

SYNOPSIS

<u>NAME OF SPONSOR/COMPANY:</u> Ortho-McNeil Janssen Scientific Affairs, LLC.	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
<u>NAME OF FINISHED PRODUCT:</u> Axert [®]		
<u>NAME OF ACTIVE INGREDIENT(S):</u> Almotriptan malate		
Protocol No.: CAPSS-334 CR002875		
Title of Study: Efficacy of AXERT [®] (Almotriptan Malate) in the Acute Treatment of Migraine: A Pilot Study of the Potential Impact of Preventive Therapy with TOPAMAX [®] (Topiramate)		
Investigator: This was a multicenter study conducted at 22 investigative sites.		
Publication (Reference): None to date.		
Study Initiation/Completion Dates: 21 Sep 2005 / 21 Jun 2007		Phase of development: IV
Objectives: The objective of this pilot study was to determine the potential impact of topiramate as preventive migraine therapy compared with placebo on the therapeutic efficacy of the acute migraine therapy, almotriptan.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group pilot study that enrolled subjects 18 to 65 years of age with a history of migraine headaches (HAs). Following a 6-week Open-Label Phase, during which eligible subjects received Topamax [®] titrated to a dose of 100 mg/day, subjects were randomized in a 1:1 distribution to continued topiramate treatment or placebo. Throughout the study, almotriptan 12.5 mg was utilized as acute treatment for the symptomatic relief of migraine HAs. Subjects recorded assessments of HA severity, associated symptoms and other assessments into the electronic subject diary (Personal Digital Assistant [PDA]) for qualifying HAs. The study consisted of 4 phases: Pretreatment, Open-Label treatment, Double-Blind, and Taper/Exit.		
Number of Subjects (planned and analyzed): Planned: 150 subjects who completed the Open-Label portion of the study and were eligible for randomization to the double-blind portion; 75 subjects per Double-Blind treatment group. Enrolled: 407; 104 randomized to continued topiramate treatment; 107 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 classification criteria for at least 6 months, were eligible to participate. Subjects had to have an average of 3 to 12 migraines per month over the prior 3 months, but had experienced less than 15 HA-days (migraine or non-migraine) per month. Subjects who successfully completed the screening procedures and met all inclusion and exclusion criteria were enrolled in the study.		
Test Product, Dose and Mode of Administration, Batch No.: Topamax [®] (topiramate) 25 mg Tablets: Batch numbers R12981, R13763, and R13293. Topiramate 25 mg Tablets: Batch numbers R12982, R13497, and R13290.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for topiramate 25 mg Tablets: Batch numbers R12983, R13498, and R13291. Axert [®] (almotriptan malate) 12.5 mg Tablets: Batch numbers R12984, R13859, R13860, and R13292.		

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<p>Duration of Treatment: The Pretreatment Phase (Visit 1) consisted of the Screening/Washout Period and a Baseline Period (at least 28 days; Visits 2-3) and lasted up to 70 days; the Open-Label Phase(Visits 3-5) consisted of a 4-week Titration Period during which the subject initiated treatment with open-label Topamax[®] 25 mg tablets and increased by 25 mg weekly until reaching 100 mg/day, and a 2-week Maintenance Period; the Double-Blind (DB) Phase (Visits 5-8), during which the subjects continued topiramate treatment or received placebo, consisted of a 1-week Taper/Conversion Period, a 6-week Stabilization Period, and a 12-week Assessment Period. Throughout the DB Phase subjects continued to take almotriptan 12.5 mg tablets for symptomatic treatment of migraine HAs. At the end of the DB Phase, an additional week (Visit 9) of follow-up was planned which was considered the Taper/Exit phase.</p>		
<p>Criteria for Evaluation:</p> <p><u>Efficacy:</u></p> <p>Subjects used their PDA to capture duration of migraine HA, migraine HA-associated symptoms, HA pain intensity, restoration of function using the Restoration of Function Questionnaire (ROFQ), development of peripheral sensitization and cutaneous allodynia using the Central Sensitization Questionnaire (CSQ-4), occurrences of vomiting and use of supplemental pain and/or anti-emetic medication for qualifying migraine HAs. For a subset of HAs, performance of daily activities was assessed using the Productivity Questions dispensed at Visits 2, 3, 4, 5, 6, and 7. The migraine-related disability and quality of life were assessed using the Migraine Disability Assessment (MIDAS) at Visits 3 and 8 and the Migraine-Specific Quality of Life Questionnaire (MSQ) at Visits 3, 5 and 8.</p> <p>In this study, a qualifying migraine study HA is defined as one that was not present upon awakening and had not spontaneously improved since its onset. The subject must also have remained migraine HA-free for 1 calendar day prior to the targeted episode. A migraine HA-free day was defined as an entire calendar day beginning at 12:00 AM midnight and ending at 11:59 PM in the evening of the same day without the migraine HA.</p> <p><i>Primary efficacy outcome:</i></p> <p>The primary efficacy outcome for a subject is the sustained pain free (SPF) response, 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-almotriptan intervention, with no recurrence of HA pain of any intensity and with no use of rescue medication from 2 to 24 hours post-almotriptan intervention, for the first qualifying HA of the Assessment Period— or experienced no migraine HAs during the DB Phase.</p> <p><i>Secondary efficacy outcome:</i></p> <p>The following in the first qualifying HA of the Assessment Period are considered secondary efficacy outcomes: pain relief, pain free, and SPF response. In addition, the maximum intensity of HA pain and duration of HA from onset to time subject was pain free, and also, the maximum intensity of migraine-associated symptoms (photophobia, phonophobia, nausea), and the proportion of subjects who experienced vomiting, peripheral sensitization, and cutaneous allodynia in the first qualifying HA of the Assessment Period were considered. Efficacy outcome measures such as a subject’s usual level of functioning (or HA success) at 2 hours post-almotriptan intervention as captured on the ROFQ, response to each of the Productivity Questions during the Assessment Period, MSQ and MIDAS scores at specified visits, were considered secondary. Number of migraine HAs during the Assessment Period was also considered.</p> <p><u>Safety:</u> Safety evaluations included adverse events (AEs), brief physical examination, brief neurological examination, vital signs and clinical laboratory tests (hematology, chemistry and urinalysis). Urine pregnancy tests were performed on women of childbearing potential.</p> <p><u>Pharmacokinetic/Pharmacodynamic Relationships:</u> Pharmacokinetic/pharmacodynamic relationships were not evaluated.</p>		

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Statistical Methods:

The sample size for this pilot study was not based on statistical considerations but rather based on practical considerations of feasibility, logistics, and potential for hypothesis generation. Data were analyzed using both a Frequentist approach and a Bayesian approach, as described in Parts 1 and 2 of the statistical analysis plan (SAP), respectively.

The primary efficacy analysis was performed using all subjects defined by the Intent-to-Treat (ITT; randomized subjects who took at least 1 dose of double-blind study medication and for whom a post-randomization efficacy assessment was available) and the Efficacy Evaluable (EE; randomized subjects who received double-blind study medication, completed the stabilization period, recorded at least 1 qualifying HA during the assessment period, had at least 1 post-baseline assessment of pain for the qualifying HA, and did not take any prohibited medication) population criteria.

All efficacy analyses were conducted on both ITT and the EE populations. Safety analyses were performed on all subjects who took at least 1 dose of either almotriptan or topiramate and for whom safety information was available (Safety population).

Primary Efficacy Outcome Analysis:

- Bayesian method: In order to relate the external knowledge (prior beliefs) of the study investigators about the various efficacy variables with observed data (likelihood) obtained from the current study and to be able to update this knowledge (called posterior belief) accordingly, the Bayesian methodology was used. Before the start of the study, individual investigators were asked about their ‘prior’ beliefs on the possible differences between 2 treatment groups for various efficacy outcome variables and a distribution for these beliefs (on the difference) was constructed for each efficacy parameter except for ROFQ, Productivity Questions, and MSQ measures. To reflect the underlying uncertainty in the prior belief distributions, 3 types of belief distributions were considered for Bayesian analysis: enthusiastic, skeptical, and non-informative. The “enthusiastic” priors were based on the elicited information from a group of investigators before the start of the study. The “skeptical” priors were to assume that these prior distributions had means of 0 and standard deviations equal to that of the elicited enthusiastic prior distributions. The “non-informative” priors assumed a mean of 0 and a large standard deviation (more uncertainty). For difference in proportions, the prior distributions were assumed to have bivariate-beta form distributions and the observed data were considered binomially distributed. The posterior probability of the difference between 2 groups for each efficacy parameter was obtained by applying Bayes’ theorem that relates a prior probability (belief) with observed data (likelihood) to yield the posterior (updated) belief.

- Frequentist method: The proportion of treatment responders was summarized by treatment group and the 2 treatment groups were compared by the Cochran-Mantel-Haenszel (CMH) row means test using modified riddit scores with stratification by pre-almotriptan pain intensity (mild, moderate, or severe) of the first qualifying HA in the Assessment Period and pooled center.

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Statistical Methods: (Continued)

Secondary Efficacy Outcome Analyses

- *Bayesian* results for the secondary efficacy outcomes are summarized in the results section of this document and are interpreted accordingly.
- Frequentist method: For the following parameters, the proportions of subjects were summarized by treatment group, and the 2 treatment groups were compared using the CMH row means test of association using modified ridit scores with stratification by pre-almotriptan pain intensity (mild, moderate, or severe) of the first qualifying HA, and pooled center: subjects who achieved pain relief, who achieved pain free, who achieved SPF; proportion of subjects with maximum intensity of HA pain; proportion of subjects in each treatment group who used rescue medication for the first qualifying HA of the Assessment Period; frequency distribution of the number of migraine HAs during the Assessment Period.
- The duration of the HA from time of onset to the time the subject was pain free of the first qualifying HA of the Assessment Period was summarized for each treatment group by the Kaplan-Meier estimator, and the treatment groups were compared using the log rank test. The Kaplan-Meier estimates are also presented graphically.
- The 2 treatment groups were compared using the CMH row means test of association using modified ridit scores with stratification by pooled center for the following parameters: proportion of subjects who experienced mild HA pain as their maximum HA pain (or who experienced no migraine HAs during the DB Phase); frequency distributions of the maximum intensity of migraine-associated symptoms (photophobia, phonophobia, nausea); proportion of subjects who experienced vomiting without use of supplemental pain medication and/or anti-emetic medication at 2 hours post-almotriptan intervention, peripheral sensitization, cutaneous allodynia, and achieved usual level of functioning.
- Productivity and activity measured on the Productivity Questions in the first qualifying HA during the Assessment Period was summarized descriptively by treatment group.
- In addition, the association between the ROFQ and productivity (Items 4 and 5) were examined. A 4x2 contingency table was constructed between each one of the 6 ROFQ function items and Item 4 or 5 in productivity (using the responder variable defined above). Therefore, twelve 4x2 contingency tables were constructed. Association between the ROFQ and productivity items was tested by the Chi-square test. Bar graphs are presented to show the relationship between ROFQ and productivity questions by plotting the number of responders/non-responders over each category from a ROFQ question.
- For each domain score of the MSQ, between-group differences for the change from baseline to Visit 8 were examined by analysis of covariance (ANCOVA) with baseline MSQ domain score as a covariate, and treatment and pooled center as fixed factors.
- The MIDAS results for each question were summarized by treatment group at Visit 3 and Visit 8 (Final Visit). For each question and the total score, between-group differences for the change from baseline to Visit 8 were examined by ANCOVA with baseline MIDAS score as a covariate, and treatment and pooled center as fixed factors.

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SUMMARY-CONCLUSIONS

Subjects were on average 37 years old in the ITT population and approximately 41 years old in the EE population; overall, most subjects were female (≥84.7%) and were white (≥71.2%) and the treatment groups were similar in baseline characteristics.

EFFICACY RESULTS:

Bayesian Approach

For each efficacy parameter, 3 prior distributions were considered: enthusiastic, non-informative, and skeptical, respectively. Using each prior distribution separately, the corresponding posterior means, posterior standard deviations and the associated 95% credible intervals were calculated. For the primary efficacy parameter, treatment response at 2 hours post-almotriptan intervention, the posterior mean for the difference in proportions between the 2 groups was 0.02 (SD = 0.05). For most of the efficacy parameters, posterior means were close to 0, signifying an inconsequential difference between the 2 groups (topiramate – placebo) except for 2 variables: pain relief at 2 hours post-almotriptan intervention and the maximum intensity migraine associated symptom of moderate nausea. For these 2 variables, the posterior means for the differences in proportions between the 2 groups ranged from 0.05 to 0.10 and 0.06 to 0.11, respectively, among the priors assumed. Further, for each efficacy parameter, the posterior probability that the observed difference between the 2 groups exceeded the 1%, 2%, 3%, 5% or 10% threshold difference respectively was calculated under different prior assumptions. The posterior probabilities decrease with increasing threshold differences suggesting a less likely chance of finding a difference that high or higher. For the enthusiastic prior case, the calculated posterior probability was observed to be uniformly higher across all efficacy variables considered, but progressively decreased for higher threshold differences within each variable. For the non-informative prior case, the posterior probabilities were relatively smaller, and also decreased for higher threshold differences within each variable. The use of skeptical priors resulted in posterior probabilities that were the smallest. For the primary efficacy parameter of treatment response, the posterior probability of exceeding a 10% threshold difference between the 2 groups was 0.07 (under the enthusiastic prior case) and 0.11 (under the non-informative prior case).

However, for the efficacy parameters, the proportion with pain relief at 2 hours post-almotriptan intervention and the proportion with moderate nausea as the maximum intensity of a migraine associated symptom, the posterior probabilities of the difference in proportions between 2 groups exceeding a 10% threshold value was 0.49 and 0.35 under the enthusiastic prior case and 0.50 and 0.56 under the non-informative prior case respectively.

Frequentist Approach

The proportion of subjects that achieved the treatment response —defined as achieving SPF or experiencing no migraine HA after almotriptan intervention during the first qualifying HA during the Assessment Period — was similar in each treatment group (25.0% vs 22.0% of subjects in the topiramate and placebo treatment groups, respectively). No significant differences between treatment groups were found for the 2 hour pain relief, 2 hour pain free, SPF, and maximum HA pain intensity outcomes. Subjects in the topiramate treatment group were pain free during the first qualifying HA at an earlier time after taking almotriptan (median = 4 hours) than subjects in the placebo group (median = 7 hours) although the between group difference was not statistically significant. Also, the topiramate group across all time points after taking almotriptan had a higher proportion of subjects reporting pain intensity as “none,” with a between group difference that was most pronounced at 4 hours. Supplemental pain medication was used more frequently by subjects in the placebo treatment group (45.8%) than in the topiramate treatment group (35.4%); the between group difference was not statistically significant.

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<p>From the 30-minutes to 4 hour time points after taking almotriptan, the proportions of subjects experiencing symptoms associated with peripheral sensitization and cutaneous allodynia were generally similar across treatment groups. At 24 hours after taking almotriptan a significantly smaller proportion of subjects in the placebo group experienced positional worsening of HA, shoulder soreness, and cutaneous allodynia during the first qualifying HA. Across these symptoms, there was a higher proportion of subjects in the topiramate group with missing information (43.8% vs 27.1%). Subjects in the placebo group used supplemental medication more frequently during this time period; this might have had an influence on various outcomes by ameliorating maximal HA pain intensity and migraine associated symptoms.</p> <p>Hours worked (median) was greater for subjects in the placebo (6.0 hours) than topiramate treatment group (2.0 hours) in the first qualifying HA during the Assessment Period. However, 11.9% of subject in the placebo treatment group indicated they were non-responders (i.e., overall effectiveness at work was less than or equal to 60%) as compared with 6.3% of subjects in the topiramate treatment group. (Inferential statistics were not performed.)</p> <p>Subjects in the topiramate and placebo treatment groups responded comparably on questionnaires of functionality, productivity, and health-related quality of life.</p> <p><u>SAFETY RESULTS:</u></p> <ul style="list-style-type: none"> • Of the 382 subjects in the Safety population, 238 subjects (62.3%) experienced AEs over the course of the study, and 163 (42.7%) experienced treatment-related AEs. • During the DB Phase, 48.8% of the Double-Blind Safety population (N = 209) experienced AEs; a higher proportion of subjects on topiramate than placebo experienced AEs (55.3% vs 42.5%), and a higher proportion of subjects on topiramate than placebo experienced treatment-related AEs (24.3% vs 8.5%). Paresthesia, abdominal pain upper, hypoesthesia, and weight decreased were treatment-related events experienced by more than 1 subject and by more subjects in the topiramate than placebo treatment group. • Common AEs during the DB Phase were upper respiratory tract infection, sinusitis, and paresthesia. Events that were more common on topiramate (those that occurred at a frequency 5 percentage points greater on topiramate than on placebo) were sinusitis (8.7% vs 1.9%) and paresthesia (6.8% vs 0%). • The proportion of subjects within each treatment group that discontinued due to an AE during the DB Phase was similar (4.9% vs 3.8% on topiramate and placebo, respectively). Memory impairment, disturbance in attention, and paresthesia were common AEs that led to discontinuation over the course of the study. During the DB Phase, with the exception of the event chest pain, reported by 1 subject from each treatment group, AEs that led to discontinuation were not reported by more than 1 subject overall. • SAEs were experienced by 3.3% of subjects during the DB Phase, and by a higher proportion of subjects in the topiramate than placebo treatment group (4.9% vs 1.9%, respectively). Abortion, chest pain, and pregnancy were the only SAEs experienced by more than 1 subject over the course of the study and during the DB Phase —and by a subject within each group. The SAE of chest pain experienced by the subject in the placebo treatment group was considered treatment-related. <p>Most of the AEs observed in this study are commensurate with AE data provided in the Investigator’s Brochure and the Prescribing Information for Axert® and Topamax®.</p>		

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<u>CONCLUSION:</u> <ul style="list-style-type: none"> • The pilot trial was set up to generate plausible hypotheses and not sized for establishing a statistical or clinical hypothesis. The prior belief distributions obtained from the individual study investigators at the very outset of this study were not dominating the observed data (likelihood) and the (derived) posterior belief distributions provided a robust measure of the underlying uncertainty on various efficacy endpoints under different prior assumptions. The Bayesian and Frequentist analyses were consistent in regard to the main conclusion that there was no significant difference between the 2 treatment groups for the efficacy endpoints considered in this study. <ul style="list-style-type: none"> • This study generated estimates of response and associated variability on efficacy outcomes that may be useful in designing future studies with adequate sample size considerations. Specifically, 2 outcomes (pain relief at 2 hours and maximum intensity of a migraine associated symptom of moderate nausea) in this study lead to belief distributions with fairly high probabilities of meaningful effects. • The AE profile observed in this study was as expected for the topiramate and the placebo treated populations and was consistent with the reported data in the Investigator's Brochure and the Prescribing Information for Axert[®] and Topamax[®]. <p>Date of the report: 28 April 2008</p>		

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