SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson and Johnson Pharmaceutical Research and Development NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR003724

Title of Study: The Safety and Efficacy of RWJ-17021 in Males with Abdominal Obesity: A 6-Month, Double-blind, Randomized Placebo-Controlled Study with a 6-Month Open-label Extension.

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Study Center: CHUL Research Center, Sainte-Foy, Quebec; Canada

Publication (Reference): None

Studied Period (years): 11 January 1999 to 15 January 2002 (3 years) **Phase of development:** 2

Objectives: The primary objective of this study was to compare the effects of RWJ-17021 (topiramate) and placebo on abdominal visceral fat accumulation after 6 months of treatment, as well as to assess the safety of topiramate and after treatment of up to 12 months.

Secondary objectives included comparison of the effects of topiramate and placebo on: total abdominal fat accumulation, subcutaneous abdominal fat accumulation, the visceral-to-subcutaneous abdominal fat ratio, body composition, sagittal diameter, body weight, body mass index (BMI), anthropometric measurements, glucose tolerance in response to oral glucose (OGTT), lipids, blood pressure (BP), food preferences, macronutrient intake, satiety in response to a standard meal, basal metabolic rate (BMR), and 24-hour energy expenditure (subset of 36 subjects) at 6 months.

Methodology: Upon completion of all screening and baseline procedures, subjects who qualified for enrollment were randomized in equal numbers to receive topiramate or placebo twice daily for 6 months. Study drug was titrated over a 12-week period until a dose of 200 mg twice daily (or the maximum tolerated dose [MTD]) was reached. Subjects who completed the double-blind phase could enter the 6-month open-label phase and receive 200 mg b.i.d (or the MTD) of topiramate.

Eligibility was determined at screening and baseline. The baseline evaluations were completed within 6 weeks of the initial screening visit. Medication was accounted for and BP, pulse rate, body weight, and adverse events were assessed at each visit (excluding medication check at screening). The following assessments were performed at baseline and at Months 3, 6, 9, and 12: underwater weighing (UWW) for evaluation of body composition, anthropometric measurements, comprehensive lipid profile, satiety in response to a standard meal, 3-day food diary, and BMR. Computed tomography (CT) for evaluation of abdominal fat accumulation and sagittal diameter and food preferences were measured at baseline and at Months 3, 6, and 12. Glucose tolerance, 24-hour energy expenditure (36 subjects), and 24-hour ambulatory BP and pulse rate were assessed at baseline and Months 6 and 12. Clinical chemistries and urinalysis were performed at screening and Months 3, 6, 9, and 12. Hematology, physical examination, and ECG were performed at screening and Months 6 and 12. Pharmacokinetic (PK) plasma samples were collected at Months 3 and 6.

SYNOPSIS (CONTINUED)

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Number of Subjects (planned and analyzed): The planned total sample size was 72 men. 68 subjects were randomized, 68 subjects were included in the Double-blind Safety population, 67 subjects were included in the Double-blind Modified Intent-to-Treat population, 49 subjects were included in the Double-blind Completer population, 48 subjects were included in the Open-label Safety population, 48 subjects were included in the Open-label Modified Intent-to-Treat population, 34 subjects were included in the Open-label Completer population.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25 mg tablets (batches R7629 and R10415), to be administered orally.

Duration of Treatment: During the double-blind treatment phase, each subject received either placebo or topiramate for up to 6 months. During the open-label phase, each subject received topiramate for up to 6 months.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets identical in appearance to topiramate were provided for the study (batches R7630 and R10416), to be administered orally.

Criteria for Evaluation:

Efficacy: The criterion for the primary efficacy variable was a statistically significant decrease in mean abdominal visceral fat based on the $L_{4,5}$ section from baseline to Month 6 in the topiramate treatment group compared with the placebo group.

Secondary efficacy variables were assessed in order to provide supportive information on changes in the primary efficacy variable and to provide information on the mechanism for a decrease in abdominal visceral fat by topiramate. These secondary efficacy variables were the mean change and the mean percent change in body weight from baseline to Month 6, and the mean change from baseline to Month 6 in:

- total abdominal fat
- abdominal visceral fat based on $L_{2,3}$ section
- subcutaneous abdominal fat
- visceral-to-subcutaneous abdominal fat ratio
- sagittal diameter
- partial abdominal visceral fat volume
- body composition (percent body fat, body fat mass, fat-free mass)
- BMI
- anthropometric measures (waist circumference, WHR, skinfold thickness)
- lipid profile
- BP including assessment with 24-hour ambulatory monitoring
- glucose tolerance

Safety: The following parameters were evaluated for safety:

- adverse events (includes abnormal changes noted on physical exam)
- clinical laboratory tests
- vital signs (BP, pulse rate) including assessments from 24-hour ambulatory monitoring
- ECGs

SYNOPSIS (CONTINUED)

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Statistical Methods: Comparisons between the 2 treatment groups for the mean change from baseline to Month 6 in continuous primary efficacy, secondary efficacy and mechanism of action evaluations were made using 2-sided t-tests. Proportions of 5% and 10% weight loss responders at Month 6 were compared between treatment groups using Fisher's exact test. Pearson's correlation coefficients between changes in abdominal visceral fat and each of the secondary efficacy evaluations and mechanism of action endpoints were estimated overall, by clinically notable categories of body weight change at Month 6, and by Month 6 plasma topiramate concentration stratum for the Completer population. Each correlation coefficient was tested to determine whether the coefficient was statistically different from 0. In addition, the difference between treatment groups was tested.

Assessment of safety was based on incidence of adverse events, and changes in laboratory parameters, vital signs and ECGs. Summaries of discontinuations and exposure to study drug are presented, as is the incidence of markedly abnormal laboratory analyte values.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The primary efficacy variable, mean change in abdominal visceral fat based on $L_{4,5}$ section from baseline to Month 6, was –4.4 cm^2 in the topiramate group and 13.3 cm^2 in the placebo group. This result was not statistically significant (p=0.237 for Double-blind Modified ITT population). Nonetheless, the data in this study demonstrated that topiramate was effective in treating obesity as evidenced by significant decreases in the topiramate group at Month 6 in total abdominal fat based on $L_{4,5}$ section and $L_{2,3}$ section, abdominal visceral fat based on $L_{2,3}$ section, subcutaneous abdominal fat based on $L_{4,5}$ section, sagittal diameter based on $L_{4,5}$ section and $L_{2,3}$ section, body weight, percent body fat, body fat mass and fat-free mass. There was a significant decrease in mean percent body weight in the topiramate group compared to placebo at 6 months

In general, during the open-label phase of the study, changes in efficacy variables from baseline to Month 12 in the placebo/topiramate group paralleled the changes from baseline to Month 6 in the topiramate/topiramate group. Also, for most efficacy variables there was little change from Month 6 to Month 12 in the topiramate/topiramate group.

SAFETY RESULTS: Paresthesia, difficulty with concentration/attention, fatigue, somnolence, upper respiratory tract infection, dry mouth, and taste perversion were the most common adverse events that occurred with greater frequency in the topiramate group compared with the placebo group during the double-blind phase. The only adverse events that led to the withdrawal of more than 1 topiramate-treated subject in the double-blind phase were difficulty with concentration/attention and impotence, which were reported by 2 topiramate-treated subjects for each event. There were no deaths during the study and there were no serious adverse events in topiramate-treated subjects in the double-blind phase. Adverse events in the placebo/topiramate group during the open-label phase of the study were similar to adverse events in the topiramate group during the double-blind phase of the study. There was one topiramate-treated subject with a serious adverse event (renal calculus) during the open-label phase. There were no noteworthy changes in laboratory parameters, vital signs, or electrocardiograms during either phase of the study.

CONCLUSION: In conclusion, topiramate was effective in treating obesity in men despite a lack of a significant treatment difference in the primary efficacy variable measured at $L_{4,5}$. Body fat parameters measured at alternative levels and body weight improved significantly. No new safety concerns were associated with the use of topiramate in men with abdominal obesity.

Date of the report: 27 May 2003

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