SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho-McNeil Neurologics, Inc. **NAME OF FINISHED PRODUCT:** TOPAMAX® (topiramate) tablets **NAME OF ACTIVE INGREDIENT(S):** 2, 3:4, 5-Di-O-isopropylidene-β-D-fructopyranose sulfamate	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**

Protocol No.: CAPSS-276

Title of Study: A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Chronic Migraine

Clinical Trial Director: Steven J. Greenberg, MD – Ortho-McNeil Neurologics, Inc. – Titusville, NJ; USA

Publication (Reference): none

Study Initiation/Completion Dates: 30 September 2003 to 21 March 2005	**Phase of development:** III

Objective: The objective of this study was to evaluate the efficacy and safety of topiramate (100 mg/day) compared to placebo for the treatment of chronic migraine.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study conducted in the United States investigating the efficacy and safety of topiramate versus placebo for the treatment of chronic migraine. The study consisted of 3 phases: A Pretreatment Phase lasting up to 56 days (Screening plus Prospective Baseline Period), a Double-Blind Phase lasting 16 weeks, and a Taper/Exit Phase that lasted up to 2 weeks. Only data collected through the end of the Double-Blind phase are included in this report.

Eligibility was determined during the Pretreatment Phase, which included a screening/washout period (Day –56 to Day –29) and a 28-day Prospective Baseline Period (Day –28 to Day 0). Prophylactic migraine medication was discontinued during the Screening/Washout Period. Subjects recorded daily entries in their headache record to capture occurrence of headaches, duration of headache(s), headache severity (average and maximum headache intensity), presence/absence of headache-associated symptoms and level of severity of headache-associated symptoms, and use of acute abortive medication. In addition, a disability assessment and a health-related quality of life instrument, including the Migraine Disability Assessment (MIDAS) and the Migraine-Specific Quality of Life Questionnaire (MSQ) were completed at various time points during the study. Physician's and Subject's Global Impression of Change (PGIC and SGIC), were completed at the final visit of the Maintenance Period.

Subject eligibility to proceed to randomization was determined based on the number of migraine headache days over the 28-day Prospective Baseline Period. Upon completion of the 28-day prospective baseline period [Visit 3, (Day 1)], subjects that had ≥ 15 headache days, on at least half of which they experienced migraine or migrainous headaches, were randomized. A total of 328 subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups (165 subjects in the topiramate group and 163 subjects in the placebo group).

The Double-Blind Phase was divided into 2 periods: titration (4 weeks) and maintenance (12 weeks). Study visits occurred twice during the titration (Days 1 and 28) and monthly during maintenance periods (Days 56, 84, and 112), and telephone contacts occurred weekly during the titration period to ensure the study medication was being titrated properly and daily headache records were being completed.

The initial dose of topiramate 25 mg/day (or placebo) was titrated upwards in weekly increments of 25 mg/day (or matching placebo) until a dose of 100 mg/day of topiramate (or matching placebo) or the subject's maximum tolerated dose (MTD) was achieved.

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Methodology continued: During the Maintenance Phase, subjects were to maintain a dose of at least 50 mg/day. Subjects were considered to have completed the Double-Blind Phase if they completed all 16 weeks of double-blind treatment (i.e., 4 weeks of titration and 12 weeks of maintenance without prematurely discontinuing study medication). Subjects who completed the Double-Blind Phase, or who discontinued the Double-Blind Phase due to lack of efficacy after completing at least 4 weeks of maintenance treatment, were given an opportunity to enroll in an Open-Label (OL) Extension Study (CAPSS 295). Subjects who elected not to enter the OL Extension study were advised to taper study medication according to the investigator's direction, and the length of taper may have varied according to the dose the subject achieved. Subjects were evaluated within 2 weeks after study medication tapering was complete. Subjects who elected to enter the OL extension study, tapered double-blind medication while they simultaneously titrated the OL medication and returned for their first OL extension study visit.

Number of Subjects (planned and analyzed): Approximately 300 subjects were planned; a total of 328 subjects were randomized (165 in the topiramate group and 163 in the placebo group). A total of 306 subjects (153 topiramate and 153 placebo) were included in the intent-to-treat (ITT) population. A total of 321 subjects (160 topiramate and 161 placebo) were included in the evaluable-for-safety population.

Diagnosis and Main Criteria for Inclusion: To be eligible to enroll in this study subjects must have been adults, 18 years of age or older, with an established diagnosis of chronic migraine according to the Lipton/Silberstein proposed criteria. In the month prior to screening, subjects must have had ≥ 15 headache days per month (a headache day was defined as a calendar day during which a subject experienced headache pain of at least 30 minutes duration). During the Prospective Baseline Period, subjects must have had ≥ 15 headache days during a 28-day period, on at least half of which they experienced migraine or migrainous headaches ≥ 30 minutes in duration. A migraine headache was defined according to the International Headache Society (IHS) criteria (other than duration). The definition of a migrainous headache was a headache of moderate to severe intensity, with 1 or more of the following migrainous features: unilateral or pain worse on 1 side of the head; pulsatile; associated with photophobia and/or phonophobia; associated with nausea and/or vomiting; pain made worse by physical activity. Subjects were excluded from the study if they had previously failed more than 2 adequate trials of migraine prophylactic medications defined as a trial of at least 3 months duration at an adequate dose of medication, had daily or almost daily (> 4 days per week) use of acute pain medications, or were taking a migraine preventive medication.

Test Product, Dose, and Mode of Administration, Batch No.: Tablets containing 25 mg of topiramate (batch numbers D00LM0570 [expiration 11/2004] and D03LK1143 [expiration 09/2007]) were orally administered once or twice daily depending on dosage.

Duration of Treatment: The Pretreatment Phase lasted up to 56 days and consisted of 2 study periods: a Screening/Washout Period (Day -56 to Day -29) and a Prospective Baseline Period (Day –28 to Day 0). The Double-Blind Phase was 16 weeks in duration and consisted of 2 study periods: a Titration Period (4 weeks) and a Maintenance Period (12 weeks).

Reference Therapy, Dose, and Mode of Administration, Batch No.: Study medication, consisting of matching placebo in identically appearing tablets, (batch numbers D00LF0452 [expiration 11/2004] and D03LK1145 [expiration 09/2007]) was orally administered once or twice daily depending on dosage.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change in the mean number of days per month with migraine/migrainous headache over the entire Double-Blind Phase relative to the Prospective Baseline Period. The second key efficacy variable was the change in the mean number of days per month with migraine headache over the entire Double-Blind Phase relative to the Prospective Baseline Period. Additional secondary variables included change in average daily headache severity and worst daily headache severity, change in the average monthly (28-day) rate of headache days, the proportion of subjects who were responders for migraine/migrainous and total headache days (e.g., subjects with a ≥ 50% reduction in mean monthly number of migraine/migrainous and total headache days), cumulative reduction in migraine/migrainous and total headache days, reduction in the use of acute abortive medications, reduction in associated symptoms of photophobia, phonophobia, nausea, and change in headache-free days. Other secondary variables included disability assessments, quality of life assessments and physician's and subject's global impressions of change. Post hoc analyses of the percent responders (≥ 25%, ≥ 30%, ≥ 40%, ≥ 50%, and ≥ 75% reduction) between treatment groups in the percent change from baseline in the mean number of days per month with migraine/migrainous headaches were performed.

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

Statistical Methods:

The primary analysis population was the ITT, which included all randomized subjects who received at least 1 dose of study medication and who provided at least 1 post-randomization efficacy evaluation.

The evaluable-for-safety population was defined as all randomized subjects who took study medication and had safety information post-dosing.

Analysis Methods for the Primary and the Second Key Efficacy Parameters

The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment and center as qualitative independent factors and baseline monthly rate of migraine/migrainous headache days as a covariate. All analyses prospectively planned in the protocol were carried out as planned. In addition to the analysis of the primary efficacy variable (change from baseline in the average number of days per month with migraine/migrainous headache) as specified in the Statistical Analysis Plan, a fixed sequence step-down approach (i.e., a gatekeeper approach) was also used to further assess the second key endpoint (change from baseline in the mean number of days per month with migraine headache). The first step involved assessing the change in the mean number of days per month with migraine/migrainous headache at the 0.05 level of significance. If significance was achieved, then the change in the mean monthly rate of migraine days was tested at the 0.05 level. If significance was again achieved, then statistical significance was declared at the 0.05 level for both parameters. If significance on the migraine/migrainous parameter was not achieved then the formal testing procedure came to an end. Testing could still have been done on the migraine days parameter, but no unqualified statements about statistical significance could have been posited.

SYNOPSIS (CONTINUED)

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Analysis Methods for the Primary and the Second Key Efficacy Parameters continued

Secondary efficacy variables were analyzed using an ANCOVA with treatment and center as qualitative independent factors and baseline value as a covariate. Longitudinal analyses on the monthly migraine/migrainous days and other secondary efficacy variables, noted above, over time were also performed. Categorical responder rates and the PGIC and SGIC were analyzed using the Cochran-Mantel-Haenszel Test. Cumulative reductions in migraine/migrainous and total headache days were plotted. Change in severity of associated migraine/migrainous symptoms, that included photophobia, phonophobia, and nausea were analyzed using ANCOVA models. The changes from baseline to the final evaluation in scores on each MSQ domain were analyzed separately using the ANCOVA model. Similar analyses were performed on the MIDAS. All statistical tests were conducted at the 2-sided 5% significance level.

A post-hoc (i.e., after the blind was broken) analysis using Cochran-Mantel-Haenszel methodology was done to assess between-treatment group differences in percent responders (25%, 30%, 40%, 50%, and 75% reduction from baseline in mean monthly days per month with migraine/migrainous headache).

SUMMARY – CONCLUSIONS

The ITT population consisted of subjects who were White (82.4% topiramate and 78.4% placebo), Black (12.4% topiramate and 17.0% placebo), Asian (0.7% topiramate and 1.3% placebo), and other (4.6% topiramate and 3.3% placebo). Higher proportions of subjects were female (83.7% topiramate and 86.9% placebo) than male (16.3% topiramate and 13.1% placebo). Ages of subjects in the topiramate group ranged from 18 to 64 years, with a mean age of 37.8 years; subjects in the placebo group ranged from 18 to 74 years, with a mean age of 38.6 years.

Mean baseline headache characteristics were similar for the 2 treatment groups for age at migraine onset (19.0 years topiramate and 20.4 years placebo), duration of chronic daily headache in years (9.31 years topiramate and 9.13 years placebo), and monthly migraine/migrainous headache days (17.1 days topiramate and 17.0 days placebo).

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Efficacy Results: Treatment with topiramate resulted in a mean reduction of 6.4 migraine/migrainous headache days relative to baseline compared to a reduction of 4.7 days for placebo ($p = 0.010$). The mean percent reduction from baseline in migraine/migrainous headache days was 37.1% for topiramate compared to 26.0% for placebo ($p = 0.012$). Half of the subjects treated with topiramate achieved a $\geq$ 41.2% reduction in migraine/migrainous days relative to baseline compared to the placebo-treated subjects who achieved a $\geq$ 28.8% reduction.

Since the primary efficacy outcome reached statistical significance, using the gatekeeper approach, we were able to make an inference about the second key parameter (decrease in migraine days) while controlling the overall type 1 error rate at 5%. For this parameter, treatment with topiramate resulted in a mean reduction of 5.6 migraine headache days relative to baseline (4.1 reduction in placebo) and was statistically significantly different from the placebo group ($p = 0.032$). The mean reduction in migraine days represented a 32.9% change from baseline (25.2% change for placebo) ($p = 0.152$).

The proportions of categorical responders were higher in the topiramate group compared to the placebo group. This was true for the pre-specified $\geq$ 50% responder rate (37% versus 29%, $p = 0.093$), and for the $\geq$ 25% responder rate (69% versus 52%, $p = 0.005$) and for the $\geq$ 75% responder rate (15% versus 9%, $p = 0.061$). Please note that the aforementioned p-values were computed post-hoc. Additional post-hoc analyses revealed that treatment with topiramate compared to treatment with placebo was higher for the $\geq$ 30% responder rate (63% versus 48%, $p = 0.012$) and for the $\geq$ 40% responder rate (52% versus 39%, $p = 0.031$).

The mean average daily dose of study medication during the Double-Blind Phase was 74.6 mg for subjects in the topiramate group and 75.5 mg equivalent for subjects in the placebo group. The mean average daily dose of study medication during the Maintenance Period was 88.2 mg for subjects in the topiramate group and 89.6 mg equivalent for subjects in the placebo group.

In addition, topiramate treatment compared to placebo resulted in a statistically significant improvement in the Role Function-Restrictive (mean change = 23.7 versus 18.8, respectively; $p = 0.028$) and Emotional Function (mean change = 26.3 versus 21.0, respectively; $p = 0.036$) domains, and approached statistical significance for Role Function-Preventive (mean change = 16.1 versus 12.6, respectively; $p = 0.061$) domain of MSQ.

Safety Results: The most commonly reported AEs in the topiramate group were paraesthesia (28.8%), upper respiratory tract infection (13.8%), and fatigue (11.9%). The most commonly reported AEs for the placebo group were upper respiratory tract infection (12.4%), fatigue (9.9%), and nausea (8.1%). Treatment-emergent AEs were reported for 132 (82.5%) subjects in the topiramate group and 113 (70.2%) subjects in the placebo group. Treatment-related AEs were reported for 104 (65.0%) subjects in the topiramate group compared to 69 (42.9%) subjects in the placebo group. A higher percentage of subjects in the topiramate group than in the placebo group withdrew from the study due to AEs: 18 (11.3%) subjects treated with topiramate and 10 (6.2%) subjects treated with placebo. The most frequent AEs leading to withdrawal in the topiramate group were paraesthesia (1.9%), anxiety (1.9%), confusion (1.9%), and difficulty with concentration/attention (1.9%). Other AEs leading to withdrawal from the study were reported for $\leq$ 2 subjects in the topiramate group and no more than 1 subject in the placebo group. There were no clinically relevant differences between the 2 treatment groups with regard to vital sign assessments and clinical laboratory test results.

CONCLUSIONS: Topiramate treatment in subjects with chronic migraine, who experienced $\geq$ 15 headache days, half of which were characterized by migraine/migrainous headaches, was effective in reducing migraine/migrainous headache days and in reducing migraine headache days. Topiramate was safe, there were no SAEs reported and topiramate was generally well tolerated.

Date of the report: 05 January 2007

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