SYNOPSIS

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

Protocol No.: CAPSS-381 CR002854

Title of Study: Topiramate INtervention to Prevent TRansformation of EPIsoDic Migraine: The Topiramate INTREPID Study

Principal Investigator: Multi-Center

Publication (Reference): none

Study Initiation/Completion Dates: Study initiation: 30 September 2005; Study completion: 23 August 2007	**Phase of development:** IV

Objectives: The objective of this study was to evaluate the effectiveness of topiramate in preventing a transformation from episodic migraine to chronic daily headache (CDH).

Methodology: This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study of adult subjects with episodic migraine who were experiencing frequent migraine headaches (9-14 episodes per month). Subjects were randomized in a 1:1 ratio to treatment with either topiramate 100 mg daily or matching placebo. Subjects were to record assessments of headache (HA) severity, associated symptoms, and other assessments in their HA records for all headaches. The study consisted of 3 phases: Pretreatment, Double Blind (DB) and Taper/Exit.

Pretreatment Phase
Subjects who had a minimum of 1 year well established history of migraine according to the International Headache Society (IHS) criteria (Attachment 1 of Protocol Amendment 1) and who met the entry criteria for the study were identified. The study was explained and informed consent was obtained. The Pretreatment Phase lasted up to 70 days and consisted of 2 study periods: a Screening/Washout Period (Day -70 to Day -28) and a Baseline Period (Day -28 to Day -1).

Double-Blind Phase
Subjects who completed the Baseline Period, who had the required HA frequency, and who continued to meet entry criteria were randomized in a 1:1 ratio to 1 of 2 double-blind treatment groups (topiramate 100 mg/day or matching placebo). The DB Phase lasted 26 weeks and consisted of 2 study periods: a 6-week Titration Period (where subjects followed a 4-6 week titration schedule) and a 20 week Maintenance Period. Once titrated, subjects were not go below the minimum maintenance dose of 75 mg/day.

Subjects were given the option of participating in further assessment to determine the contribution of certain genetic polymorphisms and mutations in predicting and correlating clinical and treatment outcomes. Subjects who agreed to participate had an additional blood sample drawn at Visit 3 to enable the processing of white blood cells that were stored for later deoxyribonucleic acid (DNA) extraction and analyses.

Taper/Exit Phase
All subjects exiting the study (either those discontinuing early or those completing the DB Phase) were recommended to taper from the study drug. Study drug was reduced to 2 tablets/day (topiramate 50 mg or matching placebo) for 7 days and then discontinued. Subjects returned for the final Taper/Exit Phase visit, Day 196 (Visit 10) approximately 1 week after study drug tapering was complete.

Number of Subjects (planned and analyzed): Approximately 350 subjects, were planned for randomization. A total of 385 subjects were randomized to study treatment (188 in the topiramate group and 197 in the placebo group). A total of 330 subjects (159 in the topiramate group and 171 in the placebo group) were included in the Efficacy Evaluable (EE) population. A total of 361 subjects (176 in the topiramate group and 185 in the placebo group) were included in the Evaluable for Safety population (randomized subjects who took at least 1 dose of study drug and had at least 1 safety assessment post dosing).

Diagnosis and Main Criteria for Inclusion: Subjects 18 to 65 years of age, with a history of migraine with or without aura of at least 1 year in duration conforming to IHS criteria were eligible. Subjects had to report a history of

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having at least 9, but less than 15 migraine headache (HA) days, and <15 total HA days in the 28-day period prior to screening. Subjects also had to have at least 9, but less than 15 migraine HA days, and <15 total HA days during the 28-day prospective baseline period.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate tablet 25 mg Tablet: Batch Numbers R13327 and R13401.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo Topiramate 25 mg Tablet: Batch Number R13328 and R13400.

Duration of Treatment: There were 3 phases in this study: up to a 6-week Titration Period, 20-week Treatment Period, and a 1 week Taper/Exit Period.

Criteria for Evaluation:

Efficacy:

Chronic daily headache (CDH) was defined as a condition of previous episodic migraine HA that develops gradually to 15 or more HA days (migraine or non-migraine) during a 28-day period.

The primary efficacy variable was whether a subject reported 15 or more HA days (migraine or non-migraine) per 28-day period at Month 6.

Secondary efficacy variables and health-related quality of life measurements are listed in **Table S1 Selected Key Secondary Measures**.

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Safety:
Safety evaluations included Adverse Events (AEs), brief physical examination, brief neurological examination, vital signs and clinical laboratory tests (hematology and chemistry). Urine pregnancy tests were performed on women of childbearing potential.

Statistical Methods:

- The EE population for this study was defined as randomized subjects who have received at least 1 dose of study drug, completed at least 28 days of the DB phase, and had at least 1 post-dose efficacy assessment.
- The Intent-to-Treat analysis set (ITT) was defined as randomized subjects who have received at least 1 dose of study drug and had at least 1 post-dose efficacy assessment.
- The evaluable for safety population was defined as randomized subjects who took at least 1 dose of study drug and had at least 1 safety assessment post-dosing. Summaries and analyses of safety variables were based on data from the safety analysis set. No imputation rules were used to estimate missing safety data.
- The randomized population was defined as subjects who had been assigned a medication code.

Primary Efficacy Analysis
A generalized linear mixed model (GLMM) using a logit link function was used to analyze the primary efficacy variable.

Secondary Efficacy Analysis
The secondary efficacy variable defined as the percentage of subjects who experienced CDH during the last 28 days in the DB phase was analyzed using logistic regression to assess treatment group differences.

Secondary efficacy variables involving change from baseline and percent change in the mean 28-day rate during the DB Phase were analyzed by an Analysis of Covariance (ANCOVA) methodology with treatment and center as qualitative independent factors and baseline value (of the dependent variable) as a covariate. Analysis of time to the first development of CDH and chronic migraine (CM) were assessed using Kaplan-Meier (with a log rank test for treatment group difference) and Cox's proportional hazards model with baseline HA days or migraine HA days as a covariate.

Secondary efficacy variables involving the proportion of subjects attaining specific percent category reductions of HA days or migraine HA days (i.e. those with an increase, no change, or <50% reduction, those with ≥50% to <75% reduction, those with ≥75% to <100% reduction, and those with 100% reduction) were analyzed using the Cochran-Mantel-Haenszel test with modified ridit score, stratified by center.

Changes in MIDAS and MSQ scores were analyzed using ANCOVA methodology. MIDAS score was categorized by grade level. Proportion of subjects in each MIDAS grade level at both baseline and endpoint were summarized, changes in MIDAS grade level were also analyzed using the Cochran-Mantel-Haenszel test with modified ridit score, stratified by center. Changes in absenteeism, presenteeism, and total lost productivity at work in hours from the Productivity Questions were analyzed by ANCOVA methodology. Changes in headache associated nausea, photophobia and phonophobia were also analyzed.

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Safety

The original terms used in the case report forms (CRFs) by investigators to identify AEs were coded using the World Health Organization Adverse Reaction Terminology (WHOART) dictionary. The percentage of subjects with specific treatment-emergent AEs was summarized for each treatment group. In addition, severity and relatedness to treatment was also summarized.

The concomitant medications were coded in accordance with a World Health Organization Drug Dictionary (WHODRL Version 2003, 2nd Quarter). The percent of subjects who took concomitant medication during treatment was summarized for each treatment group.

Laboratory data was summarized by type of laboratory test. Normal reference ranges and markedly abnormal results were assessed for each laboratory analyte at baseline and at each scheduled time point. A listing of subjects with markedly abnormal laboratory results was also provided.

Vital signs were summarized using descriptive statistics to evaluate the changes at each scheduled time point.

SUMMARY – CONCLUSIONS

For the EE population the 2 treatment groups were generally comparable in baseline demographic characteristics. Subjects ranged in age from 19 to 64 years, with a mean age of 40.3 years. The majority of the subjects were white (81.8 %) and the majority were female (89.1%). Height and weight were comparable between treatment groups. For BMI, the maximum in the topiramate group was 88.2 kg/m^2 while the maximum in the placebo group was 62.5 kg/m^2 however, the mean and median values were similar.

The 2 treatment groups were also comparable in baseline HA characteristics. The age of migraine onset ranged from 2 to 53 years, with a mean of 20.3 years. Migraine onset age for subject number 87006 (randomized to the placebo treatment arm) was 53 and a protocol violation of exclusion criterion #5. This violation was unplanned. The mean number of HA days per 28-day period was 13.1 days (range 3 to 26). The mean number of migraine HA days was 11.7 days per 28-day period (range 3 to 20). Thirty-three (20.8%) subjects in the topiramate group, reported migraine with aura only compared to 45 (26.3%) in the placebo group. One hundred and two (64.2%) subjects in the topiramate group reported migraine without aura compared to 90 (52.6%) in the placebo group. Reports of migraine headache intensity were comparable between the 2 treatment groups. Twenty-four subjects (15.1%) in the topiramate group reported having both migraine with aura and migraine without aura compared to 36 (21.1%) in the placebo group.

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EFFICACY RESULTS:

The primary efficacy variable was whether a subject reported 15 or more HA days (migraine or non-migraine) per 28-day period at Month 6 for the EE population. Analyses using GLMM methodology did not demonstrate a statistical difference between treatment with topiramate and treatment with placebo for this variable (1.40% vs. 2.26%, P = 0.589 for GLMM method). Following the same analysis (GLMM), using the ITT population, the results also demonstrated no statistically significant differences between treatment groups(1.42% vs. 2.14%, P = 0.649)

Secondary efficacy analyses for the EE population demonstrated reductions in the average 28-day rate of HA days and of migraine HA days from Baseline to the DB phase that were significantly greater in the topiramate treatment group than the placebo group (6.62 vs. 5.29; P=0.001 and 6.56 vs. 5.26; P = 0.001, respectively). The proportions of subjects reporting a ≥50% to <75% reduction response or a ≥75% to <100% reduction response for HA days and migraine HA days were greater in the topiramate treatment compared to the placebo treatment group (38.6% vs. 28.2% and 24.7% vs. 15.9%, respectively, for HA days; 36.1% vs. 29.0% and 29.7% vs. 19.5%, respectively, for migraine HA days.). There were statistically significant differences between treatment groups in the overall distributions of the categorical responses for both HA categories (P<0.001 and P = 0.001, respectively).

Additional results obtained from secondary efficacy variables are listed in Table S1.

Table S1: Additional Selected Secondary Efficacy Measures (Efficacy Evaluable Subjects)

	TPM	**Placebo**	***P*-Value**
The percentage of subjects who reported 15 or more HA days during the last 28 days of the DB phase for those subjects who completed at least 28 days of the DB phase	3.1%	3.5%	0.728
Time to the first reporting of 15 or more HA days per 28-day period, which was defined as the last day of the first 28-day period with 15 or more HAs by Day 182 (listed as percent of 15 or more HA days per 28-day period by Day 182)	0.1974	0.2827	0.188
Change in the average 28-day rate of HA days from Baseline Period to the DB Phase[+] (SD)	-6.62 (3.806)	-5.29 (3.606)	0.001
Change in the average 28-day rate of migraine HA days from Baseline Period to the DB Phase[+] (SD)	-6.56 (3.545)	-5.26 (3.594)	0.001
Change in the Number of Days per 28-day Period That Acute Abortive Medications Were Used [+] (SD)	-4.75 (3.545)	-3.76 (3.744)	0.001
Change in Migraine-Specific Quality-of-Life Questionnaire (MSQ) for Domain Role Function, Restrictive (SD)	29.77 (24.063)	25.41 (24.087)	0.033
Change in Migraine-Specific Quality-of-Life Questionnaire (MSQ) for Domain Role Function, Preventive (SD)	20.52 (23.984)	17.92 (21.677)	0.060
Change in Migraine-Specific Quality-of-Life Questionnaire (MSQ) for Domain Emotional Function (SD)	34.5 (32.590)	27.58 (28.293)	0.042
Change in Migraine Disability Assessment MIDAS score (SD)	-29.7 (33.05)	-22.6 (36.89)	0.011
Change in Total Lost Productivity at Work (SD)	-12.51 (12.579)	-8.87 (10.054)	0.038

Cross-Reference: End-of-Text Tables 6.1i, 6.2, 8.1, 8.2, 9, 13, 14, and 15.4.

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SAFETY RESULTS:

Eight subjects (3 in the topiramate group and 5 in the placebo group) reported a total of 9 serious adverse events (SAE). Treatment-emergent AEs were reported for 145 (82.4%) subjects in the topiramate group and 136 (73.5%) subjects in the placebo group. Treatment-related AEs were reported for 113 (64.2%) subjects in the topiramate group and 68 (36.8%) subjects in the placebo group. The most commonly reported AE for the topiramate group was paresthesia (32.4% vs. 7% of placebo subjects). Fatigue was reported by 14.8% of topiramate treated subjects and by 8.6% of placebo subjects. Thirty-nine subjects discontinued from the study due to AEs, 21 in the topiramate group and 18 in the placebo group. The most frequent AEs leading to withdrawal in the topiramate group were nausea (4.0%), fatigue (2.3%), abnormal vision (2.3%), dizziness (1.7%) and paresthesia (1.7%), myalgia (1.1%), somnolence (1.1%), nervousness (1.1%), and agitation (1.1%). Mydriasis was not an expected AE for topiramate per US product package labeling. No subjects in the placebo group reported mydriasis as an AE.

No clinically relevant differences between the 2 treatment groups in mean vital signs or clinical laboratory test results were observed.

CONCLUSIONS:

In this study, topiramate treatment did not demonstrate effectiveness in preventing a transformation from episodic migraine to CDH in subjects with a baseline frequency of 9-14 migraine HA days per month, which was believed to be a risk factor for the progression of migraine headache patterns. Topiramate treatment did reduce the number of monthly HA days and monthly migraine HA days in this population of subjects with high frequency episodic migraines. Topiramate treatment was associated with a greater chance to achieve at least a 50% reduction in the number of days with HA or migraine HA. In addition, topiramate treatment was associated with improvements in some measures of migraine-related quality of life and productivity. Overall, topiramate treatment was found to be safe and generally well tolerated for migraine prophylaxis in this group of subjects.

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