SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: topiramate NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-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.: CR003715

Title of Study: A Double-Blind Placebo-Controlled Study with a Blinded Crossover Transition to Open-Label Extension Evaluating the Safety and Effect of Topiramate on Insulin Sensitivity in Overweight/Obese Diabetic Type 2 Subjects

Study Initiation/Completion Dates: 18 May 2000 / 16 May 2002	**Phase of development:** 2

Objectives: The primary objectives of this study were to compare the effects of topiramate and placebo on insulin sensitivity in type 2 diabetic subjects and evaluate the safety of topiramate in subjects with diabetes. Secondary objectives included comparison of the effects of topiramate and placebo on total and subcutaneous abdominal fat accumulation, the abdominal visceral-to-subcutaneous fat ratio, body composition (percent body fat, body fat mass, and fat-free mass), body weight, body mass index (BMI), anthropometric measurements (waist circumference and waist-hip ratio), metabolic control including both glucose and lipid levels, and blood pressure (BP).

Methodology: This was a randomized, double-blind, parallel-group, placebo-controlled, single-center study with 2 parallel treatment groups (topiramate 192 mg/day and placebo) in the treatment of obese subjects with type 2 diabetes. The study consisted of a 6-week screening phase, an 8-week titration phase, a 9-month maintenance phase, an 8-week crossover period to the optional open-label extension phase, an optional 1-year open-label extension phase, and a 6-week follow-up phase. After a 6-week screening phase, subjects were to be randomized into 1 of the 2 treatment groups. During the titration phase, topiramate-treated subjects were to be started at 16 mg/day and have their dose increased to 32 mg/day (16 mg b.i.d.) in the second week, and in 32 mg/day increments thereafter until the assigned dose was reached. Subjects were to continue on their assigned dose throughout the maintenance phase. After completion of the double-blind maintenance phase, subjects were to have the option to begin open-label topiramate treatment for 1 year. During the open-label phase, subjects in the topiramate group were to continue on their final double-blind dose with the option of going to 256 mg/day (128 mg twice daily [b.i.d.]) and topiramate was to be introduced to subjects in the placebo group (titrated over an 8-week period until a dose of 96 mg b.i.d. was reached, with the option of going to 256 mg/day [128 mg b.i.d.]). Subjects were to be evaluated every 2 weeks during initial titration and every month until completion during the double-blind and open-label phases. All subjects were to have their study drug gradually reduced (tapered) over 2 weeks upon completion or premature discontinuation from the double-blind or open-label extension phases of the study. A follow-up visit was to be performed 4 weeks after the last dose of study drug. The planned sample size was 40 subjects (approximately 20 subjects per group). Subjects were to be nonsmoking men aged 35 to 75 years and postmenopausal women aged 45 to 75 years who had had type 2 diabetes for at least 6 months prior to enrollment, glycosylated hemoglobin (HbA_{1c}) between 6.5 and 10%, and BMI between 27 and 50 kg/m^2. Subjects must have been on a stable diet or treated with a stable dose of a second-generation sulfonylurea for at least 6 months prior to enrollment. Due to early termination of the study by the sponsor, some subjects were not able to complete the double-blind phases of the study. All subjects were encouraged to complete the follow-up phase. This report presents results primarily from the double-blind phases of the study.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

The efficacy analyses and results are presented in terms of change from baseline to Month 11 (at the end of the double-blind phase), whereas the protocol refers to change from baseline to Month 9 (of the double-blind maintenance phase). These are equivalent, as the double-blind phase includes a 2-month titration period and a 9-month maintenance phase.

Efficacy: The primary efficacy variable was mean change in insulin sensitivity, adjusted for lean body mass using the Total Body Potassium Method [^{40}K methodology], from baseline to Month 11 for the Intent-to-treat (ITT) population. The ITT population was the primary population for efficacy analysis and included all randomized subjects who received at least 1 dose of study drug and provided at least 1 post-baseline primary or secondary efficacy evaluation. Because there was significant doubt about the validity of outcome of the ^{40}K methodology for measuring lean body mass, an alternative methodology was also used to estimate the lean body mass: the computed tomography (CT) methodology, and the relationship between lean body mass measurements taken using ^{40}K and CT methodology was assessed using correlation analyses. The study was exploratory in nature and was not formally powered to detect differences in insulin sensitivity between groups.

Since the study was terminated prematurely, the following secondary efficacy parameters were evaluated at the end of the double-blind phase using the ITT population, last observation carried forward (LOCF), and are presented in this report: mean change in insulin sensitivity unadjusted for lean body mass from baseline to Month 11; mean change in lean body mass using ^{40}K and CT methodologies from baseline to Month 11; mean change in total body fat mass using the ^{40}K methodology from baseline to Month 11; mean change in visceral abdominal fat from baseline to Month 11; mean percent change in body weight and mean change in HbA_{1c} from baseline to Month 11 and over time; body weight responders (subjects with ≥5% and ≥10% reductions in body weight from baseline to Month 11); mean changes in fasting plasma glucose (FPG) and lipid profile from baseline to Month 11; and mean changes in hepatic glucose production and peripheral glucose disposal rate from baseline to Month 11.

Safety: Safety assessment was based on reported adverse events and change from baseline in clinical laboratory tests, vital sign measurements, physical examinations, and electrocardiogram (ECG) findings.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Key efficacy results are summarized in Table A. The mean change in insulin sensitivity adjusted for lean body mass (^{40}K methodology) from baseline to Month 11 (LOCF) in the ITT population was 1.2 mg/[kg fat-free mass × min] in the placebo group and 1.1 mg/[kg fat-free mass × min] in the topiramate 192 mg/day group, and there was no statistically significant difference between the 2 treatment groups. There was also no statistically significant difference between the 2 treatment groups in mean change from baseline to Month 11 (LOCF) in insulin sensitivity adjusted for lean body mass (CT methodology).

Table A: Summary of Key Efficacy Results
(Protocol CR003715)

	Placebo (N=19)	TPM 192 mg/day (N=19)
Insulin sensitivity (^{40}K methodology)		
Mean Change (SD) mg/[kg fat free mass × min]	1.15 (1.38)	1.07 (2.13)
Insulin sensitivity (CT methodology)		
Mean Change (SD) mg/[kg fat free mass × min]	0.89 (1.35)	0.69 (2.17)
Body Weight (kg)		
Mean % Change (SD)	0.38 (2.59)	–4.84[a] (3.95)
5% responders; N (%)	1 (5)	7 (37)
10% responders; N (%)	0	3 (16)
HbA_{1c} (%)		
Mean % Change (SD)	0.19 (0.71)	−1.01[a] (0.91)

[a] p value <0.001 (t-test, for differences from placebo)

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Subjects in the topiramate 192 mg/day group had a statistically significant greater reduction in body weight from baseline to Month 11 (LOCF) compared with the placebo group (mean percent weight change of –4.8% in the topiramate 192 mg/day group and 0.4% in the placebo group, $p<0.001$). The topiramate 192 mg/day group had a statistically significant greater mean change in HbA_{1c} from baseline to Month 11 (LOCF) than the placebo group: mean change was 0.2% in the placebo group and –1.0% in the topiramate 192 mg/day group, $p<0.001$.

SAFETY RESULTS: Common treatment-emergent adverse events that occurred more frequently in topiramate-treated subjects than in placebo-treated subjects were generally related to the central nervous system (CNS) (Table B).

Table B: Incidence of Common[a] Treatment-Emergent Adverse Events
(Safety Population; Protocol CR003715)

Body System Preferred Term	Placebo (N=19) N	%	TPM 192 mg/day (N=19) N	%
Any Adverse Event	18	(95)	18	(95)
CNS-Related[b]				
Paresthesia	4	(21)	15	(79)
Headache	4	(21)	6	(32)
Fatigue	4	(21)	6	(32)
Dizziness	2	(11)	3	(16)
Anorexia	0		3	(16)
Depression	1	(5)	2	(11)
Difficulty with Concentration/Attention	0		2	(11)
Insomnia	1	(5)	2	(11)
Nervousness	0		2	(11)
Other Body Systems				
Breast Neoplasm Malignant Female[c]	0		1	(20)
Nausea	1	(5)	3	(16)
Gastritis	0		2	(11)
Mouth Dry	0		2	(11)
Tooth Caries	0		2	(11)
Muscle Weakness	0		2	(11)

[a] Includes events that occurred in ≥10% of topiramate-treated subjects and occurred more often in topiramate-treated than placebo-treated subjects.
[b] Central nervous system (CNS)-related events include those that involved the central or peripheral nervous system, were psychiatric in nature, and include fatigue.
[c] Only female subjects are included as denominators for female-specific adverse events (placebo, N=8, topiramate 192 mg/day, N=5).

Overall, 1 (5%) of 19 subjects in the placebo group and 8 (42%) of 19 subjects in the topiramate 192 mg/day group discontinued during the double-blind phase due to an adverse event. Adverse events resulting in discontinuation of therapy in >10% of topiramate-treated subjects (i.e., at least 2 subjects) were generally CNS-related and included paresthesia (5 subjects, 26%), fatigue (4 subjects, 21%), and anorexia (2 subjects, 11%). No subjects died during the study. One (5%) of 19 subjects in the placebo group and 3 (16%) of 19 subjects in the topiramate 192 mg/day group experienced 1 or more serious adverse events during the double-blind phase of the study. No serious adverse events were considered related to study medication. There were no major noteworthy differences between the treatment groups in changes from baseline to the final visit (LOCF) in the majority of laboratory values.

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CONCLUSION: In this exploratory trial in obese subjects with type 2 diabetes, there was no statistically significant difference in the change in insulin sensitivity adjusted for lean body mass (^{40}K methodology or CT methodology) baseline to Month 11 between subjects in the placebo group and subjects in the topiramate 192 mg/day group. The study was not powered to detect a difference in insulin sensitivity between the 2 treatment groups and thus the effects of topiramate on insulin sensitivity remain to be fully defined.

Body weight and HbA_{1c} were significantly reduced on topiramate treatment compared to placebo.

Common treatment-emergent adverse events that occurred more frequently in topiramate-treated subjects than in placebo-treated subjects were generally CNS-related, including the central or peripheral nervous system, events that were psychiatric in nature, or fatigue.

Date of the report: 10 November 2003

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