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-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.: CR003730 **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 Subjects With Dyslipidemia		
Study Initiation/Completion Dates: 25 April 2001 / 10 June 2002		**Phase of development:** 3
Objectives: The primary objective of this clinical study was to compare the efficacy (in terms of change in body weight and fasting triglycerides) and safety of 96 mg and 192 mg of topiramate daily with placebo for the treatment of obese subjects with dyslipidemia.		
Methodology: This was a randomized, double-blind, placebo-controlled study with 3 parallel treatment groups (topiramate 96 and 192 mg/day, and placebo) in the long-term treatment of obese subjects with dyslipidemia. The study was conducted at 40 sites in South America, Western Europe, Eastern Europe, and North America. The study consisted of 4 phases: a 4-week enrollment (screening) phase, an 8-week titration phase, a 52-week maintenance phase, and a 6-week follow-up phase. After completing the enrollment phase, subjects who met study eligibility criteria and had a body mass index (BMI) ≥27 kg/m^2 and <50 kg/m^2 were to be randomized into 1 of the 3 treatment arms. 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 then have their dose increased in increments of 32 mg/week thereafter according to a specific titration schedule until the assigned dose was reached. During the maintenance phase, subjects were to continue to receive their assigned dosage for 52 weeks. During the follow-up phase, treatment with topiramate was to be gradually reduced (tapered) over 2 weeks and subjects were to return for their final study visit 4 weeks after last dose of study medication. Total participation for each subject was to be approximately 70 weeks. Subjects were instructed to follow non-pharmacologic therapy, which consisted of an individual diet, a behavioral modification program, and a physical activity program, for the duration of the study including the follow-up phase. Subjects were evaluated 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). The planned sample size was 360 subjects (120 subjects per group). Subjects were to be 18 to 75 years of age, inclusive, with a BMI ≥27 kg/m^2 and <50 kg/m^2 with hypertriglyceridemia (fasting serum triglyceride level of ≥175 mg/dL and <1000 mg/dL [≥2.0 mmol/L and <11.3 mmol/L, respectively]) at enrollment (screening) Visit 1 (Week –4) and the mean of the 3 fasting serum triglyceride measurements at Visits 1, 2, and 3 (Weeks –4, -2, and –1) were to be ≥175 mg/dL and <1000 mg/dL (≥2.0 mmol/L and <11.3 mmol/L, respectively) on or off a concomitant stable dose of background lipid-lowering monotherapy. In addition, subjects must have had either a low high density lipoprotein (HDL) level (fasting serum HDL <40 mg/dL [<1.0 mmol/L]), or a high low density lipoprotein (LDL) level (fasting serum LDL ≥130 mg/dL and <190 mg/dL [≥3.4 mmol/L and <4.9 mmol/L, respectively]) at enrollment (screening) Visits 1 and 3 (Weeks –4 and –1). Fasting serum triglyceride levels were not to vary more than 30% from the first screening measurement to the subsequent screening measurements, if the first screening fasting serum triglyceride was ≤250 mg/dL (≤2.8 mmol/L) or not to vary more than 40% if the first screening fasting triglyceride was >250 mg/dL (>2.8 mmol/L). Subjects on lipid-lowering medication were to have been on monotherapy with the same drug for at least 4 months, and with the same dose for at least 2 months prior to the first enrollment (screening) visit. Subjects who required pharmacologic therapy with new or increased doses of lipid-lowering medications during the course of the study were to be excluded. The study was terminated prior to completion to focus on the development of a controlled release formulation with the potential for improved tolerability in this population. Due to early termination of the study by the sponsor, no subjects completed the full 52-week maintenance phase. All subjects were encouraged to complete the follow-up phase.		

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Efficacy: Since the study was terminated prematurely, only the 2 primary efficacy parameters – mean percent change in body weight and mean percent change in fasting serum triglycerides from baseline (randomization) to the final last observation carried forward (LOCF) value – and selected secondary efficacy parameters – mean percent change in body weight and mean percent change in fasting serum triglycerides over time – are presented for the Intent-to-Treat (ITT) population in this report.

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 early. The median duration of exposure to study medication (including titration) was 167, 151, and 161 days, for the placebo and topiramate 96 and 192 mg/day groups, respectively.

Key efficacy results are summarized in Table A. At dosages of 96 and 192 mg/day topiramate, subjects in the ITT population achieved mean percent changes in body weight from baseline to final value of –6.0%, and –7.6%, respectively, while placebo-treated subjects had a mean percent change of –2.8%. Each of the 2 topiramate treatment groups was superior to placebo as indicated by statistically greater mean percent reductions from baseline body weight ($p<0.001$) (LOCF analysis). In general, over time (secondary endpoint), subjects in the 96 mg/day and 192 mg/day topiramate groups continued to lose weight gradually through Week 32. Subjects in the placebo group continued to lose weight gradually through Week 24 and fluctuated through Week 40. Subjects in the 192 mg/day topiramate treatment group experienced a statistically significantly greater mean percent reduction from baseline fasting serum triglycerides than subjects in the placebo group ($p=0.020$) (LOCF analysis). The mean percent change in fasting serum triglycerides was –8.6% in the placebo group, –8.6% in the 96 mg/day topiramate group, and -17.8% in the 192 mg/day topiramate group. Subjects in all 3 treatment groups had a gradual reduction in serum triglyceride values through Week 32 (LOCF).

Table A: Summary of Key Efficacy Results
(Protocol CR003730; ITT Population)

	Placebo (N=55)		TPM 96 mg/day (N=54)		TPM 192 mg/day (N=62)	
Body Weight						
N [a]	54		54		62	
Mean % change (SD)	-2.82	(3.659)	-6.01 [b]	(4.656)	-7.62 [b]	(5.547)
Fasting Serum Triglycerides						
N [a]	46		45		54	
Mean % change (SD)	-8.58	(47.097)	-8.57	(45.774)	-17.82 [c]	(34.121)

[a] Only subjects with both baseline and post-baseline values are included.
[b] $p<0.001$ topiramate vs. placebo; p values from contrast statements.
[c] $p=0.020$ topiramate vs. placebo; p values from contrast statements.

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 B). The adverse events most often resulting in discontinuation of study therapy across the topiramate dosage groups were CNS-related and included paresthesia (7 subjects, 6%), headache (4 subjects, 3%), insomnia (4 subjects, 3%), and fatigue (3 subjects, 3%). Overall, 7 (12%) subjects in the placebo group and 21 (18%) topiramate-treated subjects discontinued due to an adverse event.

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Overall, 3 (5%) subjects in the placebo group and 6 (5%) topiramate-treated subjects experienced 1 or more serious adverse events during double-blind therapy. Serious adverse events in topiramate-treated subjects that were considered to be of at least possible relationship to study medication were glaucoma in 1 subject, and hallucination, psychosis, depression, and suicidal tendency (not a true suicide attempt) in another subject in the 192 mg/day group. This subject had a history of questionable postpartum depression. A second subject (in the 96 mg/day topiramate group) had suicidal ideation that was not coded as an adverse event with the preferred term of suicide. No subjects died during the study. No subjects became pregnant during the study. Serum bicarbonate values shifted from normal (i.e., 17 to 30.6 mmol/L) baseline values to low post-baseline values in 8% of topiramate-treated subjects. This is most probably due to the known carbonic anhydrase inhibitor activity of topiramate. One case of metabolic acidosis (low bicarbonate) was reported as a treatment-emergent adverse event in the topiramate 192 mg/day group. There were no other noteworthy changes in clinical laboratory test results. There were no laboratory abnormalities reported as serious treatment-emergent adverse events. Hematuria was reported as a limiting adverse event in 1 subject in the topiramate 192 mg/day group. Hyperglycemia was reported as a limiting adverse event in 2 subjects, 1 in the placebo group and 1 in the topiramate 192 mg/day group.

Table B: Incidence of the Most Common[a] Treatment-Emergent Adverse Events
(Protocol CR003730; Safety Population)

Body System Preferred Term	Placebo (N=57) N (%)	TPM 96 mg/day (N=55) N (%)	TPM 192 mg/day (N=63) N (%)	Total TPM (N=118) N (%)
CNS-Related[b]				
Paresthesia	5 (9)	24 (44)	24 (38)	48 (41)
Dizziness	4 (7)	6 (11)	7 (11)	13 (11)
Somnolence	3 (5)	7 (13)	6 (10)	13 (11)
Depression	3 (5)	5 (9)	6 (10)	11 (9)
Insomnia	3 (5)	5 (9)	4 (6)	9 (8)
Anorexia	1 (2)	3 (5)	5 (8)	8 (7)
Anxiety	1 (2)	6 (11)	0	6 (5)
Difficulty with memory NOS	1 (2)	2 (4)	4 (6)	6 (5)
Other Body Systems				
Infection viral	3 (5)	3 (5)	8 (13)	11 (9)
Arthralgia	3 (5)	7 (13)	4 (6)	11 (9)
Bronchitis	4 (7)	4 (7)	5 (8)	9 (8)
Dyspepsia	2 (4)	4 (7)	6 (10)	10 (8)
Mouth dry	1 (2)	4 (7)	4 (6)	8 (7)
Conjunctivitis	3 (5)	5 (9)	2 (3)	7 (6)
Menstrual disorder[c]	1 (3)	3 (8)	2 (4)	5 (6)
Taste perversion	1 (2)	5 (9)	1 (2)	6 (5)
Rash	0	4 (7)	2 (3)	6 (5)

[a] Includes events that occurred in ≥5% topiramate-treated subjects across the 2 treatment groups 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.
[c] Denominators for female-specific adverse events (placebo, N=34; TPM 96 mg/day, N=37; TPM 192 mg/day, N=51; Total TPM, N=88)
TPM=Topiramate; NOS = Not otherwise specified

CONCLUSION: In this study in obese subjects with dyslipidemia, even though the study was terminated early and did not achieve full enrollment, both topiramate dosages – 96 and 192 mg/day – were superior to placebo as indicated by statistically greater mean percent reductions in body weight. The 192 mg/day topiramate dosage was superior to placebo as indicated by a statistically greater mean percent reduction in fasting serum triglycerides.

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

Date of the report: 08 February 2005

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