CAPSS-278 CLINICAL STUDY REPORT 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	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**

Protocol No.: CAPSS-278 (CR004681)

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Flexible Dose Study to Assess the Safety and Efficacy of Topiramate in the Treatment of Alcohol Dependence

Clinical Trial Director: Frank Wiegand, MD – Ortho-McNeil Janssen Scientific Affairs LLC – Titusville, NJ; USA

Publication (Reference): None

Study Initiation/Completion Dates: 15 March 2004 to 04 August 2006 | **Phase of Development:** IIb

Objective: The primary objective of this study was to evaluate the safety and efficacy of topiramate compared with placebo in the treatment of adult subjects with alcohol dependence.

Methodology: This was a 14-week, outpatient, multicenter, randomized, double-blind, placebo-controlled, flexible-dose study of topiramate in subjects with alcohol dependence. Male and female subjects, between 18 and 65 years of age, with alcohol dependence were randomized in a double-blind fashion according to a 1:1 ratio, to 1 of 2 treatment groups (topiramate or placebo) across 17 U.S. study centers. The study consisted of 2 phases: a Pre-Randomization Phase that included a Washout/Screening Period and a Double-Blind Treatment Phase, which included a 6-week Titration Period, an 8-week Maintenance Period, and a Taper Period of approximately 7-16 days. Eligibility was assessed during the Pre-Randomization Phase. Study visits occurred every 7 days during the Double-Blind treatment phase. At each visit, subjects received Brief Behavioral Compliance Enhancement Treatment (BBCET), a manual-driven, low-intensity supportive program to foster, maintain, and promote compliance with the medication regimen and to promote continuation in the study.

The Pre-Randomization Phase lasted up to 35 days and consisted of 2 study periods: a Washout Period (Day -35 to Day -7) and a Screening Period (Day -7 to Day 1). During Visit 1A (Day -35), subjects who were alcohol dependent and who met the entry criteria were identified. The study was explained and informed consent was obtained. Subjects who reported drinking an average of ≥ 28 standard alcohol units per week for women or ≥ 35 standard alcohol units per week for men during the 28 days prior to Visit 1B (Day –7), as measured by Alcohol Timeline FollowBack (TLFB), entered the Screening Period (Visit 1B, Day -7). These subjects were instructed to continue reporting their drinking until Visit 2 (Day 1).

Subjects who completed the Screening Period, who had the required level of alcohol dependence and who continued to meet the remainder of the entry criteria were randomized in a double-blind fashion according to a 1:1 ratio, to 1 of 2 treatment groups: topiramate (up to 300 mg/day) or placebo. The Double-Blind Treatment Phase was 14 weeks in duration and consisted of 2 study periods: a Titration Period (6 weeks) and a Maintenance Period (8 weeks) that was followed by a blinded Taper Period of approximately 7-16 days.

SYNOPSIS (CONTINUED)

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Methodology continued: The Titration Period immediately followed the Pre-Randomization Phase and lasted 6 weeks (42 days). All subjects had the same titration schedule, which started with a single evening dose of 25-mg topiramate (or matching placebo) for the first week followed by a twice-daily regimen (50 mg/day topiramate or matching placebo) for the second week. Subjects titrated the study medication until they reached 300 mg/day of topiramate (or matching placebo) or their maximum tolerated dose, whichever was less. The minimum tolerated dose to continue in the study was 50 mg/day.

Following the Titration Period, subjects entered the 8-week (56-day) Maintenance Period. During the Maintenance Period, subjects were to maintain the dose that they had attained at the end of the Titration Period. A single dose reduction was permitted during the Maintenance Period to manage tolerability.

Number of Subjects (planned and analyzed): Approximately 368 subjects were planned – a total of 371 subjects (183 in the topiramate group and 188 in the placebo group) were randomized.

Diagnosis and Main Criteria for Inclusion: Subjects between the ages of 18 and 65 years (inclusive); who had a current DSM-IV-TR™[14] diagnosis of alcohol dependence supported by the Structured Clinical Interview for DSM-IV-TR™ Axis I Disorders Patient Edition; who drank an average of ≥ 28 standard alcohol units/week (women) or ≥ 35 standard alcohol units/week (men) during the 28 days prior to Visit 1B (Day –7) and during the 7-day Screening Period prior to Visit 2 (Day 1); who had a score of > 8 on the Alcohol Use Disorder Identification Test at Visit 1B (Day –7); who expressed a desire to completely stop drinking alcohol or reduce alcohol consumption with the possible long-term goal of abstinence; and who had a breath alcohol concentration (BrAC) of < 0.02% at the time informed consent was signed.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was provided as 25-mg tablets (film-coated tablets, round, white) and 100-mg tablets (film-coated tablets, round yellow) (batch number D03LK1143 [expiration 9/06] and D03LK1157 [expiration 9/06]).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was provided as identically appearing tablets, (batch number D03LK1145 and D03LK115 [expiration 9/06]).

Duration of Treatment: The Pre-Randomization Phase lasted up to 35 days and consisted of 2 study periods: a Washout Period (Day -35 to Day -7) and a Screening Period (Day -7 to Day 1). The Double-Blind Treatment Phase was 14 weeks in duration and consisted of 2 study periods: a Titration Period (6 weeks), and a Maintenance Period (8 weeks) that was followed by a blinded Taper Period of approximately 7-16 days.

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Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the Percent Heavy Drinking Days (PHDD) during the Double-Blind Treatment Phase in the intent-to-treat (ITT) population. A heavy drinking day was defined as at least 5 drinks/day for men and at least 4 drinks/day for women. Additional efficacy evaluations were as follows: Drinks/Drinking Day (DDD), Drinks/Day (DD), Percent Days Abstinent (PDA), Time to Abstinence (TTA), Obsessive-Compulsive Drinking Scale (OCDS), Drinker Inventory of Consequences (DrInC-2R), Clinical Global Impressions Scale Severity (CGI-S) and Improvement (CGI-I), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LESQ), Profile of Mood States-Brief (POMS-B), Cigarettes/Day, Percent Days Abstinent of Cigarettes, Clinical Institute Withdrawal Assessment (CIWA-Ar), Medical Outcomes Sleep Scale (MOS-Sleep), Montgomery-Asberg Depression Rating Scale (MADRS), Categorized Drinks/Day (CDD), and Categorized Drinks/Drinking day (CDDD). Gamma-glutamyl transferase (GGT) samples were analyzed as biochemical measures of alcohol consumption. Blood samples for serum topiramate and carbohydrate deficient transferrin (CDT) levels were also obtained. The samples for CDT level were stored for possible analysis at a later date.

Safety:

Safety evaluations included: BrAC, adverse events (AEs), physical examination, electrocardiogram (ECG), temperature, resting pulse, blood pressure, clinical laboratory tests (including urinalysis at Visits 1B and 16; and electrolytes, Prothrombin Time [PT], and liver function tests [LFTs] every 28 days through Visit 14). The CIWA-Ar and MADRS were also safety measures. Urine pregnancy tests were performed every 28 days on women of childbearing potential.

Statistical Methods: The primary efficacy endpoint, PHDD was analyzed using a repeated measures model with treatment, center, week, sex, baseline PHDD, age, age of onset, and treatment by week interaction as factors/covariates. An unstructured covariance matrix was used to model the correlations between repeated measurements within subjects. This analysis was based on the ITT population defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 post baseline efficacy measurement. Each of the following secondary endpoints were analyzed using a repeated measures model with treatment, center, week, sex, baseline value, age, age of onset, and treatment by week interaction as factors/covariates: DDD, DD, PDA, Cigarettes/Day and Percent Days Abstinent of Cigarettes. Weight, BMI, serum GGT level, and all scores from the following scales: OCDS, CIWA-Ar, Q-LES-Q, MOS-Sleep, DrInC-2R, POMS-B, MADRS were analyzed using a repeated measures model with treatment, center, week, baseline value, and treatment by week interaction. A fixed sequence procedure was used to control family-wise error rate when determining the earliest time point at which the between-treatment difference became significant and remained so for the subsequent time points. Between-treatment difference at DB endpoint for each of the above measures was tested using an ANCOVA model including treatment, center, and baseline value as factors/covariate. The CGI-I and CGI-S were analyzed using Cochran-Mantel-Haenszel test stratified by sex and center using modified ridit scores. For the CDD, a chi-square test was used to assess: none versus above none; none and mild versus moderate and heavy; heavy versus non-heavy based on data from the final week of the study. The difference in TTA between treatment groups was tested using a log-rank test and a Cox regression model including treatment, sex, and baseline PHDD as factors/covariate. Cumulative mean function (CMF) for heavy drinking was estimated for each treatment group and between-treatment difference was tested using proportional rates/means model. All statistical tests were conducted at the 2-sided, 5% significance level.

SYNOPSIS (CONTINUED)

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SUMMARY

Demographics and Baseline Characteristics: A total of 371 subjects were randomized in the study (183 topiramate and 188 placebo); 364 (179 topiramate and 185 placebo) subjects were included in the ITT analysis. The ITT population consisted of subjects who were white (84.9% both topiramate and placebo), black (6.7% topiramate and 8.6% placebo), Asian (0.6% topiramate and 1.1% placebo), and other (7.8% topiramate and 5.4% placebo). Higher proportions of subjects were male (74.3% topiramate and 71.9% placebo) than female (25.7% topiramate and 28.1% placebo). Ages of subjects in the topiramate group ranged from 22 to 66 years, with a mean age of 46.7 years; subjects in the placebo group ranged from 21 to 65 years of age, with a mean age of 47.8 years. Weight of subjects in the topiramate group ranged from 54.9 to 149.2 kg, with a mean weight of 85.5 kg; subjects in the placebo group ranged from 48.1 to 154.0 kg, with a mean weight of 87.2 kg. Body mass index of subjects in the topiramate group ranged from 17.9 to 44.8 kg/m^2, with a mean BMI of 28.0 kg/m^2; subjects in the placebo group ranged from 19.3 to 48.6 kg/m^2, with a mean BMI of 28.7 kg/m^2.

The 2 treatment groups were generally well matched in baseline alcohol dependence characteristics. The age of alcohol dependence onset ranged from 4 to 62 years with a mean of 32.7 years for topiramate-treated subjects and 14 to 64 years with a mean of 34.4 years for placebo-treated subjects. The majority of subjects in either treatment group had no previous inpatient treatment (82.7% topiramate and 88.6% placebo) but had alcohol counseling (95.0% topiramate and 97.3% placebo). The mean total PHDD at screening and baseline were similar (83.1 and 82.0). Less than half of the subjects were smokers (44.1% topiramate and 35.1% placebo).

Efficacy Results:

Percent heavy drinking days for the 14-week Double-Blind treatment phase was significantly lower for subjects in the topiramate group compared to subjects in the placebo group (least squares means 37.8% ± 2.15% vs. 54.0% ± 2.00%, $p<0.0001$). A statistically significant difference was first observed at the end of Week 2 (63.7% ± 2.19% vs. 69.7% ± 2.11%, $p=0.0378$) and continuing through Week 14 (22.9% ± 3.02% vs. 42.2% ± 2.72%, $p<0.0001$).

Over the 98 treatment days, subjects in the topiramate group on average had 18 fewer days of heavy drinking as compared to subjects in the placebo group (37.5 days compared to 55.0 days, respectively, $p<0.0001$).

Topiramate was superior to placebo for the secondary endpoints DD, DDD, PDA, OCDS, DrInC-2R, and serum GGT levels. Furthermore, alcohol abstinence and days without any heavy drinking was seen in a greater percentage of subjects in the topiramate group for a 7-, 14-, 21-, and 28-day abstinence period compared to the placebo group. From Week 3 onward, significantly lower proportion of topiramate subjects were in the heavy DD and DDD categories than the placebo subjects. There were no statistically significant changes in the CIWA-Ar scores when comparing the topiramate group to the placebo group.

Significant improvements in CGI-S and CGI-I were seen for the topiramate group compared to the placebo group. Topiramate led to improvements in the sleep disturbance and snoring subscales (MOS-Sleep) and anger-hostility subscale of the POMS-B questionnaire when compared to placebo. Placebo subjects showed greater improvement in the confusion-bewilderment subscales.

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Safety Results:

The evaluable for safety population was defined as all randomized subjects who had received at least 1 dose of study drug and for whom at least 1 safety measurement was available.

A total of 371 (100.0%) randomized subjects contributed safety data in the Double-Blind Phase and were included in the safety analysis: 183 in the topiramate group and 188 in the placebo group. The more commonly reported treatment-emergent adverse events (TEAEs) in the topiramate group were: paraesthesia (50.8%), headache (24.0%), taste perversion (23.0%), fatigue (22.4%), and anorexia (meaning decreased appetite) (19.7%). The more commonly reported TEAEs for the placebo groups were: headache (31.9%), fatigue (17.6%), nausea (16.5%), insomnia (16.0%), and sinusitis (13.8%). Treatment-emergent AEs were reported for 169 (92.3%) subjects in the topiramate group and 178 (94.7%) subjects in the placebo group. Treatment-related AEs were reported for 158 (86.3%) subjects in the topiramate group and 119 (63.3%) subjects in the placebo group. Withdrawals due to TEAEs were 34 (18.6%) in the topiramate group compared to 8 (4.3%) in the placebo group. The more frequent TEAEs leading to withdrawal in the topiramate group were: confusion (1.6%), difficulty with concentration/attention (1.6%), fatigue (1.1%), cognitive problems not otherwise specified (NOS) (1.1%), depression (1.1%), and somnolence (1.1%). All other TEAEs leading to withdrawal from the study were reported for 1 subject each (0.5%) in the topiramate group. All TEAEs leading to withdrawal in the placebo group were reported in 1 subject each (0.5%) and included the following: headache, abdominal pain, cardiac arrest, pathological fracture, cognitive problems NOS, depression, suicidal ideation, and menstrual disorder. A total of 8 subjects experienced 12 treatment-emergent SAEs (4 subjects in the topiramate group and 4 subjects in the placebo group). One death was reported in the placebo group, Subject 10011 died due to cardiac arrest during the study.

CONCLUSION:

Topiramate was superior to placebo at reducing the mean (± SE) PHDD (from 82.1% ±1.50% to 22.9% ±3.02% in the topiramate group versus 81.8%±1.47% to 42.2%±2.72% in the placebo group) as well as all other alcohol related secondary outcome parameters ($p<0.0001$ for all comparisons).

Topiramate's efficacy over placebo was evident as early as the third week of Double-Blind treatment when the dose was only 100 mg/day – well below the ceiling dose of 300 mg/day. The therapeutic effect of topiramate at improving drinking outcomes grew as the study progressed, and appeared still to be rising at the end of the study.

Abstinence for ≥ 28 days was achieved in almost $1/5^{th}$ (18.8%) of the topiramate group compared to 3.7% of the placebo group. As seen in the CIWA-Ar, this was accomplished without a significant increase in withdrawal symptoms.

There was no difference between treatment groups in the proportion of subjects that reported TEAEs, although more patients on topiramate discontinued the study due to side effects. Adverse events more likely to be associated with topiramate were anorexia (meaning decreased appetite), difficulty with concentration, difficulty with memory, nervousness, and taste perversion. These AEs were usually reported to be mild to moderate in nature and consistent with the known AE profile of topiramate. At the end of the study, the topiramate group showed a reduction in body weight, BMI and liver enzymes (aspartate aminotransferase and alanine aminotransferase).

Date of the report: 06 December 2007

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