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.: CR003718 **Title of Study:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Topiramate (RWJ-17021) in the Treatment of Obese Type 2 Diabetic Subjects Treated with Metformin		
Study Initiation/Completion Dates: 11 October 2000; 14 June 2002.		**Phase of development:** 3
Objectives: The primary objective of this clinical study was to compare the efficacy (in terms of changes in weight and glycosylated hemoglobin [HbA_{1c}]) and safety of 96 mg or 192 mg topiramate daily with placebo in the treatment of obese type 2 diabetic subjects treated with metformin.		
Methodology: This was a randomized, double blind, placebo-controlled, multicenter study with 3 parallel treatment groups (topiramate 96 and 192 mg/day, and placebo) in the treatment of obese subjects with type 2 diabetes who were being treated with metformin. The study consisted of 4phases: a 6-week run-in phase, an 8-week titration phase, a 52-week maintenance phase, and a 6-week follow-up phase. After completing the run-in phase (a single-blind placebo-treatment period in which subjects began non-pharmacologic therapy), subjects who met study inclusion criteria and were deemed compliant with run-in placebo medication and non-pharmacologic therapy and did not lose ≥6% of their enrollment body weight were to be randomized into 1of the 3 treatment arms. Non-pharmacologic therapy consisted of a 600 kcal hypocaloric diet and behavioral advice and was administered to all study subjects during the full study duration, irrespective of treatment allocation. During the titration phase, topiramate-treated subjects were to be started at 16 mg/day for the first week, 32 mg/day for the second week, and have a dose increase in increments of 32 mg/week thereafter until the assigned dose was reached. Subjects were to continue on their assigned dose throughout the maintenance phase. During the follow-up phase, all subjects were to have their dose of study medication gradually reduced over 2 weeks upon completion or premature discontinuation from the study, and a follow-up visit was to be performed 4 weeks after the last dose of study medication. Total participation for each subject was to be approximately 72 weeks. Subjects were to be instructed to follow non-pharmacologic therapy for the duration of the study, including the run-in and follow-up phases. Subjects were to be evaluated every 2 weeks during the run-in and titration phases, every 4 weeks during the maintenance phase, and twice during the follow-up phase (after the 2-week taper and again 4 weeks later). The planned sample size was 540 subjects (approximately 180 per group). Subjects were to be aged 18 to 75 years, with a body mass index (BMI) ≥27 kg/m^2 and <50 kg/m^2 and a history of Type 2 diabetes mellitus treated with a stable dose of metformin monotherapy, and have had a glycosylated hemoglobin (HbA_{1c}) level <11% and fasting plasma glucose (FPG) level ≥7 mmol/L (126 mg/dL) and <13.1 mmol/L (240 mg/dL) at the enrollment and baseline visits. Subjects must have been on metformin monotherapy for the previous 4 months with a stable daily dose (not exceeding 2.1 g/day) for 2 months prior to enrollment. Subjects were not permitted to alter background metformin therapy except for protocol-specified criteria of reaching a target HbA_{1c} (6.5%) on 2 consecutive occasions or severe or recurrent hypoglycemia. Subjects may have had an established diagnosis of controlled hypertension or dyslipidemia, with their anti-hypertensive and hypolipidemic medication stable for at least 2 months prior to enrollment. Due to early termination of the study by the Sponsor, the majority of subjects were not able to complete the full 52-week maintenance phase of the study. All subjects were encouraged to complete the follow-up phase.		

SYNOPSIS (Continued)

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Criteria for Evaluation:

Efficacy: The primary efficacy variables were percent change in weight and absolute change in HbA_{1c} from baseline to Week 24 in the Modified intent-to-treat (MITT) population. The MITT population was predefined prior to database lock and was the primary population for efficacy analysis. It consisted of all randomized subjects who received at least 1 dose of study drug and provided at least 1 on-treatment primary or secondary efficacy evaluation AND who had the opportunity to complete at least 24 weeks of double-blind (8-week titration and 16-week maintenance) treatment before announcement of early termination of the study. Efficacy results are presented for the MITT and ITT populations. The ITT population included all randomized subjects who received at least 1 dose of study medication and had at least 1 on-treatment primary or secondary efficacy evaluation.

Since the study was terminated prematurely, only the 2 primary efficacy parameters and selected secondary efficacy parameters are presented in this abbreviated report. These include the data for the MITT population presented by last observation carried forward (LOCF) analysis of percent changes in body weight and absolute changes in HbA_{1c} over time, mean absolute changes in FPG, fasting insulin, and absolute changes in metformin doses from baseline to Week 24, absolute changes in HbA_{1c} from baseline to Week 24 for subjects who had at least 7% and at least 8% HbA_{1c} levels at baseline, body weight treatment responders (subjects with ≥5% and ≥10% reductions in body weight from baseline to Week 24), mean changes from baseline to Week 24 for lipids, mean changes from baseline to Week 24 for blood pressure, and mean changes from baseline to Week 24 for blood pressure for subjects with baseline systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. These efficacy analyses are also presented for the ITT population using change from baseline to the final value obtained during titration/maintenance treatment.

Safety: Safety assessment was based on reported adverse events, clinical laboratory parameters, vital sign measurements, and electrocardiogram (ECG) findings.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: At topiramate dosages of 96 and 192 mg/day, topiramate-treated subjects in the MITT population achieved mean percent reductions in body weight from baseline to Week 24 of -4.5% and -6.5%, while placebo-treated subjects had a mean percent reduction from baseline body weight of -1.7% (LOCF analysis). Topiramate-treated subjects achieved mean reductions in HbA_{1c} levels from baseline to Week 24 of -0.4% and -0.6%, while placebo-treated subjects had a mean percent reduction from baseline HbA_{1c} of -0.1% (LOCF analysis). Each of the 2 topiramate treatment groups was superior to placebo as indicated by statistically greater ($p<0.001$) mean percent reductions in body weight and mean reductions in HbA_{1c} levels from baseline to Week 24. See Table A.

The primary efficacy results for the ITT population were similar to those for the MITT population (see Table B).

Table A Summary of Key Efficacy Results
(Protocol CR003718; MITT Population, LOCF)

	Placebo (N=100)		TPM 96 mg/day (N=102)		TPM 192 mg/day (N=105)	
Body Weight						
Mean % change (SD)	-1.69	(3.02)	-4.49[a]	(3.74)	-6.54[a]	(4.77)
HbA_{1c} (%)						
Mean change (SD); %	-0.09	(0.579)	-0.41[a]	(0.627)	-0.57[a]	(0.569)

[a] $p<0.001$ topiramate vs. placebo; adjusted p values from Dunnett and Tamhane step-down multiple testing procedure.

Table B Summary of Key Efficacy Results
(Protocol CR003718; ITT Population, LOCF)

	Placebo (N=207)		TPM 96 mg/day (N=217)		TPM 192 mg/day (N=213)	
Body Weight (kg)						
Mean % change (SD)	-1.20	(3.29)	-4.49[a]	(3.90)	-5.78[a]	(5.10)
HbA_{1c} (%)						
Mean change (SD); %	0.11	(0.604)	-0.30[a]	(0.652)	-0.42[a]	(0.646)

[a] $p<0.001$ topiramate vs. placebo; p values from contrast statements.

Among subjects who received topiramate, there were consistent mean decreases from baseline to Week 24 in fasting plasma glucose, diastolic blood pressure, and systolic blood pressure; these decreases were greater in the topiramate groups compared to placebo. There was a greater percentage of body weight responders (5% and 10% responders) in each of the topiramate groups compared to placebo. Mean changes in fasting insulin were variable. The majority of subjects in each group (placebo and topiramate) had no change in their metformin use during the study. Most mean changes in lipid values were variable and modest. There was a statistically significant reduction in triglycerides for the topiramate 192 mg/day group vs. placebo. There were small but statistically significant increases in LDL-to-HDL cholesterol ratios and lipoprotein A in the topiramate 192 mg/day group.

In general, the efficacy results for the ITT were similar to those for the MITT population. The statistically significant, placebo-subtracted improvements in body weight and HbA_{1c} were similar for the MIT T and ITT populations.

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SAFETY RESULTS: Common treatment-emergent adverse events (i.e., occurring in ≥5% of topiramate-treated subjects and greater than placebo) that occurred more frequently in topiramate-treated than in placebo-treated subjects are presented in Table C.

Table C: Incidence of the Most Common[a] Treatment-Emergent Adverse Events (Protocol CR003718; Safety Population)

Body System Preferred Term	Placebo (N=208) N (%)	TPM 96 mg/day (N=219) N (%)	TPM 192 mg/day (N=213) N (%)	Total TPM (N=432) N (%)
CNS-Related[b]				
Paresthesia	16 (8)	57 (26)	82 (38)	139 (32)
Headache	25 (12)	22 (10)	38 (18)	60 (14)
Fatigue	11 (5)	24 (11)	28 (13)	52 (12)
Hypoesthesia	0	15 (7)	20 (9)	35 (8)
Dizziness	10 (5)	15 (7)	19 (9)	34 (8)
Depression	9 (4)	11 (5)	23 (11)	34 (8)
Anorexia	4 (2)	13 (6)	20 (9)	33 (8)
Insomnia	8 (4)	16 (7)	8 (4)	24 (6)
Difficulty with concentration/attention	1 (<1)	6 (3)	14 (7)	20 (5)
Other Body Systems				
Upper respiratory tract infection	51 (25)	71 (32)	74 (35)	145 (34)
Back pain	21 (10)	28 (13)	27 (13)	55 (13)
Diarrhea	19 (9)	20 (9)	23 (11)	43 (10)
Infection viral	17 (8)	25 (11)	17 (8)	42 (10)
Coughing	11 (5)	15 (7)	19 (9)	34 (8)
Nausea	8 (4)	15 (7)	17 (8)	32 (7)
Constipation	4 (2)	13 (6)	18 (8)	31 (7)
Taste perversion	1 (<1)	11 (5)	18 (8)	29 (7)
Pain	6 (3)	10 (5)	17 (8)	27 (6)
Pharyngitis	8 (4)	14 (6)	12 (6)	26 (6)
Hypoglycemic reaction	11 (5)	14 (6)	10 (5)	24 (6)
Mouth dry	1 (<1)	12 (5)	12 (6)	24 (6)
Dyspepsia	5 (2)	14 (6)	9 (4)	23 (5)

[a] Includes events that occurred in ≥5% topiramate-treated subjects and greater than placebo across the 2 treatment groups.
[b] Central nervous system (CNS)-related events include events that involved the central or peripheral nervous system, including fatigue, or were psychiatric in nature.

The adverse events most often resulting in discontinuation of therapy across the topiramate dosage groups were mainly CNS-related, defined as including the central or peripheral nervous system, events that were psychiatric in nature, or fatigue. These included paresthesia (12 subjects, 3%), depression (9 subjects, 2%), fatigue and headache (8 subjects, 2%), and dizziness and hypoesthesia (7 subjects, 2% each). Overall, 15 (7%) of 208 subjects in the placebo group and 58 (13%) of 432 topiramate-treated subjects discontinued due to an adverse event. Overall, 8 (4%) of 208 subjects in the placebo group and 29 (7%) of 432 topiramate-treated subjects experienced 1 or more serious treatment-emergent adverse events. Serious adverse events in topiramate-treated subjects that were considered to be of at least possible relationship to study medication were: increased phosphatase alkaline and increased hepatic enzymes (1 subject); and diarrhea, fever, viral infection, hepatic failure, leukopenia, acute renal failure, hemorrhage, and death (in 1 subject). One subject reported suicidal tendency and depression as a non-serious, limiting adverse event, assessed by the investigator as possibly related to study medication. One subject in the topiramate 192 mg/day group died during the study from hemorrhage secondary to hepatic failure. The investigator considered the events leading to the death as possibly related to the study medication.

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Laboratory abnormalities were reported as adverse events in 2 subjects (hypokalemia and increased hepatic enzymes), and 1subject experienced exacerbation of diabetes; these subjects discontinued topiramate therapy. Serum bicarbonate levels were reported as markedly low (<17 mmol/L + >5 mmol/L decrease) in 2% of placebo-treated subjects and in 15% of topiramate-treated subjects. This is most probably due to the carbonic anhydrase inhibitory activity of topiramate. There were no adverse events of metabolic acidosis. There were no other noteworthy changes in laboratory values. One topiramate-treated subject experienced limiting, non-serious renal calculus and renal pain.		
CONCLUSION: In this study in obese type 2 diabetic subjects treated with metformin, both topiramate dosages – 96 and 192 mg/day – were superior to placebo as indicated by statistically greater mean reductions in percent body weight and HbA_{1c} level. Reductions in HbA_{1c} were greatest for patients with elevated baseline values. Reductions were also noted in fasting plasma glucose and systolic and diastolic blood pressure (change in diastolic blood pressure for the MITT population was not statistically significant, however). In topiramate-treated obese diabetic subjects, notable treatment-emergent adverse events that occurred more frequently in topiramate-treated than in placebo-treated subjects included, but were not limited to, paresthesia, fatigue, hypoesthesia, depression, taste perversion, and difficulty with concentration and attention. Topiramate was generally well tolerated in this diabetic obese population. Date of the report: 11 November 2003		

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