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.: CR003712 **Title of Study:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Topiramate (RWJ-17021) in the Treatment of Type 2 Diabetic, Obese Subjects Treated With Diet Alone		
Study Initiation/Completion Dates: 08 January 2001 / 24 May 2002		**Phase of development:** 3
Objectives: The primary objectives of this study were to compare the safety and efficacy of topiramate (96 or 192 mg daily) as compared to placebo in obese type 2 diabetic subjects treated with diet alone as determined by the percent change in body weight and the absolute change in glycosylated hemoglobin (HbA_{1c}) from enrollment Visit 1b (Week –6) to Visit 21 (Week 60).		
Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study with 3 parallel treatment groups (topiramate 96 mg/day and 192 mg/day and placebo). The study was conducted at 20 sites in Sweden. The study consisted of 5 phases: a 5-week pre-enrollment phase, a 6-week run-in phase, an 8-week titration phase, a 52-week maintenance phase, and a 6-week follow-up phase. The double-blind phase refers to the titration and maintenance phases. Non-pharmacologic therapy consisting of a 600 kcal hypocaloric diet, behavioral modification, and a physical activity program was administered to each subject during the full study duration, irrespective of treatment group allocation. Subjects must have had stable weight (increase or decrease of no more than 3 kg [6.6 lbs]) during the pre-enrollment to be eligible for enrollment, and a decrease of <6% of their enrollment weight during the single-blind placebo run-in phase to be eligible for randomization. During the titration phase, subjects randomly assigned to receive topiramate were to receive 16 mg/day topiramate for the first week, 32 mg/day for the second week, and dose increased at increments of 32 mg/week thereafter until the assigned dose was reached. Subjects continued on their assigned dose throughout the maintenance phase for 1 year. During the follow-up phase, all subjects had their study drug gradually reduced (tapered) over 2 weeks upon completion or premature discontinuation from the study, with a follow-up visit performed 4 weeks after the last dose of study medication. Subjects were evaluated twice during the pre-enrollment phase, 4 times during the run-in phase, every 2 weeks during the titration phase, every 4 weeks during the maintenance phase, and twice during the follow-up phase. Study duration was to be approximately 77 weeks. The planned sample size was 540 subjects (approximately 180 per group). Subjects were to be age 18 to 75 years with a diagnosis of type 2 diabetes mellitus treated by diet alone, with no previous history of anti-diabetic drug treatment, a body mass index (BMI) ≥27 kg/m^2 and <50 kg/m^2, HbA_{1c} level ≤10.5% by the Diabetes Control and Complications Trial (DCCT) technique at enrollment, and fasting plasma glucose (FPG) <13.1 mmol/L (240 mg/dL) at the baseline visit (Week 0). Subjects with an established diagnosis of controlled hypertension or dyslipidemia could have been enrolled; anti-hypertensive and hypolipidemic medications must have been stable for at least 2 months prior to enrollment. Subjects were encouraged to maintain stable doses of background anti-hypertensive and lipid-lowering therapies. Due to early termination of the study by the sponsor, no subjects completed the 52-week maintenance phase of the study. All subjects were encouraged to complete the follow-up phase.		
Criteria for Evaluation: Efficacy: The primary efficacy variables were percent change in weight and absolute change in HbA_{1c} from baseline to Week 40 in the Modified intent-to-treat (MITT) population. The MITT population predefined prior to database lock was the primary population for efficacy analysis and 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 40 weeks of double-blind (8-week titration and 32-week maintenance) treatment before announcement of early termination of the study.		

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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. The data for MITT and ITT populations are presented using last observation carried forward (LOCF) approach.

Since the study was terminated prematurely, the 2 predefined primary efficacy parameters and selected secondary efficacy parameters are presented in this abbreviated report. These include, for the MITT population, using change from baseline to Week 40, percent changes in body weight and absolute changes in HbA_{1c} over time, mean absolute changes in FPG, absolute changes in HbA_{1c} for subjects with HbA_{1c} at least 7% and 8% at baseline, body weight treatment responders (subjects with ≥5% and ≥10% reductions in body weight from baseline to Week 40), mean changes for fasting lipids, mean changes in sitting blood pressure, and mean changes 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. Also presented for ITT observed analyses only are mean absolute changes from baseline to Week 32 value in body composition, 24-hour urinary albumin excretion, and 2.0 hour plasma glucose and insulin.

Safety: Safety data are presented for all randomized subjects with at least 1 post-baseline safety assessment. These include adverse events, clinical laboratory parameters, vital sign measurements, electrocardiogram (ECG) findings, echocardiogram assessments, renal ultrasound evaluations, and ophthalmic/visual assessments.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Key efficacy results are summarized in Table A for the MITT population (LOCF analysis). At dosages of 96 and 192 mg/day topiramate, subjects in the MITT population achieved mean percent reductions in body weight from baseline to Week 40 of 6.6% and 9.1%, respectively, while placebo-treated subjects had a mean percent reduction of 2.5%. Subjects in the MITT population who were treated with 96 and 192 mg/day topiramate also achieved mean reductions in HbA_{1c} levels of 0.6% and 0.7%, respectively, compared to a mean percent reduction of 0.2% in the placebo group. Each of the 2 topiramate groups was superior to placebo as indicated by statistically greater mean percent reductions from baseline body weight and statistically greater mean reductions from baseline HbA_{1c} levels (adjusted $p<0.001$). The primary efficacy results for the ITT population were similar to those for the MITT population (see Table B).

Table A: Summary of Primary Efficacy Results (Change from Baseline to the Week 40 LOCF Value)
(Protocol CR003712; MITT Population)

	Placebo (N=78)		TPM 96 mg/day (N=74)		TPM 192 mg/day (N=77)	
Body Weight (kg)						
Mean % change (SD)	-2.53	(3.604)	-6.64[a]	(5.462)	-9.12[a]	(5.664)
HbA_{1c} (%)						
Mean change (SD), %	-0.16	(0.565)	-0.59[a]	(0.544)	-0.66[a]	(0.500)

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

Table B: Summary of Primary Efficacy Results (Change from Baseline to the Final LOCF Value)
(Protocol CR003712; ITT Population)

	Placebo (N=78)		TPM 96 mg/day (N=74)		TPM 192 mg/day (N=77)	
Body Weight (kg)						
Mean % change (SD)	-2.62	(3.791)	-6.92[a]	(5.688)	-8.92[a]	(6.120)
HbA1c (%)						
Mean change (SD), %	-0.06	(0.553)	-0.50[a]	(0.541)	-0.51[a]	(0.563)

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

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The statistically significant placebo-subtracted improvements in body weight and HbA_{1c} levels were similar for the MITT and ITT populations.

Among subjects who received topiramate, there were consistent mean decreases from baseline to Week 40 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. Changes in most fasting lipid values were variable and modest compared to placebo.

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

Table C: Incidence of the Most Common[a] Treatment-Emergent Adverse Events (Protocol CR003712; Safety Population)

Body System Preferred Term	Placebo (N=180) N (%)	TPM 96 mg/day (N=178) N (%)	TPM 192 mg/day (N=177) N (%)	Total TPM (N=355) N (%)
CNS-Related[b]				
Paresthesia	21 (12)	67 (38)	95 (54)	162 (46)
Fatigue	42 (23)	43 (24)	48 (27)	91 (26)
Hypoesthesia	8 (4)	21 (12)	31 (18)	52 (15)
Vertigo	4 (2)	12 (7)	6 (3)	18 (5)
Other Body Systems				
Injury	15 (8)	23 (13)	20 (11)	43 (12)
Vision abnormal	8 (4)	16 (9)	19 (11)	35 (10)
Nausea	15 (8)	17 (10)	16 (9)	33 (9)
Mouth dry	8 (4)	11 (6)	20 (11)	31 (9)
Difficulty with concentration/attention	5 (3)	19 (11)	13 (7)	32 (9)
Difficulty with memory	7 (4)	15 (8)	13 (7)	28 (8)
Taste perversion	6 (3)	8 (4)	20 (11)	28 (8)
Constipation	5 (3)	10 (6)	11 (6)	21 (6)

[a] Includes events that occurred in ≥5% all topiramate treated subjects and occurred more often in topiramate-treated than placebo-treated subjects.

[b] Central nervous system (CNS)-related events include events that involved the central or peripheral nervous system, were psychiatric in nature, or fatigue.

The adverse events most often resulting in discontinuation of therapy across the topiramate dosage groups were CNS-related (defined as including the central or peripheral nervous system, events that were psychiatric in nature, or fatigue). These included paresthesia (5%), difficulty with memory (3%), depression (3%), headache (2%), fatigue (2%), hypoesthesia (2%), and difficulty with concentration/attention (2%). Overall, 12% of subjects in the placebo group and 19% of topiramate-treated subjects discontinued due to an adverse event. Overall, 4% of subjects in the placebo group and 6% of topiramate-treated subjects experienced 1 or more serious adverse events during double-blind phase. Serious adverse events in topiramate-treated subjects that were considered to be of at least possible relationship to study medication were injury due to right fibular fracture and glaucoma (1 subject each). One topiramate-treated subject died following the study from pancreatic cancer, considered of doubtful relationship to study medication. There was a reduction in bicarbonate plasma levels to below the normal range (i.e. 18-30.6 mmol/L) in 13% of topiramate-treated subjects, compared to 2% in placebo. No clinical cases of metabolic acidosis were reported. There were no other noteworthy changes in laboratory values from baseline to Week 40. Four topiramate-treated subjects experienced non-serious, non-limiting adverse events of renal calculus.

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CONCLUSION: In this trial in obese subjects with type 2 diabetes who were treated with diet alone, both topiramate dosages – 96 and 192 mg/day – were superior to placebo as indicated by statistically greater mean percent change in body weight and statistically greater mean change in HbA_{1c} level. Reductions in HbA_{1c} were greatest with subjects with elevated baseline values. Reductions were also noted in fasting plasma glucose and sitting systolic and diastolic blood pressure. Notable common 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, injury, vision abnormal, dry mouth, difficulty with concentration and attention, difficulty with memory, and taste perversion. Date of the report: 11 November 2003		

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