing of the first HA attack, significantly more subjects treated with almotriptan than placebo reported being pain free, and having pain relief and modified pain relief ($p \leq 0.0314$).
- Median time to pain free, pain relief, and modified pain relief was significantly less for almotriptan treated subjects compared with placebo treated subjects ($p < 0.01$).
- A significantly greater percentage of almotriptan treated subjects achieved sustained HA pain free in the first attack compared with the placebo treated group (24.7% vs. 16.1%; p=0.0397).
- At 1, 2, 4, and 24 hours post-dosing of the first attack the distributions of HA pain intensities for the almotriptan treated subjects were consistently less intense compared with the placebo treated subjects ($p \leq 0.0345$). The average between group HA pain intensity difference (PID) was statistically significantly different as early as 1 hour post-dosing and observed at subsequent time points of 2, 4, and 24 hours ($p \leq 0.0174$).
- Treatment with almotriptan led to significantly greater symptomatic relief of the migraine-associated symptoms phonophobia and photophobia beginning at 2 hours post-dosing, and of nausea at 4 hours post-dosing of the first attack ($p \leq 0.0024$).

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EFFICACY RESULTS (continued):

- Almotriptan treated subjects more frequently reported no functional disability at 2 hours (54.4% vs. 38.1%) and 4 hours (74.5% vs. 54.3%) post-dosing of the first attack compared with placebo treated subjects. The mean difference between treatment groups in functional disability was statistically significant at 2 hours (p=0.0069) and 4 hours (p=0.0002) post-dosing.
- Treatment with almotriptan compared with placebo led to higher (more favorable) scores on the MQOL 24 hours post-dosing of the first attack in the work, social, and feelings/concerns domains ($p \leq 0.0329$).
- Allodynia associated symptoms were present in approximately half of the subjects prior to treatment (53.1% vs. 51.6%, almotriptan vs. placebo, respectively).
- A smaller percentage of subjects treated with almotriptan than placebo manifested allodynia at 4 hours post-dosing (p=0.0008).
- A greater proportion of subjects who treated 3 HA attacks with almotriptan achieved pain free and modified pain relief compared with subjects treated with placebo ($p<0.01$).
- The percentage of attacks for which 2 hour pain free, pain relief, and modified pain relief was achieved was significantly greater for almotriptan than placebo treated subjects ($p<0.01$).
- Mean differences from baseline to Final Visit of health-related quality of life measures on the MSQ were not significantly different between treatment groups.
- At the Final Visit, subjects treated with almotriptan had significantly higher scores on the Migraine-ACT assessment (p=0.0073) indicating that they experienced a more satisfactory response to treatment than subjects who received placebo.

SAFETY RESULTS:

- Adverse events (AEs) were reported at a similar frequency across treatment groups (23.0% for almotriptan treated subjects and 23.7% for placebo treated subjects).
- Serious AEs (SAEs) were uncommon; there were 3 SAEs reported by 2 subjects. None of these events were treatment-related. (One almotriptan treated subject experienced SAEs of appendicitis perforated and peritoneal infection, and 1 placebo treated subject experienced a SAE of pneumonia.)
- Two subjects (1 subject from each treatment group) experienced 3 AEs that led to study discontinuation. These events were considered treatment-related.
- No death occurred during the study.
- AEs assessed as severe were infrequent, reported by just 2.3% of almotriptan treated subjects and 2.9% of placebo treated subjects.
- The percentage of subjects experiencing 1 or more treatment-emergent AEs was 9.8% for almotriptan treated subjects and 6.4% for placebo treated subjects. Treatment-emergent AEs that occurred with a frequency of ≥1% (equivalent to 2 or more subjects) in the almotriptan and placebo treated groups, respectively, were somnolence (1.1% and 2.3%), nausea (1.1% and 1.7%), vomiting (1.1% and 0.6%), and fatigue (1.1% and 0%).

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CONCLUSION:

- Almotriptan early intervention treatment, compared to placebo, resulted in a significantly greater proportion of subjects achieving 2 hour pain free, 2 hour pain relief, 2 hour modified pain relief, and sustained pain free.
- Significant differences in pain free and pain relief and modified pain relief between almotriptan and placebo treatment were observed as early as 1 hour post dosing.
- Almotriptan early intervention treatment compared with placebo resulted in a significantly greater proportion of subjects reporting no functional disability at 2 hours and 4 hours post-dosing.
- At 24 hours post treatment for migraine HA a greater proportion of almotriptan than placebo treated subjects reported more favorable outcomes regarding work, social, and feelings/concerns.
- The tolerability profile of almotriptan in this study was similar with placebo and is consistent with results of previous placebo controlled studies[17] and with information provided in the Prescribing Information and Investigator's Brochure.
- Almotriptan acute migraine HA intervention effectively relieved HA pain and associated symptoms, reduced disability and favorably influenced performance of daily activities, and was well tolerated.

Date of the report: 25 September 2007

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