

SYNOPSIS

<p><u>NAME OF SPONSOR/COMPANY:</u> Johnson & Johnson Pharmaceutical Research & Development, L.L.C.</p> <p><u>NAME OF FINISHED PRODUCT:</u> Topiramate</p> <p><u>NAME OF ACTIVE INGREDIENT(S):</u> 2,3:4,5-bis-Di-<i>l</i>-isopropylidene)-β-D-fructopyranose sulfamate</p>	<p><u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u></p> <p>Volume:</p> <p>Page:</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
<p>Protocol No.: CR002251</p>		
<p>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</p>		
<p>Study Initiation/Completion Dates: 29 March 2001 / 05 June 2002</p>	<p>Phase of development: 3</p>	
<p>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.</p>		
<p>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) ≥ 27 kg/m² and < 50 kg/m², an established diagnosis of type 2 diabetes mellitus, glycosylated hemoglobin (HbA_{1c}) $< 11\%$ and a fasting plasma glucose (FPG) ≥ 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 maximum 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, glimepiride, glibenclamide/glyburide, and gliclazide. 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.</p>		
<p>Criteria for Evaluation:</p> <p><u>Efficacy:</u> 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.</p>		

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