SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) 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.: CR002674

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Assess the Efficacy and Safety of Topiramate OROS® Controlled-Release in the Treatment of Obese, Type 2 Diabetic Subjects Managed With Diet or Metformin

Coordinating Investigator(s): Julio Rosenstock, M.D., Dallas Diabetes and Endocrine Center, Dallas, TX; USA

Publication (Reference): none

Study Initiation/Completion Dates: 02 February 2004 to 06 October 2004 **Phase of development:** 2a

Objectives: The primary objective of this study was to evaluate the efficacy (in terms of percent change in body weight) and safety of topiramate 175 mg when administered once daily as topiramate OROS CR, as compared with placebo, in the treatment of obese, type 2 diabetic subjects managed with either diet alone or combined with metformin monotherapy. Secondary objectives were to evaluate other improvements in metabolic control that included changes in body mass index (BMI), anthropometric measurements, HbA_{1C}, fasting plasma glucose (FPG), response to oral glucose challenge, fasting lipids, and blood pressure.

In an exploratory analysis, health-related quality of life (HRQOL) measures were collected to examine the correlation between weight change and change in the HRQOL measures, as well as between changes in metabolic measures (e.g., HbA_{1C} and FPG) and change in the HRQOL measures. However, due to the termination of the program this analysis was not performed.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study with 2 parallel treatment groups (topiramate CR 175 mg per day and placebo) in the treatment of obese subjects with type 2 diabetes who were managed with diet or diet combined with metformin. The study was conducted at 15 sites in the United States. The study consisted of 2 screening visits, a baseline visit, 7 weeks of titration, 9 weeks of maintenance, a 2-week taper phase, and a follow-up visit 2 weeks after discontinuation of the study drug. Non-pharmacologic therapy consisted of a fixed calorie diabetic diet (600 kcal daily deficit based on calculated energy requirement), behavioral advice, and a physical activity program, and was administered to all subjects during the full study duration beginning at the baseline visit. During the titration phase, subjects in the topiramate CR group were to receive 25 mg per day topiramate CR for the first week; the daily dose was increased at increments of 25 mg each week thereafter over 7 weeks until the assigned dose of 175 mg per day was reached. Subjects continued on their assigned dose throughout the maintenance phase for 9 more weeks. During the follow-up phase after completion or premature discontinuation from the study, all subjects had their study drug gradually reduced (tapered) over 2 weeks, with a follow-up visit performed 2 weeks after the last dose of study drug. Subjects were evaluated twice during the screening phase, at baseline, every 2 weeks during the titration and maintenance phases, at the end of 2-week taper phase, and 2 weeks after discontinuation of the study drug. Study duration was approximately 21 weeks. The planned sample size was 108 subjects (approximately 54 subjects per group).

Number of Subjects (planned and analyzed): A total of 113 subjects were randomized; of these, 111 subjects contributed to the safety and efficacy analyses.

SYNOPSIS (CONTINUED)

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Diagnosis and Main Criteria for Inclusion: Subjects were required to have a stable weight (increase or decrease of no more than 3 kg [6.6 lbs]) for at least 2 months before screening visits. Other inclusion criteria included: age 18 to 75 years with a diagnosis of type 2 diabetes mellitus controlled by diet alone or combined with metformin, BMI ≥27 kg/m^2 and <50 kg/m^2, HbA_{1c} level 6.5 to 11%, and a FPG > 126 mg/dL and ≤240 mg/dL at screening. Subjects with an established diagnosis of controlled hypertension or dyslipidemia were eligible but anti-hypertensive and hypolipidemic medications must have been stable for at least 2 months prior to enrollment.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate CR was supplied as 25-mg (Batch No. 0012932) and 100-mg (Batch No. 0012788) OROS systems. Subjects were administered 1 to 4 OROS systems orally once daily.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match topiramate CR in appearance as 25 mg systems (Batch No. 0012933) and 100 mg systems (Batch No. 0012789) was supplied, and was administered orally once daily.

Duration of Treatment: The planned duration of double-blind treatment was 16 weeks, which included 7 weeks of titration and 9 weeks of maintenance therapy. There was a 2-week taper phase after maintenance therapy or at early withdrawal.

Criteria for Evaluation:

Efficacy: The primary efficacy analysis was the mean percent change in body weight from baseline to Week 16 (using the LOCF approach). Secondary efficacy endpoints included changes from baseline in mean absolute weight, BMI, anthropometric assessments, and the proportion of subjects who achieved a reduction of at least 5% and 10% of baseline weight . Other secondary efficacy endpoints included measures of glycemic control and lipid profiles, urinary albumin excretion, C-reactive protein, adiponectin, and blood pressure. A homeostatic model assessment was utilized to derive estimates of beta-cell function and insulin sensitivity. HRQOL measurements were also performed.

Safety: Safety was evaluated by examining adverse events, changes in physical examination, vital signs (blood pressure, pulse rate, and respiration rate), 12-lead electrocardiogram (ECG), and clinical laboratory test results. The abbreviated Diagnostic Interview Schedule (DIS) was administered to assess for potential development of significant depression or suicidal ideation during the study.

Statistical Methods:

Efficacy Analysis:

All efficacy analyses were based on the modified-intent-to-treat (MITT) analysis set, defined as all randomized subjects who received at least 1 dose of randomized study drug and had at least 1 post-treatment primary or secondary efficacy evaluation. The primary efficacy variable, mean percent change in body weight from baseline, was analyzed using an analysis of covariance (ANCOVA) model with treatment, diabetes treatment, and baseline body weight as factors in the model. Secondary efficacy variables evaluated other changes in metabolic control. The changes from baseline to final visit were calculated. The number and percent of 5% and 10% weight loss responders from baseline to final value were presented by treatment group and also were analyzed by the CMH test.

Safety Analysis:

The evaluation of safety was based on the incidence and severity of adverse events, including hypoglycemic events, and on changes from Baseline in 12-lead ECG results clinical laboratory tests and vital sign results. The safety analysis set consisted of all subjects who received at least one dose of randomized study drug and had at least 1 post-treatment assessment of safety.

SYNOPSIS (CONTINUED)

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SUMMARY - CONCLUSIONS

Efficacy Results: The mean percent reduction in body weight from baseline to Week 16 LOCF was statistically significantly greater in the topiramate CR group compared to the placebo group (topiramate CR, -5.8% versus placebo, -2.3%, $p<0.001$). Differences in the change in body weight were apparent between the 2 treatment groups as early as Week 2 (-1.5% versus -0.8%, respectively). The proportion of subjects with ≥5% and ≥10% weight loss was greater for the topiramate CR-treated subjects than for the placebo-treated subjects (50% versus 19%, and 20% versus 2%, respectively). Statistically significant differences were seen in the mean change in HbA_{1c} from Baseline to Week 16 (LOCF) in the topiramate CR group compared with the placebo group (-0.9% versus -0.4%, respectively). A greater percentage of subjects were 0.5%, 0.7%, and 1.0% HbA_{1c} treatment responders in the topiramate CR group compared with the placebo group. The percentage of topiramate CR-treated subjects and placebo-treated subjects who experienced reductions in HbA_{1C} level of at least 0.5% from Baseline to Week 16 (LOCF) was 65% and 33%, respectively.

Safety Results: A total of 91% and 74% of subjects in the topiramate CR and placebo groups, respectively, reported at least 1 treatment-emergent adverse event. Common treatment-emergent adverse events reported more frequently in the topiramate CR group compared to the placebo group were related to the central and peripheral nervous system (CNS and PNS; 43% versus 21%, respectively) or were neuropsychiatric in nature (33% versus 21%, respectively). Notable common treatment-emergent adverse events (≥5% of subjects) that occurred more frequently in the topiramate CR-treated than in placebo-treated subjects included but were not limited to paresthesia (28% versus 0%), dizziness (15% versus 4%), difficulty with memory, neuropathy, insomnia, somnolence, appetite increased, hypoesthesia, anxiety, and confusion (ranged from 6% to 7% versus 0% to 4%). The majority of the treatment-emergent adverse events were considered mild to moderate in severity. No clinically noteworthy differences were observed in the frequencies of treatment-emergent adverse events for subjects managed by diet alone or in combination with metformin treatment. Three subjects (2 in the placebo and 1 in the topiramate CR group) reported treatment-emergent serious adverse events. The only serious adverse event reported in the topiramate CR group was a renal calculus; this subject recovered without any clinical sequelae, but discontinued study drug. Nine subjects discontinued the study drug because of treatment-emergent adverse events. The adverse events which led to study drug discontinuation in 5 subjects in the topiramate CR group included depression, anxiety, dizziness, confusion, fatigue, and renal calculus. One subject in the topiramate CR group reported to be pregnant after she discontinued the study due to adverse events; she had a spontaneous abortion and fully recovered. Four subjects in the placebo group discontinued the study drug because of adverse events that included depression, aggravated diabetes mellitus, and hyperglycemia.

In the topiramate CR group, 3 subjects experienced markedly abnormal decreases in bicarbonate (>5 mmol/L with an absolute value of <17 mmol/L), although no cases of metabolic acidosis were reported. No other clinically relevant changes in laboratory values were seen during the study. Topiramate CR-treated subjects showed greater decreases of blood pressure and most anthropometric measurements (e.g., hip and waist circumference) compared to the placebo-treated subjects. One placebo-treated subject was hospitalized due to an ECG abnormality, but completed the study as planned.

Conclusions:

In this study involving obese subjects with type 2 diabetes managed on diet alone or in combination with metformin, topiramate CR 175 mg per day was clinically superior in efficacy to placebo, as indicated by statistically greater mean percent reductions in body weight.

Notable treatment-emergent adverse events that occurred more frequently in topiramate CR-treated subjects than in placebo-treated subjects were generally CNS or PNS related events, or events that were psychiatric in nature. The safety results with topiramate CR were consistent with the safety profile observed in clinical trials with topiramate IR in obese subjects with type 2 diabetes.

Date of the report:

07 JUNE 2005

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