CLINICAL STUDY REPORT SYNOPSIS – CAPSS-277

Document No.: EDMS-USRA-10656322:2.0

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-277

Title of Study: A Comparison of Topiramate Versus Amitriptyline in Migraine Prophylaxis

Principal Investigator: Multicenter, 32 sites.

Publication (Reference): None

Study Period: 20 February 2004 to 31 October 2005 | **Phase of Development:** IIIB

Objectives: The primary objective of this study was to compare the efficacy and safety of topiramate versus amitriptyline for migraine prophylaxis in adults. In order to further characterize the profile of these agents in subjects with migraine, secondary objectives included determination of changes in weight and impact of treatment and weight changes on quality of life and other subject-reported outcomes.

Methodology: This was a multicenter, randomized, double-blind, parallel group study conducted in the United States, investigating the efficacy and safety of topiramate versus amitriptyline in adult subjects with migraine. The study consisted of 3 phases: A Pretreatment Phase lasting up to 56 days (Screening/Washout plus Prospective Baseline Periods), a Double-Blind Phase lasting 26 weeks (Titration plus Maintenance Periods), and a Taper/Exit Phase that lasted 2 weeks.

Eligibility was assessed 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, level of functional disability, presence/absence of headache characteristics, level of severity of headache-associated symptoms (nausea, photophobia, phonophobia), presence/absence of vomiting, and use of acute abortive medication. In addition, disability and quality of life assessments including the Migraine Disability Assessment (MIDAS), the Migraine-Specific Quality of Life Questionnaire (MSQ), and the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) were completed at various time points during the study. Another subject-reported assessment, the Weight Satisfaction Scale, was completed at screening and Visit 8.

In order to be eligible for randomization, subjects must have had between 3 and 12 migraine episodes and no more than 15 headache-days (migraine or non-migraine) during the prospective baseline period based on completed headache records. A total of 347 subjects were randomized in a double-blind fashion in a 1:1 ratio to 1 of 2 treatment groups; 178 in the topiramate-treatment group and 169 in the amitriptyline-treatment group.

The Double-Blind Phase was divided into 2 periods: titration (4 weeks) and maintenance (22 weeks). Study visits occurred twice during the Titration Period (Day 1 and Day 28) and monthly during the Maintenance Period (Days 56, 84, 133, and 182). Telephone contacts were conducted 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 or amitriptyline was 25 mg. Medication was titrated in weekly increments of 25 mg/day until a dose of 100 mg/day of topiramate or amitriptyline or the subject's maximum tolerated dose (MTD) was achieved. Following the Titration Period, subjects entered the 22-week (154-day) Maintenance Period. Subjects were to maintain a dose of at least 50 mg/day of study medication to continue into the Maintenance Period. Clinic visits occurred on Day 56 (Visit 5), Day 84 (Visit 6), Day 133 (Visit 7), and the Final Maintenance Visit on Day 182 (Visit 8). Subjects were considered to have completed the study if they completed all assessments through Visit 8/Day 182 of the Double-Blind Phase. Subjects who completed the Double-Blind Phase were given an opportunity to enroll in an Open-Label (OL) Extension Study (CAPSS-296). Subjects who elected not to enter the OL Extension study or who discontinued early were advised to taper study medication according to the investigator's discretion, and the length of taper may have varied according to the dose the subject achieved. Subjects were evaluated approximately 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 visit.

Number of Subjects (planned and analyzed): Approximately 330 subjects were planned; a total of 347 subjects were randomized (178 in the topiramate-treatment group and 169 in the amitriptyline-treatment group). A total of 331 subjects (172 topiramate and 159 amitriptyline) were included in the intent-to-treat (ITT) population. A total of 346 subjects (177 topiramate and 169 amitriptyline) 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 a history of migraine ≥6 months in duration, with or without aura, conforming to the International Headache Society (IHS) criteria, and must have had between 3 and 12 migraine episodes and no more than 15 headache-days (migraine or non-migraine) during the 28-day Prospective Baseline Period. 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 previously failed an adequate trial of topiramate or amitriptyline therapy due to lack of efficacy or adverse event (AE), had used analgesic or specific agents >15 treatment days per month for the acute abortive treatment of migraine and/or were taking a migraine preventive medication.

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 daily depending on dosage.

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.

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 26 weeks in duration and consisted of 2 study periods: a Titration Period (4 weeks) and a Maintenance Period (22 weeks). At the end of study participation subjects also tapered their study medication. The length of the taper was at the investigator's discretion and varied according to the dose the subject achieved.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was defined as the change in the mean monthly (28-day) migraine episode rate from the Prospective Baseline to the Double-Blind Phase. The secondary efficacy variables included the change in mean monthly rate of days with migraine headache from the Prospective Baseline Phase to the Double-Blind Phase; change in the mean monthly rate of total headache days from the Prospective Baseline Phase to the Double-Blind Phase; change in the average monthly rate of acute abortive medication use from the Prospective Baseline Phase to the Double-Blind Phase; change in the mean monthly migraine duration from the Prospective Baseline Phase to the Double-Blind Phase; change in the average migraine severity from the Prospective Baseline Phase to the Double-Blind Phase; change in the average severity of migraine associated symptoms (photophobia, phonophobia, and nausea) and average severity of functional disability from the Prospective Baseline Phase to the Double-Blind Phase; change in the average monthly rate of vomiting, 1-sided pain during the attack, throbbing pain, and increased pain with physical activity from the Prospective Baseline Phase to the Double Blind Phase. Other secondary variables included changes in disability, quality of life and weight satisfaction assessments.

Safety: Safety evaluations included AEs, brief physical examination, brief neurological examination, height, weight and vital sign 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 ITT population, which included all randomized subjects who received at least 1 dose of study medication and provided at least 1 post-randomization efficacy assessment. Subjects who did not return any of their headache records were not included in the efficacy analysis.

The evaluable for safety population was defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 on-treatment safety measurement.

Analysis Methods for the Primary Efficacy Variable

All analyses prospectively planned in the protocol and Statistical Analysis Plan were completed. A closed testing procedure was applied under the context of switching between non-inferiority and superiority. The overall type I error rate was controlled at level 0.05.

The change from the Prospective Baseline to the Double-Blind Phase in the mean monthly (28-days) migraine episode rate was derived from the reduction in the migraine episode rates. A 2-sided 95% confidence interval (CI) about mean difference (topiramate minus amitriptyline) from the least-squares means in the change in the mean

monthly migraine episode rates was calculated to evaluate non-inferiority for efficacy. The least-squares means were obtained from an analysis of covariance (ANCOVA) model using treatment and center as qualitative independent factors, and baseline mean monthly migraine episode rate as a covariate. If the lower bound of the 2-sided 95% CI was greater than –1, then non-inferiority was established. If the interval lay entirely above –1 and was also above zero, then superiority was established, i.e., topiramate was superior to amitriptyline for the primary efficacy variable at the significance level of 5%. The actual p-value for testing the superiority was then to be obtained from the ANCOVA model.

Analysis Methods for the Secondary Efficacy Variables

All analyses prospectively planned in the protocol and Statistical Analysis Plan were completed. Secondary efficacy variables, were analyzed using an ANCOVA with treatment and center as qualitative independent factors and baseline value as a covariate. The Cochran-Mantel-Haenszel methodology was used to assess the proportion of categorical responder rates in the topiramate and amitriptyline treatment groups based on mean monthly migraine days and total headache days. The changes in clinical migraine characteristics (i.e. duration, therapy, migraine associated symptoms) and severity of functional disability were summarized.

The analyses of MSQ domain scores (Role Function-Restrictive, Role Function-Preventive and Emotional Function) used the ANCOVA model with treatment and center as main effects and baseline score as the covariate. Each MSQ domain was summarized for each of the following: Visit 4 (Day 28), Visit 5 (Day 56), Visit 6 (Day 84), Visit 7 (Day 133), and Visit 8 (Day 182). Two data summaries were created, a LOCF summary and an observed data summary.

The analyses of MIDAS scores used the ANCOVA model with treatment and center as main effects and baseline score as the covariate. ANCOVA was used to analyze the responses from Q-LES-Q-SF and Weight Satisfaction Scale.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Treatment with topiramate for migraine prophylaxis was not inferior to amitriptyline treatment in the reduction of the mean monthly (28-day) migraine episode rate from the Prospective Baseline to the Double-Blind Phase (topiramate: mean reduction = -2.7, amitriptyline: mean reduction = -2.6; 95% CI from least squares [LS] mean difference: -0.6, 0.7, p=0.874).

The proportion of responders having a ≥50% reduction and a ≥75% reduction in mean monthly migraine days were greater in the topiramate-treatment group compared with the amitriptyline-treatment group (55.6% versus 45.9% and 26.0% versus 20.4%, respectively). The proportion of responders having a ≥50% reduction and a ≥75% reduction in mean monthly total headache days were greater in the topiramate-treatment group compared with the amitriptyline-treatment group (54.4% versus 43.9% and 24.3% versus 15.9%, respectively). The overall distributions of categorical responses for reduction in mean monthly migraine days and for reduction in mean monthly total headache days were not statistically significantly different between the 2 treatment groups (p = 0.342 and 0.220, respectively).

The decrease in average severity of functional disability associated with migraine episodes was significantly greater for the topiramate-treatment group (topiramate: −0.35, amitriptyline: −0.17) and the between group difference was statistically significant (p = 0.040). In addition, the topiramate-treatment group achieved improvements in all 3 domains of the MSQ that were statistically significantly greater than those attained by the amitriptyline-treatment group (topiramate versus amitriptyline, mean change: Role Function-Restrictive [25.0 versus 17.3; p = 0.012], Role Function-Preventive [17.7 versus 11.5; p = 0.014], and Emotional Function [26.3 versus 20.0; p = 0.029]). Improvements in the Q-LES-Q-SF (topiramate: 4.6, amitriptyline: 5.2; p = 0.860) and MIDAS (topiramate: -12.1, amitriptyline: -14.2; p = 0.288) were similar in both treatment groups.

Overall, the topiramate-treatment group had significantly greater satisfaction and the amitriptyline-treatment group had less satisfaction with their body weight based on the Weight Satisfaction Scale scores from baseline to last visit (topiramate-treatment group: 0.70, amitriptyline-treatment group: -0.21). The between group difference was statistically significant (p<0.001).

SAFETY RESULTS:

The evaluable for safety population consisted of 99.7% of randomized subjects (N = 346; 177 topiramate and 169 amitriptyline).

A summary of the treatment-emergent AEs were reported in the following table:

Overall Summary of Treatment-Emergent Adverse Events
(Subjects Evaluable for Safety)

	Topiramate (N= 177)		Amitriptyline (N=169)	
	n	(%)	n	(%)
Number (%) of subjects with any adverse event regardless of relationship to study medication	152	(85.9)	150	(88.8)
Number (%) of subjects with any adverse event related[a] to study medication	121	(68.4)	128	(75.7)
Number (%) of subjects with any adverse event causing withdrawal from study	35	(19.8)	38	(22.5)
Number (%) of subjects with any serious adverse event regardless of relationship to study medication	4	(2.3)	7	(4.1)
Number (%) of subjects with any serious adverse event related[a] to study medication	0	(0.0)	1	(0.6)

[a] Related included possible, probable, and very likely related.
[b] Subject 11004 was not included in this table as she experienced a non-treatment-emergent AE. The subject experienced gastroenteritis prior to receiving study medication (Day -12).

The TEAEs reported for ≥ 10% of subjects in the topiramate-treatment group were paraesthesia (29.9%), fatigue (16.9%), somnolence (11.9%), hypoaesthesia (10.7%), and nausea (10.2%). The TEAEs reported for ≥ 10% of subjects in the amitriptyline-treatment group were dry mouth (35.5%), fatigue (24.3%), somnolence (17.8%), weight increase (13.6%), dizziness (10.7%), and sinusitis (10.7%). Twelve subjects experienced 14 SAEs (one amitriptyline-treated subject experienced a non-treatment-emergent SAE prior to receiving study medication). No clinically relevant differences between the 2 treatment groups in mean vital signs or ECGs were observed. Twenty-seven (15.3%) subjects in the topiramate-treatment group and 13 (7.7%) subjects in the amitriptyline-treatment group had values that met the criteria for markedly abnormal laboratory values. Markedly low carbon dioxide values were reported for 8 (4.5%) subjects in the topiramate-treatment group and 1 (0.6%) subject in the amitriptyline-treatment group. The abnormalities in carbon dioxide values may be explained by the known pharmacologic effect of topiramate to inhibit carbonic anhydrase. Reductions in body weight, BMI and BMI categories were seen in the topiramate-treatment group from baseline to final visit while increases were seen in the amitriptyline-treatment group. No clinically significant trends were observed for changes in physical examination variables in either treatment group.

CONCLUSION: Treatment with topiramate for migraine prophylaxis was at least as effective as amitriptyline treatment for the reduction of monthly migraine episodes. The topiramate-treated subjects reported a decrease in average severity of functional disability associated with migraine episodes and greater improvement in the MSQ scores compared to amitriptyline-treated subjects. Other measurements of patient satisfaction and migraine-related disability outcomes used in this study were similar for each treatment group. Amitriptyline-treated subjects gained an average of 2.37 kg body weight with nearly one-third experiencing a 5% or greater weight gain during the course of treatment. In contrast, topiramate-treated subjects lost an average of 2.38 kg with nearly one-third experiencing a 5% or greater reduction in their weight. Accordingly, a greater number of subjects treated with topiramate reported a significant increase in body weight satisfaction compared with amitriptyline-treated subjects who were generally less satisfied. The safety and tolerability profiles for both medications were consistent with their product labels and historical clinical observations.

Issue Date of the Clinical Study Report: 26 March 2008

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.