SYNOPSIS

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-296

Title of Study: An Open-Label Study of the Safety and Efficacy of Topiramate for Migraine Prophylaxis: Extension Study to CAPSS-277

Principal Investigator: Multicenter, 25 sites.

Publication (Reference): None

Study Period: 23 September 2004 to 27 January 2006 | **Phase of Development:** IIIB

Objectives: The objective of this open-label extension (OLE) study was to evaluate the long-term safety and efficacy of topiramate for the prophylaxis of migraine headache.

Methodology: This was a multicenter, open-label (OL) study investigating the efficacy and safety of topiramate for the prophylaxis of migraine headache. This study consisted of 3 phases. A Blinded Transition Phase lasting up to 28 days, an OL Maintenance Phase lasting up to 84 days, and a Taper/Exit Phase lasting up to 14 days. Subjects who successfully completed the CAPSS-277 (A Comparison of Topiramate Versus Amitriptyline in Migraine Prophylaxis) double-blind protocol were eligible to enter the 4-month CAPSS-296 OLE study.

At the final maintenance visit of Study CAPSS-277 (Visit 8) subjects decided if they wanted to participate in the OLE study. Open-label Visit 1 of the CAPSS296 study occurred on the same day as the final maintenance visit (Double-Blind Visit 8) of the CAPSS-277 study. During this 4 week Blinded Transition Phase, study visits occurred on Day 1 (OL Visit 1) and Day 28 (OL Visit 2). Subjects were tapered from double-blind study medication in a blinded fashion while simultaneously titrating upward on OL topiramate. All subjects had the same titration schedule with a starting dose of 25 mg/day of OL topiramate for 7 days, followed by dose increases of 25 mg/week while simultaneously tapering their double-blind medication by 25 mg/week.

During the Blinded Transition Phase subjects titrated the study medication until they reached 100 mg/day of topiramate, or their maximum tolerated dose (MTD), whichever was less. By OL Visit 2 (Day 28), all subjects could no longer be taking any double-blind study medication. On OL Day 14, study sites contacted subjects by telephone to verify appropriate taper/titration of study medication.

Following the Blinded Transition Phase, subjects entered 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. Clinic visits occurred on Day 56 (OL Visit 3) and on Day 112 (OL Visit 4), the final visit for the OL Maintenance Phase. The total daily dose of topiramate was not to exceed 400 mg/day. In the event a subject discontinued prematurely, final visit procedures (OL Visit 4 [Day 112]) were performed at the time of discontinuation.

It was recommended that all subjects exiting the study taper from study medication. The length of the taper was at the investigator's discretion and varied according to the dose the subject achieved. Subjects were evaluated approximately 2 weeks after study medication tapering was complete. This was at the final Taper/Exit visit, OL Visit 5 (Day 126).

Number of Subjects (planned and analyzed): A total of 142 subjects (74 subjects in the TPM/TPM group and 68 subjects in the AMI/TPM group) entered this OLE study. The TPM/TPM group of subjects consisted of those randomized to topiramate during the Double-Blind Study CAPSS-277, and who received at least 1 dose of OL topiramate tablet. The AMI/TPM group consisted of subjects randomized to amitriptyline during the Double-Blind Study CAPSS-277, entered this OLE study, and who received at least 1 dose of OL topiramate tablet. A total of 138 subjects were included in the efficacy population. A total of 140 subjects 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 history of migraine, with or without aura, conforming to the International Headache Society (IHS) criteria, and must have successfully completed the CAPSS 277 study. Subjects were excluded from the study if they had a more painful condition than their headache pain, took any of the prohibited concomitant medications/therapies listed in the protocol, had a history of liver function tests ≥ 2 times the upper limit of the normal range or had history of poor compliance during the CAPSS 277 study, as judged by the investigator.

Test Product, Dose and Mode of Administration, Batch No.: Study medication consisting of topiramate 25 mg capsules or placebo (Batch numbers R12383 and R12420, [expiration 10/2004], R12792 [re-label, expiration 03/2005] and R13087 and R13088 [expiration 02/2006]) 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 R12399 [expiration 09/2005] and batch number R13503 [expiration 04/2007]) 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.: Identically-appearing study medication, consisting of matching amitriptyline 25 mg or placebo (batch numbers R12384 and R12421 [expiration 10/2004], R12792 [re-label, expiration 03/2005] and R13089 and R13090 [expiration 02/2006]) was orally administered once or twice daily depending on dosage during the Blinded Transition Phase only.

Duration of Treatment: The OL Phase lasted approximately 16 weeks and consisted of 3 study periods: a Blinded Transition Phase, the OL Maintenance Period, and the Taper/Exit Period.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change from baseline in the mean monthly (28-day) migraine episode rate over the last 28 days prior to tapering of OL topiramate. Baseline was defined as the mean monthly migraine episode rate over the last 28 days prior to the date of the first dose of OL topiramate. The secondary efficacy variables included the change in the mean monthly (28-day) rate of days with migraine headache, change in the mean monthly (28-day) rate of headache (migraine and non-migraine) days, change in the average monthly (28-day) rate of acute abortive medication use, change in the average monthly (28-day) migraine duration, change in the average migraine severity, change in average severity of functional disability from Baseline to the last 28 days prior to tapering of the OL Phase, and change in the average severity of migraine associated symptoms of photophobia, phonophobia, and nausea. Other variables included disability assessments, quality of life assessments and weight satisfaction assessments.

Safety: Safety evaluations included adverse events (AE), brief physical examination, vital signs measurements, body mass index (BMI) and weight measurements, electrocardiogram (ECG) evaluations, 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 efficacy population, which included all subjects who received at least 1 dose of OL topiramate and who provided at least 1 efficacy evaluation after the first OL dose.

The evaluable for safety population was defined as all subjects who received at least 1 dose of OL topiramate and had safety information after the first OL dose.

Analysis Methods for the Primary and the Secondary Efficacy Parameters

For the analysis of subjects who entered the OLE study, 2 analysis groups, TPM/TPM and AMI/TPM were introduced. The TPM/TPM analysis group included all subjects formally randomized to topiramate during the Double-Blind study CAPSS-277, entered the OLE study and received at least 1 dose of OL topiramate tablet. The AMI/TPM analysis group included all subjects formerly randomized to amitriptyline during the Double-Blind study CAPSS-277, entered the OLE study and received at least 1 dose of OL topiramate tablet. The total group was the combination of TPM/TPM and AMI/TPM groups and included subjects in both groups who received at least 1 dose of OL topiramate tablets.

No formal testing was performed for the difference in these 2 groups. However, test for the change from baseline in the mean monthly (28-day) migraine episode rate over the last 28 days prior to tapering of the OL was performed within each treatment group using a paired t-test. Similar testing was done for the change from baseline in the mean monthly (28-day) rate of migraine days and change from baseline in the mean monthly (28-day) rate of total headaches.

This study was an OLE to a previous study, CAPSS-277, therefore no additional sample size calculation was performed.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: The primary efficacy variable was the change from baseline in the mean monthly (28-day) migraine episode rate over the last 28 days prior to tapering of OL topiramate. Baseline was defined as the mean monthly migraine episode rate over the last 28 days prior to the date of the first dose of OL topiramate. Mean changes in the mean migraine episode rate per month were 0.1 in the TPM/TPM group and –0.5 in the AMI/TPM group (p=0.750 and p=0.084, respectively). Overall, treatment with topiramate resulted in a mean reduction of 0.2 in the average monthly migraine episode rate.

The secondary efficacy outcomes are summarized in the following table:

Summary of Secondary Efficacy Variables (ITT Population)

	TPM/TPM N=71	**AMI/TPM N=67**	**Total N=138**
	Change from baseline (SD)		
Mean monthly (28-day) rate of			
Migraine days	0.0 ± 2.62	-0.5 ± 2.40	-0.3 ± 2.52
Total headache days	-0.3 ± 2.69	-0.6 ± 2.83	-0.4 ± 2.75
Acute abortive medication use	-0.1 ± 2.01	-0.6 ± 2.32	-0.3 ± 2.18
Mean Average migraine duration	-0.1 ± 1.47	-0.1 ± 1.36	-0.1 ± 1.41
Mean Average migraine severity	0.0 ± 0.50	-0.2 ± 0.56	-0.1 ± 0.53
Mean Average severity of			
Nausea	0.0 ± 0.66	-0.1 ± 0.67	0.0 ± 0.66
Photophobia	0.1 ± 0.63	-0.2 ± 0.70	0.0 ± 0.68
Phonophobia	0.1 ± 0.67	-0.2 ± 0.76	0.0 ± 0.72
Functional disability	0.0 ± 0.61	-0.1 ± 0.69	-0.1 ± 0.65
Mean Monthly (28-day) rate of:			
Nausea	0.2 ± 1.95	-0.5 ± 2.07	-0.2 ± 2.03
Vomiting	0.0 ± 1.05	-0.2 ± 0.84	-0.1 ± 0.96
Photophobia	0.1 ± 2.36	-0.5 ± 2.40	-0.2 ± 2.39
Phonophobia	0.1 ± 2.33	-0.6 ± 2.14	-0.2 ± 2.26
One-sided pain	0.0 ± 2.15	-0.3 ± 2.06	-0.1 ± 2.11
Throbbing pain	0.0 ± 2.41	-0.5 ± 2.16	-0.3 ± 2.30
Pain increase w/physical activity	0.1 ± 2.29	-0.2 ± 2.16	-0.1 ± 2.23
Response rates based on monthly:			
Migraine days			
≥50% reduction	21 (38.9%)	20 (39.2%)	41 (39.0%)
≥75% reduction	13 (24.1%)	13 (25.5%)	21 (24.8%)
100% reduction	11 (20.4%)	12 (23.5%)	21 (21.9%)
Migraine episodes			
≥50% reduction	19 (35.2%)	23 (45.1%)	42 (40.0%)
≥75% reduction	12 (22.2%)	13 (25.5%)	25 (23.8%)
100% reduction	11 (20.4%)	12 (23.5%)	23 (21.9%)
Headache days			
≥50% reduction	21 (38.9%)	20 (39.2%)	41 (39.0%)
≥75% reduction	13 (24.1%)	13 (25.5%)	26 (24.8%)
100% reduction	11 (20.4%)	12 (23.5%)	23 (21.9%)
Quality of Life scores (SD):	Change from baseline (SD)		
MIDAS	-1.8 ± 11.86	-0.6 ± 14.11	-1.2 ± 12.96
MSQ			
Role function-restrictive*	0.1 ± 12.56	6.6 ± 20.16	3.2 ± 16.88
Role function-preventive*	-0.1 ± 11.30	3.5 ± 18.48	1.6 ± 15.20
Emotional function*	0.0 ± 15.88	3.5 ± 13.48	1.7 ± 14.83
Q-LES-Q-SF overall score*	0.3 ± 9.56	1.8 ± 9.92	1.0 ± 9.73
Weight satisfaction score*	0.1 ± 1.09	1.4 ± 1.90	0.8 ± 1.66

SD=standard deviation; Min=minimum; Max=maximum; OL = open-label; TPM =

topiramate; AMI = amitriptyline. MIDAS= Migraine Disability Assessment, MSQ = Migraine Specific Quality of Life Questionnaire, Q-LES-Q-SF = Quality of Life Enjoyment & Satisfaction Questionnaire-Short
* Increase from baseline indicates improvement

Overall, subjects in both groups demonstrated sustained benefit from topiramate treatment for migraine prophylaxis. On average, subjects in the AMI/TPM group experienced sustained migraine preventive efficacy after transitioning from amitriptyline to topiramate treatment in this OLE study and subjects in the TPM/TPM group experienced sustained efficacy with long-term topiramate treatment for migraine prophylaxis.

SAFETY RESULTS: Topiramate treatment for migraine prophylaxis in adults was generally safe and the incidence and type of adverse events observed are consistent with topiramate's previously documented safety and tolerability profile.

Of the 140 subjects in the evaluable for safety population who were treated with topiramate in the OLE study, 119 (85.0%) experienced AEs [61 (83.6%) subjects in the TPM/TPM group and 58 (86.6%) subjects in the AMI/TPM group] and 79 (56.4%) experienced treatment related AEs [39 (53.4%) subjects in the TPM/TPM group and 40 (59.7%) subjects in the AMI/TPM group].

A total of 5 (6.8%) subjects in the TPM/TPM group and 8 (11.9%) subjects in the AMI/TPM group withdrew from the OLE study due to AEs. The AEs leading to withdrawal in the TPM/TPM group were each experienced by 1 subject (1.4%): chest pain, fatigue, aggravated migraine, involuntary muscle contractions, dry mouth, difficulty with concentration/attention, eye abnormality, and eye pain. The most frequent AE leading to withdrawal in the AMI/TPM group, Cognitive Problems NOS, was experienced by 2 subjects (3.0%). All other AEs leading to discontinuation in the AMI/TPM group were each experienced by 1 subject (1.5%): alcohol intolerance, fatigue, paresthesia, diarrhea, flatulence, nausea, vomiting, anorexia, difficulty with concentration.

The most commonly reported AEs in the TPM/TPM group were paraesthesia (21.9%), fatigue, viral infection, and sinusitis (each, 11.0%). The most commonly reported AEs for the AMI/TPM group were paraesthesia (23.9%), nausea (11.9%), and diarrhea, difficulty with concentration/attention, and sinusitis (each 10.4%). During the total topiramate exposure period (Double Blind and OLE), similar results were observed in the total TPM group, (paraesthesia, 28.7%, fatigue, 15.2%, and nausea, 11.9%).

Only one subject (Subject 06001, TPM/TPM group) experienced an SAE (vaginal hemorrhage) that the subject's investigator determined to be not related to study treatment.

No deaths were reported during the study or within 30 days of study completion.

Overall, the mean changes for clinical laboratory analyte values within and between groups were not clinically significant. Ten (13.7%) subjects in the TPM/TPM group and 5 (7.5%) subjects in the AMI/TPM group had values that met the criteria for markedly abnormal laboratory values.

Overall, mean changes in vitals sign measurements within and between groups were not clinically significant. Marked abnormalities for vital sign were observed for pulse rate in 2 subjects: 1 in the TPM/TPM treatment group (Subject 05011) and 1 in the AMI/TPM treatment group (Subject 21006) during the OLE study.

Subjects in the AMI/TPM group experienced a greater mean reduction in average body weight than subjects in the TPM/TPM group (-4.4 versus 0.5 kgs). Overall, treatment with topiramate resulted in a mean reduction in average body weight of 2.3 kgs. In the AMI/TPM group a greater number of subjects had BMI categorical decreases (12 versus 4 subjects) and fewer subjects had a categorical increase (0 versus 2) from baseline to the final visit.

CONCLUSION: Findings from this OLE study of topiramate for the prophylaxis of migraine in adults indicated that treatment with topiramate maintained overall efficacy and safety in both a group of subjects who continued topiramate from the double-blind study treatment and in a group of subjects who converted from amitriptyline to topiramate treatment.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.