CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS USRA-8619242:3.0

Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, LLC.	
Name of Finished Product	TOPAMAX® (topiramate) tablets	
Name of Active Ingredient(s)	2, 3:4, 5-Di-O-isopropylidene-β-D-fructopyranose sulfamate	

Protocol No.: CAPSS-295 (CR004672)

Title of Study: An Open-Label Study of the Safety and Efficacy of Topiramate for the Prophylaxis of Chronic Migraine: Extension Study to CAPSS-276

Principal Investigator: Multicenter, 41 sites

Publication (Reference): None

Study Period: 02 February 2004 to 22 July 2005 | **Phase of Development:** III

Objectives: The objective of this open-label (OL) study was to evaluate the long-term safety and efficacy of topiramate in prophylaxis of chronic migraine.

Methodology: This was a multicenter open-label extension (OLE) study where subjects with chronic migraine who either successfully completed the Double-Blind protocol study, CAPSS-276 (A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Chronic Migraine), or who discontinued study medication after completing at least 4 weeks of maintenance treatment due to lack of efficacy were enrolled. The study consisted of 3 phases: Blinded Transition, OL Maintenance and Taper/Exit. The duration of the study was approximately 4 months. Subjects enrolled in this study at the final double-blind visit in study CAPSS-276, after final visit procedures were completed for that study. During the 4-week Blinded Transition Phase subjects tapered blinded study medication while simultaneously titrating OL topiramate upward (starting with 25 mg/day and increasing each week in increments of 25 mg/day). Subjects were titrated to 100 mg/day of topiramate, or their maximum tolerated dose (MTD), whichever was less. Following the Blinded Transition Phase, subjects were entered into the 12-week (84-day) OL Maintenance Phase. During the OL Maintenance Phase, the dose of OL topiramate may have been adjusted based on efficacy and tolerability. The total daily dose was not to exceed 400 mg/day.

Subjects recorded daily entries in their headache record to capture occurrence of headaches, duration of headache(s), headache severity (average and worst headache intensity), presence/absence and level of severity of headache associated symptoms, and use of acute abortive medication. In addition, a disability and health-related quality of life assessments, 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.

Number of Subjects (planned and analyzed): A total of 200 subjects entered the OLE study (98 in the TPM/TPM group [subjects randomized to topiramate during the Double-Blind Study CAPSS-276, entered this OLE study, and received at least 1 dose of OL topiramate tablet] and 102 in the PBO/TPM group [subjects randomized to placebo during the Double-Blind Study CAPSS-276, entered this OLE study, and received at least 1 dose of OL topiramate tablet]). A total of 196 subjects (94 TPM/TPM and 102 PBO/TPM) were included in the efficacy population (subjects who received at least 1 dose of OL topiramate and provided at least 1 efficacy evaluation after the first OL dose). A total of 197 subjects (95 TPM/TPM and 102 PBO/TPM) were included in the evaluable for safety population (subjects who took at least 1 dose of OL topiramate and had safety information after the first OL dose).

Diagnosis and Main Criteria for Inclusion: Subjects who successfully completed the Double-Blind Phase of the protocol (CAPSS-276) or discontinued the Double-Blind Phase after a minimum of 4 weeks of maintenance treatment due to lack of efficacy were entered into this OLE study.

Test Product, Dose and Mode of Administration, Batch No.: Study medication consisting of topiramate 25 mg tablets, (Batch numbers D00LM0570 [expiration 11/2004] and D03LK1143 [expiration 09/2007]) was orally administered once or twice a day depending on the dosage during the Blinded Transition Phase only. Tablets containing 25 mg of topiramate (batch number D03LK1124 [expiration 31 July 2005]) were orally administered once or twice daily depending on dosage during the Open-label Maintenance and Taper Phases.

Reference Therapy, Dose and Mode of Administration, Batch No.: Study medication, consisting of matching

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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 during the Blinded Transition Phase only.

Duration of Treatment: The Blinded Transition Phase lasted up to 4 weeks, the Maintenance Phase lasted 12 weeks, and the Taper/Exit Phase lasted up to 2 weeks. The entire planned duration of the OLE study was approximately 4 months.

Criteria for Evaluation:

Efficacy: The primary efficacy outcome was the change in the mean number of migraine/migrainous headache days per month over the entire OL Maintenance Phase relative to the Prospective Baseline Period for the efficacy population. Secondary variables included change in headache index days, average daily headache severity and worst daily headache severity, change in the mean monthly (28-day) rate of migraine and 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 frequency for unilateral pain, pulsatile pain, and worsened pain due to physical activity along with 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. Subjects recorded daily entries in their headache record to capture occurrence, duration of headache(s), headache severity (average and worst), as well as headache associated symptoms and use of acute abortive medication. In addition, quality of life instruments, 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 OL Visit 1 and the final visit.

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

Statistical Methods: The efficacy analysis population included all subjects who received at least 1 dose of OL topiramate during the OLE study and provided at least 1 efficacy evaluation after first OL dose.

Analysis Methods for the Primary Efficacy

The primary efficacy variable was the change in the average number of days per month with migraine/migrainous headache over the entire OL Maintenance Phase relative to the Prospective Baseline Period for subjects who were randomized to topiramate in the Double-Blind study. For subjects who were randomized to placebo, change was relative to the last 28 days prior to the first dose of OL topiramate. Descriptive statistics were used to summarize both the absolute change and percent change from baseline. The monthly summary statistics during the OLE study were combined with the results from the Double-Blind Phase to assess the long-term efficacy of topiramate use.

Absolute change and percent change in the headache index relative to the baseline in Double-Blind study CAPSS-276 were presented by descriptive statistics. Change in daily headache severity and worst daily headache severity, change in the average monthly (28-day) rate of migraine and headache days, change of average severity of migraine/migrainous associated symptoms (photophobia, phonophobia and nausea), change in monthly headache-free days, and change in monthly acute abortive medication days were presented by descriptive statistics using the same approach.

Physician's and subject's global impression of change were presented as frequency distributions. The changes from baseline to the final evaluations in each MSQ domain score (Role-Restrictive, Role-Preventive and Emotional-Function) were summarized using descriptive statistics along with the changes from baseline to the final evaluations in MIDAS scores.

Safety: Safety evaluations included AEs, clinical laboratory tests, vital signs, and urine pregnancy tests performed on women of childbearing potential.

SUMMARY - CONCLUSIONS

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The efficacy population consisted of 196 subjects ranging in age from 18 to 64 years, with a mean age of 38.8 years. The majority of the subjects were white (80.6%) and female (85.7%). The age of migraine onset ranged from 5 to 50 years with a mean of 19.9 years. The mean duration of chronic daily headache was 8.7 years (range was 0.2 to 50.0 years).

Efficacy Results: A decrease in the mean number of migraine/migrainous days per month was 10.7 in the TPM/TPM group, while in the PBO/TPM group a decrease of 3.3 was seen following topiramate treatment. Overall, treatment with topiramate resulted in a mean decrease of 6.9 migraine/migrainous days per month.

For the secondary efficacy variables, overall, treatment with topiramate (TPM/TPM and PBO/TPM) resulted in mean decreases in headache index days, average daily headache severity, worst daily headache severity, migraine days, total headache days, the number of days per month of acute abortive medication use, severity of headache associated symptoms (nausea, photophobia and phonophobia), frequency of monthly headache associated symptoms, (nausea, vomiting, photophobia, phonophobia), unilateral pain frequency, pulsatile pain frequency, and the frequency for worsened pain due to physical activity. In addition, an increase in the mean number of headache free days was also observed.

Overall, topiramate treatment showed that the proportion of categorical responses based on monthly migraine/migrainous days was 49.4% for the $\geq$ 50% reduction, 31.2% for the $\geq$ 75% reduction, and 4.7% for the 100% reduction. Similar results were observed for the proportion of categorical responses based on monthly migraine days (49.7%, 30.3%, and 6.7% respectively) and total headache days (45.1%, 23.1%, and 3.5% respectively).

In addition, the mean change scores from baseline for the MSQ in the TPM/TPM group were 34.0, 24.1, and 39.3 for Role Function-Restrictive, Role Function-Preventive, and Emotional Function, respectively and 12.6, 8.4, and 14.4, respectively in the PBO/TPM group. Mean decreases from baseline in the MIDAS scores in the TPM/TPM group were 45.7 and 12.7 in the PBO/TPM group. Improvement was demonstrated by the reduction in overall mean score of 28.6 with topiramate treatment.

Overall, subjects in the PBO/TPM exhibited improvement in the primary and secondary efficacy variables when treated with topiramate in this OLE study. Subjects in the TPM/TPM group demonstrated continued benefit from topiramate treatment. The difference in mean numbers may be attributed to the difference in respective baselines for the 2 treatment groups since for subjects randomized to placebo, change was relative to the last 28 days prior to the first dose of OL topiramate.

Safety Results: Treatment with topiramate for migraine prophylaxis was generally safe and the incidence and type of adverse events observed are consistent with topiramate's safety profile. A total of 150 (76.1%) subjects treated with topiramate experienced AEs: 66 (69.5%) subjects in the TPM/TPM group and 84 (82.4%) subjects in the PBO/TPM group. A total of 115 (58.4%) subjects experienced treatment-related AEs: 47 (49.5%) subjects in the TPM/TPM group and 68 (66.7%) subjects in the PBO/TPM group. A lower percentage of subjects in the TPM/TPM group than subjects in the PBO/TPM group withdrew from the study due to AEs: 4 (4.2%) subjects treated with TPM/TPM and 16 (15.7%) subjects with PBO/TPM in the evaluable for safety population. The most frequent AEs leading to withdrawal in the TPM/TPM group were difficulty with memory NOS (2.1%), and fatigue, bacterial infection, and dyspepsia (each 1.1%). The most frequent AEs leading to withdrawal in the PBO/TPM group were fatigue (3.9%) and dizziness, language problems, paraesthesia, anorexia, confusion, and depression (each 2.9%). The most commonly reported AEs in the TPM/TPM group were paraesthesia (23.2%), fatigue (13.7%), and upper respiratory tract infection (9.5%). The most commonly reported AEs for the PBO/TPM group were paraesthesia (35.3%), fatigue (14.7%), and dizziness (8.8%). During the total topiramate exposure period (Double Blind and OLE), similar results were observed in the total TPM group, (paraesthesia, 34.0%, fatigue, 15.3%, and upper respiratory tract infection, 13.0%). A total of 5 subjects experienced SAEs: 2 in the TPM/TPM group and 3 in the PBO/TPM group with 1 of them possibly related to study treatment (PBO/TPM group). No deaths were reported during the study or within 30 days of study completion. No clinically relevant differences between the 2 treatment groups following topiramate treatment in mean vital signs and clinical laboratory test results were observed.

CONCLUSION: In subjects with chronic migraine, the long-term efficacy data in this OLE study indicated that topiramate continued to be effective in migraine prophylaxis. Subjects in the PBO/TPM group exhibited overall improvement when treated with topiramate, while subjects in the TPM/TPM group demonstrated continued

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benefit from topiramate treatment.

Compared with the known safety profile of topiramate, there was no unusual or unexpected safety concerns with long-term treatment in the migraine population in this study.

Issue Date of the Clinical Study Report: 13 February 2008

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