# SYNOPSIS

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

**Protocol No.:** CAPSS-220

**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 Moderate to Severe Binge-Eating Disorder Associated with Obesity

**Principal Investigators:** Multicenter, 19 Investigators

**Publication (Reference):** None

| **Study Initiation/Completion Dates:** 15 October 2003 – 28 February 2005 | **Phase of development:** IIb |
|---|---|

**Objectives:** The primary objective of this study was to evaluate the efficacy and safety of topiramate compared to placebo in the treatment of moderate to severe binge-eating disorder associated with obesity. A secondary objective was to evaluate the relationship between genetic variability in drug metabolizing enzymes (e.g., CYP2C19) and inter-individual variability in plasma exposure to topiramate within each treatment group.

**Methodology:** This was a 16-week, multicenter, randomized, double-blind, placebo-controlled, flexible-dose, study of topiramate in subjects with moderate to severe binge-eating disorder associated with obesity. The study consisted of 3 phases: pre-randomization phase (washout plus screening period), double-blind, and open-label extension phase. Only data collected through the end of the double-blind phase are included in this report. Eligibility was assessed during the pre-randomization phase, which lasted up to 42 days and included a washout period and a 2-week screening period. Subject diaries were used to capture binge days and binge episodes during the 2-week screening period prior to randomization and throughout the treatment period. Subjects were provided instructions for determining a binge episode and instructed to record binge episodes and time spent binging on a daily basis. Site personnel reviewed the subject diary with the subject at each visit and evaluated the number of binge days and episodes per day according to the following criteria: 1) eating in a certain period of time (e.g., within a 2-hour period), an amount of food that was definitely larger than most people would eat in a similar period of time under similar circumstances, and 2) experiencing a lack of control over eating during the episode (e.g., a feeling that one could not stop eating or control what or how much one was eating). At Baseline (Visit 2, Day 1), subjects who had continued to meet entry criteria and had 3 or more binge days in each of the 2 weeks during the screening period were randomized to 1 of 2 treatment groups (180 per group): topiramate up to 400 mg/day or placebo. Study visits (Days 1, 7, 14, 21, 28, 42, 56) or telephone contacts (Days 35 and 49) occurred weekly during the titration period (weeks 1-8) and monthly during the maintenance period (weeks 9-16). Study medication compliance was assessed by tablet count (number of tablets dispensed minus the number returned divided by the number prescribed during the interval) at each visit.

Upon completion of the maintenance period, subjects either tapered their double-blind medication and returned for a final post-taper visit (Day 119) or simultaneously tapered double-blind medication while they titrated open-label medication and returned for their first open-label extension phase visit (Day 140). Subjects exiting the study during any phase were encouraged to taper study medication in an amount equal to approximately 1/3 of their dose every 3 days.

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|---|---|---|

**Number of Subjects (planned and analyzed):** Approximately 360 subjects were planned; a total of 407 subjects were randomized (204 topiramate and 203 placebo); 401 (199 topiramate and 202 placebo) were included in the intent-to-treat (ITT) population (all randomized subjects dispensed study medication with 1 valid post-baseline efficacy measure); 394 (195 topiramate and 199 placebo) were included in the modified intent-to-treat (mITT) population (ITT population excluding subjects with any of the following major protocol violations: no diagnosis of binge eating disorder, <3 binge days per week during the 2-week screening period, Body Mass Index (BMI) <30 $kg/m^2$, and/or Montgomery-Asberg Depression Rating Scale (MADRS) >24 at Screening or Baseline); 404 (202 topiramate and 202 placebo) were included in the Evaluable-for-Safety population (all subjects randomized to double-blind study medication with at least 1 post-baseline safety measure); 283 (142 topiramate and 141 placebo) were included in the Completer population (all subjects who completed all study visits up to and including Visit 10 and exceeded 99 days of taking study medication).

**Diagnosis and Main Criteria for Inclusion:** Subjects were to be men and women diagnosed with binge-eating disorder according to Diagnosis and Statistical Manual–IV (DSM-IV-TR™) and supported by the Structured Clinical Interview for DSM – IV Axis I Disorder Patient Edition (SCID – I/P) between the ages of 18 and 65, inclusive. In addition, subjects must have been obese as defined by a BMI of $\geq$ 30 $kg/m^2$ and $\leq$ 50 $kg/m^2$, have had 3 or more binge days per week in the 2-week period prior to Baseline (Visit 2, Day 1), a MADRS $\leq$ 24 at Screening and Baseline, and must not have used any psychotropic medication within 5 serum half-lives of Baseline.

**Test Product, Dose and Mode of Administration, Batch No.:** Topiramate was provided in tablet form containing 25 mg (batch numbers R12267, R12344) and 100 mg (batch numbers R12268, R12345). Subjects randomized to topiramate began at 25 mg taken orally in the evening for 7 days, followed by weekly increases of 25 mg/day through Day 28 taken twice daily. Dosing was increased by 50 mg/week up to Day 42, and by 100 mg/week up to Day 56 up to a maximum dose of 400 mg/day or to the subject's maximum tolerated dose (MTD). At the investigators discretion the rate of titration may have been adjusted, however, after the second week of titration, subjects must have achieved a dose of 50 mg/day. During the maintenance period, the dose of study medication was to remain constant. A single dose reduction to the previously tolerated dose was permitted during the maintenance period if necessary to manage tolerability.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Matching placebo was provided in tablet form (batch numbers R12269, R12346) to match 25 mg topiramate tablets and (batch numbers R12270, R12347) to match 100 mg topiramate tablets. Matching placebo tablets were administered according to the same schedule as topiramate tablets.

**Duration of Treatment:** Washout period within 28 days of the start of the screening period; screening period (2 weeks); double-blind phase (16 weeks) consisting of a titration period (8 weeks) and maintenance period (8 weeks). Subjects who did not wish to continue into the open-label extension phase tapered their study medication by decreasing the dose approximately 30% every three days over a one-week period until they were no longer taking study medication. Subjects who entered the open-label extension phase simultaneously tapered double-blind medication while titrating open-label medication. After completion of the open-label extension phase subjects tapered study medication by decreasing the dose approximately 30% every three days over a one-week period until they were no longer taking study medication.

**Criteria for Evaluation:**

Efficacy: The primary efficacy endpoint was the rate of change in the number of binge days per week in the mITT population. Additional efficacy evaluations were as follows: weekly binge episodes, Clinical Global Impression Scale Severity (CGI-S) and Improvement (CGI-I), Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating (Y-BOCS-BE), Barratt Impulsiveness Scale, Version 11 (BIS-11), Three Factor Eating Questionnaire (TFEQ) (Eating Inventory), Hamilton Anxiety Rating Scale (HAM-A), BMI, weight, Sheehan Disability Scale

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|---|---|---|
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| NAME OF ACTIVE INGREDIENT: 2, 3:4, 5-Di-*O*-isopropylidene-ß-D-fructopyranose sulfamate | Page: | |

(SDS), and MADRS. In addition, percent change in binge days was used to determine response category. Response categories were defined as <50% = None/No Response, 50-74% = Moderate, 75-99% = Marked, and 100% = Remission. The cumulative distribution of time to recovery and the cumulative distribution of time to response were also evaluated.

Safety: Safety evaluations included: adverse events, physical examination, temperature, pulse, blood pressure, clinical laboratory tests (complete labs including urinalysis at Visits 1 and 10; liver function tests and electrolytes every 28 days through Visit 9; $HgbA_{1C}$ every 28 days through Visit 10 for subjects with Type II diabetes). Urine pregnancy tests were performed every 28 days on women of childbearing potential.

**Statistical Methods:** All efficacy analyses were performed on the mITT Population and the ITT Population. The primary analysis was the weekly average number of binge days per week for each treatment group. The difference in rates of change was estimated by a repeated-measures random regression analysis. The model included center, treatment, time, and treatment-by-time interaction. Time was represented by the week the measurement was taken; for the two-week binge periods, the second week was used. Baseline was Week 0. Time was transformed using a logarithmic transformation of week + 1. Rate of binge days per week was normalized with a logarithmic transformation, log ((binge days/week) + 1).

The same repeated measures random regression analysis was used to analyze the other continuous secondary efficacy variables including weekly binge episodes per week, CGI-S, Y-BOCS-BE, BIS-11, TFEQ, HAM-A, SDS and MADRS, as well as weight and BMI. Rate of binge episodes per week were normalized with a logarithmic transformation, log((binge episodes/week) + 1). All variables were tabulated and graphed by week or study visit.

Final binge days per week, binge episodes per week, Y-BOCS-BE, CGI-S, BIS-11, TFEQ, HAM-A, SDS, MADRS, weight and BMI were analyzed using a two-way analysis of covariance (ANCOVA) with treatment and center as factors and the baseline value as a covariate. Final CGI-I scores were summarized by counts and percents in each response category and analyzed using a Cochran-Mantel-Haenszel (CMH) test using modified ridit scores, stratified by investigator group. The final percent change in binge days and binge episodes was analyzed using a two-factor ANCOVA after applying a logarithmic transformation to the responses. All final efficacy variables were analyzed in the Completer Population in addition to the mITT and ITT populations.

Response categories for percent change from baseline in binge days and binge episodes were tabulated for each weekly period and at the final period. The response categories of final percent change from baseline were analyzed with a CMH test using modified ridit scores, stratified by center. The final percent change from baseline was also analyzed with a two-way analysis of variance (ANOVA) with center and treatment as predictor variables. All binge day and binge episode response categories and the percent change were analyzed in the Completer Population in addition to the mITT and ITT populations.

Time to recovery and time to response were analyzed with a log rank test for the mITT and ITT populations.

All statistical tests were conducted at the two-sided, 5% significance level.

**SUMMARY – CONCLUSIONS:**

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: A total of 407 subjects were randomized in the study (204 topiramate and 203 placebo); 401 (199 topiramate and 202 placebo) subjects were included in the ITT analysis (6 subjects did not have postbaseline efficacy data); 394 subjects were included in the mITT analysis (195 topiramate and 199 placebo) with 13 subjects excluded from the mITT analysis (ITT population excluding subjects with any of the following major protocol violations: no diagnosis of binge eating disorder, <3 binge days per week during the 2-week screening period, BMI <30 $kg/m^2$, and/or MADRS >24 at Screening or Baseline). The 2 groups

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|---|---|---|

in the mITT population were generally well matched in baseline demographics. Subjects ranged in age from 18 to 70 years, with a mean age of 44.3 years. The majority of the subjects were white (309 subjects, 78.4%) and female (330, 83.8%). Sixty-four (16.2%) subjects were black. Subjects ranged in weight from 70.5 to 177.5 kg, with a mean weight of 106.6 kg. Subjects ranged in BMI from 30.1 to 51.6 kg/$m^2$, with a mean BMI of 38.5 kg/$m^2$. For subjects in the mITT population, the baseline binge days (number of binge days recorded in diary during the 14 days prior to first dose divided by 2) ranged from 3.0 to 7.0 days, with a mean of 4.63 days and the baseline binge episodes (number of binge episodes recorded in diary during the 14 days prior to first dose divided by 2) ranged from 3.0 to 35.0 episodes, with a mean of 6.42 episodes.

EFFICACY RESULTS: Subjects receiving topiramate showed a significantly greater rate of reduction in binge days per week, the primary endpoint, compared to those receiving placebo, $p<0.001$.

Topiramate was statistically significantly superior to placebo for those secondary endpoints that evaluated binge eating symptoms including: the rate of reduction in the number of binge episodes per week, the final mean change from baseline in the number of binge days per week and binge episodes per week, the number of subjects who showed a moderate improvement, marked improvement, or were in remission in the final percent change in binge days and binge episodes per week, the percent of subjects who achieved recovery, and the percent of subjects who achieved response, by Week 16, BIS-11 Overall Score and Motor Impulsiveness and Nonplanning Impulsiveness subscale scores of BIS-11, Y-BOCS-BE Overall score and Obsessive and Compulsiveness subscale scores of Y-BOCS-BE, Cognitive Restraint, Disinhibition and Hunger subscores of TFEQ, SDS Overall score and Social Life Disability and Family Life Disability subscale score of SDS, CGI-S and CGI-I, Body weight and BMI.

Topiramate was not statistically superior to placebo for the following secondary endpoints: MADRS score, Attentional Impulsiveness subscale score of BIS-11, HAM-A score and Work/School Disability subscale of SDS. A summary with the rate of change of all outcome variables is presented in the accompanying table.

The median final daily dose of topiramate was 300 mg/day

PHARMACOGENOMIC RESULTS:

The results of this study did not require any analysis at the time of the writing of this report.

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|---|---|---|
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| NAME OF ACTIVE INGREDIENT: 2, 3:4, 5-Di-*O*-isopropylidene-ß-D-fructopyranose sulfamate | Page: | |

**Effect of Topiramate Treatment on Outcome Measures for Patients with Binge Eating Disorder (N=394) Randomly Assigned to 16 Weeks of Double-Blind Treatment with Topiramate or Placebo (mITT population)**

| | Effect of Topiramate | | Analysis | |
|---|---|---|---|---|
| Outcome Measures | Treatment-by-Time Interaction[a] | SE | $\chi^2$ (df=1) | p |
| Binge Days[b] | -0.211 | 0.027 | 50.97 | <0.001 |
| Binge Frequency[c] | -0.232 | 0.031 | 48.21 | <0.001 |
| Montgomery & Asberg Depression Rating Scale | 0.232 | 0.212 | 1.20 | 0.274 |
| Barratt Impulsiveness Scale, Version 11 | | | | |
| Overall Change | -0.980 | 0.322 | 9.02 | 0.003 |
| Motor Impulsiveness | -0.340 | 0.142 | 7.67 | 0.006 |
| Nonplanning Impulsiveness | -0.608 | 0.149 | 15.87 | <0.001 |
| Attentional Impulsiveness | 0.027 | 0.130 | 0.04 | 0.835 |
| Yale-Brown Obsessive Compulsive Scale (modified for binge eating) | | | | |
| Total Change | -3.154 | 0.352 | 64.21 | <0.001 |
| Obsessions | -1.527 | 0.178 | 60.04 | <0.001 |
| Compulsions | -1.621 | 0.191 | 59.00 | <0.001 |
| Three Factor Eating Questionnaire | | | | |
| Cognitive Restraint | 0.837 | 0.171 | 22.12 | <0.001 |
| Disinhibition | -1.310 | 0.161 | 54.98 | <0.001 |
| Hunger | -1.156 | 0.167 | 41.24 | <0.001 |
| Hamilton Anxiety Rating Scale | 0.245 | 0.167 | 2.14 | 0.143 |
| Sheehan Disability Scale | | | | |
| Overall Score | -1.072 | 0.266 | 15.44 | <0.001 |
| School/Work Disability | -0.168 | 0.095 | 3.07 | 0.080 |
| Social Life Disability | -0.459 | 0.105 | 18.14 | <0.001 |
| Family Life Disability | -0.459 | 0.104 | 18.38 | <0.001 |
| CGI Severity | -0.584 | 0.063 | 68.15 | <0.001 |
| Weight Change | -1.995 | 0.165 | 100.13 | <0.001 |
| Body Mass Index | -0.712 | 0.059 | 100.10 | <0.001 |

[a] Difference in rate of change between the topiramate and placebo groups, with time modeled as log(weeks + 1).
[b] Log([binge days/week] + 1).
[c] Log([binges/week] + 1).

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**Summary of Efficacy Measures: Mean Change of Scores at Final Visit (mITT Population) .**

| Outcome Measures | Topiramate N = 195 | Placebo N = 199 | P Value |
|---|---|---|---|
| **Primary efficacy measures** | | | |
| Binge days per week | –3.5 ± 1.9 | –2.5 ± 2.1 | <0.001 |
| **Secondary efficacy measures** | | | |
| Binge episodes per week | –5.0 ± 4.3 | –3.4 ± 3.8 | <0.001 |
| Montgomery-Åsberg Depression Rating Scale | –0.2 ± 7.0 | –0.7 ± 6.2 | 0.893 |
| Barratt Impulsiveness Scale, Version 11 | | | |
| Overall score | –3.9 ± 9.0 | –1.4 ± 7.9 | <0.001 |
| Motor Impulsiveness | –1.8 ± 3.8 | –0.9 ± 3.7 | 0.004 |
| Nonplanning Impulsiveness | –1.6 ± 4.5 | 0.01 ± 3.7 | <0.001 |
| Attentional Impulsiveness | –0.6 ± 3.6 | –0.5 ± 3.1 | 0.230 |
| Yale-Brown Obsessive Compulsive Scale (modified for binge eating) | | | |
| Overall score | –14.3 ± 8.9 | –7.9 ± 8.9 | <0.001 |
| Obsessive | –6.7 ± 4.6 | –3.8 ± 4.8 | <0.001 |
| Compulsive | –7.6 ± 4.8 | –4.2 ± 4.8 | <0.001 |
| Three Factor Eating Questionnaire | | | |
| Cognitive restraint | –3.5 ± 4.5 | –1.6 ± 4.5 | <0.001 |
| Disinhibition | –5.0 ± 4.7 | –2.0 ± 3.5 | <0.001 |
| Hunger | –4.5 ± 4.6 | –1.9 ± 4.1 | <0.001 |
| Hamilton Anxiety Rating Scale | –0.7 ± 4.9 | –1.3 ± 4.5 | 0.493 |
| Sheehan Disability Scale | | | |
| Overall score | –6.8 ± 7.6 | –4.9 ± 7.6 | 0.001 |
| School/Work Disability | –1.6 ± 2.6 | –1.4 ± 2.9 | 0.181 |
| Social Life Disability | –2.6 ± 3.2 | –1.7 ± 3.1 | <0.001 |
| Family Life Disability | –2.7 ± 3.0 | –1.8 ± 2.9 | <0.001 |
| Clinical Global Impression-Severity Score | –2.2 ± 1.6 | –1.1 ± 1.4 | <0.001 |
| Weight Change | –4.4 ± 5.1 | 0.2 ± 3.2 | <0.001 |
| Body Mass Index | –1.6 ± 1.8 | 0.1 ± 1.2 | <0.001 |

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|---|---|---|

SAFETY RESULTS: Topiramate was well tolerated in subjects with binge eating disorder associated with obesity. Of the subjects in the Evaluable-for-Safety population, 183 (90.6%) subjects in the topiramate group and 158 (78.2%) subjects in the placebo group experienced adverse events. The most commonly reported adverse events in the topiramate group were paraesthesia (55.9%), upper respiratory infection (18.8%), somnolence (16.8%), nausea (15.8%), taste perversion (13.9%), mouth dry (13.4%), difficulty with concentration/attention (12.9%), difficulty with memory NOS (12.4%) and headache (12.4%). The most commonly reported adverse events in the placebo group were headache (14.4%), somnolence (12.9%), paraesthesia (12.4%), nausea (12.4%) and mouth dry (10.9%). The majority of adverse events were mild to moderate in severity. Thirty-four subjects (16.8%) in the topiramate group and 22 (10.9%) in the placebo group experienced adverse events that were marked in severity.

Three subjects (1.5%) each, in the topiramate and placebo group respectively, reported serious adverse events. One subject each, in the topiramate and placebo groups, respectively, had a serious adverse event that was possibly related to study medication. One (0.5%) subject in the topiramate group and 2 (1.0%) subjects in the placebo group had serious adverse events whose relationship to study medication was considered doubtful. For 1 subject in the topiramate group, the serious adverse event was considered unrelated to study medication.

Discontinuations were 30% in both groups with the most common reason for discontinuation in the topiramate group being adverse events (16% topiramate and 8% placebo). Two subjects in the topiramate group and 1 subject in the placebo group discontinued due to serious adverse events.

No clinically relevant differences between the two treatment groups in mean vital signs and clinical laboratory test results were observed.

No deaths were reported.

CONCLUSION: In this trial, topiramate was safe and effective for the treatment of moderate to severe binge eating disorder associated with obesity. Topiramate was well tolerated, the majority of adverse events were mild to moderate in severity and no safety issues were identified.

Date of the report: [insert issue date]

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