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.: CR002251 **Title of Study:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese, Type 2 Diabetic Subjects Inadequately Controlled on Sulfonylurea Therapy		
Study Initiation/Completion Dates: 29 March 2001 / 05 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 HbA_{1c}) and safety of 96 mg, 192 mg, and 256 mg topiramate daily with placebo in the treatment of obese, type 2 diabetic subjects who have failed to achieve adequate glycemic control on sulfonylurea therapy.		
Methodology: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study with 4 treatment groups (topiramate 96 mg, topiramate 192 mg, topiramate 256 mg, and placebo) in the treatment of obese, type 2 diabetic subjects who had failed to achieve adequate glycemic control on sulfonylurea therapy. The study consisted of 4 phases: a 4-week enrollment phase, an 8-week titration phase, a 44-week maintenance phase, and a 6-week follow-up phase. After completing the enrollment phase, subjects who met study eligibility criteria were to be randomized into one of the 4 treatment arms using the Interactive Voice Response System (IVRS). Subjects were to be instructed to follow non-pharmacologic therapy for the duration of the study, including the enrollment and follow-up phases. Non-pharmacologic therapy (Pathways to Change®) consisted of an individual diet, a behavioral modification program, and a physical activity program. During the titration phase, subjects randomized to receive active topiramate treatment were to receive 16 mg/day topiramate initially. Study medication was increased to 32 mg/day (16 mg b.i.d.) in the second week, and then at 32 mg/day increments until the target dose was reached. During the maintenance phase, subjects were to continue to receive their assigned dosage for 44 weeks. During the follow-up phase, treatment with topiramate was to be tapered over 2 weeks and subjects were to return for their final study visit 4 weeks later. Total participation for each subject was to be approximately 62 weeks. Subjects were to be evaluated 3 times during the enrollment phase, every 2 weeks during the titration phase, every 4 weeks during the maintenance phase, and twice during the follow-up phase (after the 2-week taper and again 4 weeks later). There were 580 subjects planned (approximately 145 subjects per group). Subjects were to be aged 18 to 75 years, with a body mass index (BMI) $\geq$27 kg/m^2 and <50 kg/m^2, an established diagnosis of type 2 diabetes mellitus, glycosylated hemoglobin (HbA_{1c}) <11% and a fasting plasma glucose (FPG) $\geq$7 mmol/L (126 mg/dL) and <13.1 mmol/L (240 mg/dL), and on a stable maximal or sub-maximal dose of second generation sulfonylurea monotherapy at enrollment. Subjects must have been taking sulfonylurea therapy (a dose of at least 50% of the labeled maximim dose) for at least 4 months and on a stable dose for at least 2 months prior to the enrollment visit. Subjects were encouraged to maintain a stable sulfonylurea dose during the study. Down-titration of the dose was allowed on 1 occasion in the presence of protocol-defined severe or recurrent hypoglycemia. Permitted sulfonylurea therapies included glipizide, gliclazide, glimepiride, glibenclamide/glyburide, and gliquadone. Subjects could have 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, no subjects completed the full 44-week maintenance phase. All subjects were encouraged to complete the follow-up phase.		
Criteria for Evaluation: Efficacy: Since the study was terminated prematurely, only the 2 primary efficacy parameters – mean percent change in body weight and change in HbA_{1c} from baseline to final last observation carried forward (LOCF) value – and selected secondary efficacy parameters – observed percent changes in body weight over time, observed changes in HbA_{1c} over time, observed changes in fasting plasma glucose over time, and observed changes in fasting insulin over time – are presented for the Intent-to-Treat (ITT) population in this report.		

SYNOPSIS (CONTINUED)

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

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The study was terminated relatively early into its conduct. The median exposure to study medication (including titration) was 97, 70, 70, and 86 days, for the placebo, topiramate 96, 192, and 256 mg/day groups, respectively.

Key efficacy results are summarized in Table A. At dosages of 96, 192, and 256 mg/day topiramate, subjects in the ITT population achieved mean percent changes in body weight from baseline to final value of –3.3%, -3.1%, and -3.5%, respectively, while placebo-treated subjects had a mean percent change of -0.7%. Each of the 3 topiramate treatment groups was superior to placebo as indicated by statistically greater mean percent reductions from baseline body weight ($p<0.001$) (LOCF analysis). Subjects in each of the 3 topiramate treatment groups experienced a statistically significantly greater reduction from baseline HbA_{1c} than subjects in the placebo group ($p\leq0.022$) (LOCF analysis). The mean change in HbA_{1c} was 0.1% in the placebo group and –0.3% in each of the topiramate groups.

Table A : Summary of Key Efficacy Results
(Protocol CR002251; ITT Population)

	Placebo (N=59)		TPM 96 mg/day (N=51)		TPM 192 mg/day (N=56)		TPM 256 mg/day (N=55)	
Body Weight								
Mean % change (SD)	-0.65	(1.950)	-3.33 [a]	(2.816)	-3.05 [a]	(3.313)	-3.50 [a]	(3.669)
HbA_{1c} (%)								
Mean change (SD)	0.10	(0.877)	-0.30 [b]	(0.746)	-0.34 [b]	(0.882)	-0.28 [b]	(0.808)

[a] $p<0.001$ topiramate vs. placebo; p values from contrast statements.
[b] $p\leq0.022$ topiramate vs. placebo; p values from contrast statements.

SAFETY RESULTS: Notable common treatment-emergent adverse events that occurred more frequently in topiramate-treated than in placebo-treated subjects were generally central nervous system (CNS)-related, including the central or peripheral nervous system, events that were psychiatric in nature, and fatigue (see Table B).

The adverse events most often resulting in discontinuation of therapy for topiramate-treated subjects were mainly CNS-related and included depression and difficulty with concentration/attention (each in 4 subjects, 2%) and anxiety, difficulty with memory, nervousness, dizziness, and headache (each in 3 subjects, 2%). The proportion of subjects who experienced limiting events was higher among topiramate-treated subjects (15%, 25 subjects) than among placebo-treated subjects (8%, 5 subjects), and was higher in the 192 mg/day and 256 mg/day groups (21%, 12 subjects and 20%, 11 subjects, respectively) than in the 96 mg/day group (4%, 2 subjects). Five percent (3 subjects) of placebo-treated subjects and 2% (4 subjects) of topiramate-treated subjects experienced 1 or more serious adverse events. All of the serious adverse events were assessed by the investigators as not related or of doubtful relationship to study medication. Two deaths occurred in subjects who had withdrawn from the study because of adverse events that began during the study. One subject in the placebo group withdrew from the study because of kidney failure, liver failure, and right groin/loin pain and died 6 days later (due to psoas abscess and septicemia); the investigator considered the events to be of doubtful relationship to study medication. One subject in the 192 mg/day group withdrew from the study because of ovarian cancer and died almost 10 months later; the investigator considered the event to be not related to study medication.

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Table B: Incidence of the Most Common[a] Treatment-Emergent Adverse Events (Protocol CR002251; Safety Population)

Body System Preferred Term	Placebo (N=59) N (%)	TPM 96 mg/day (N=51) N (%)	TPM 192 mg/day (N=56) N (%)	TPM 256 mg/day (N=56) N (%)	Total TPM (N=163) N (%)
CNS-Related[b]					
Paresthesia	3 (5)	16 (31)	12 (21)	15 (27)	43 (26)
Headache	6 (10)	3 (6)	7 (13)	8 (14)	18 (11)
Fatigue	5 (8)	5 (10)	6 (11)	6 (11)	17 (10)
Difficulty with memory	1 (2)	5 (10)	3 (5)	5 (9)	13 (8)
Anorexia	1 (2)	3 (6)	4 (7)	2 (4)	9 (6)
Depression	0	3 (6)	3 (5)	3 (5)	9 (6)
Somnolence	2 (3)	3 (6)	4 (7)	2 (4)	9 (6)
Hypoesthesia	2 (3)	2 (4)	4 (7)	2 (4)	8 (5)
Difficulty with concentration/attention	1 (2)	2 (4)	1 (2)	5 (9)	8 (5)
Other Body Systems					
Hypoglycemic reaction	6 (10)	6 (12)	11 (20)	8 (14)	25 (15)
Infection viral	2 (3)	3 (6)	3 (5)	6 (11)	12 (7)
Hypoglycemia	1 (2)	2 (4)	3 (5)	3 (5)	8 (5)
Injury	2 (3)	5 (10)	2 (4)	1 (2)	8 (5)
Arthralgia	2 (3)	3 (6)	1 (2)	4 (7)	8 (5)
Vision abnormal	2 (3)	4 (8)	1 (2)	3 (5)	8 (5)
Taste perversion	1 (2)	2 (4)	1 (2)	5 (9)	8 (5)

[a] Includes events that occurred in at least 5% topiramate treated subjects across the 3 treatment groups and with a greater incidence than placebo.

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

There was a reduction in bicarbonate plasma levels to below the normal range (18 to 30.6 mmol/L) in 5% of topiramate-treated subjects. This is most probably related to the carbonic anhydrase inhibitory activity of topiramate. There was a tendency for slight decreases over time in alanine transaminase (ALT) and aspartate transaminase (AST) levels. No subjects, however, had markedly abnormal levels of hepatic enzymes. No laboratory abnormalities were reported as serious or limiting adverse events. The incidence of injuries was highest in the 96 mg/day topiramate group (10%, 5 subjects) compared to the other groups (3% [2 subjects] in the placebo group, 4% [2 subjects] in the topiramate 192 mg/day group, and 2% [1 subject] in the topiramate 256 mg/day group). None of the injuries were reported as serious adverse events or led to discontinuation of study medication. Most events were reported as strain. One case in the 96 mg/day topiramate group (shoulder and rib injury due to fall down stairs) was reported as possibly related to study medication; all other cases were reported as not related. One topiramate-treated subject experienced serious renal calculus (in the 192 mg/day group). Hypoglycemia was reported more frequently in topiramate-treated subjects compared to placebo. This is likely related to topiramate-induced weight loss in combination with maintenance of a stable sulfonylurea dose, in the majority of subjects.

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CONCLUSION: In this trial in obese subjects who had type 2 diabetes inadequately controlled with sulfonylurea therapy, all 3 topiramate dosages – 96, 192, and 256 mg/day – were superior to placebo as indicated by statistically greater mean percent reductions in body weight and mean reductions in HbA_{1c} level. This was despite a short median duration of treatment (70 to 97 days).

The most common treatment-emergent adverse events that occurred more frequently in topiramate-treated than in placebo-treated subjects were generally central nervous system (CNS)-related, including the central or peripheral nervous system, events that were psychiatric in nature, and fatigue. Longer-term studies are needed to fully evaluate the safety and efficacy of topiramate in combination with sulfonylurea therapy in obese subjects with type 2 diabetes.

Date of the report: 13 November 2003

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