

SYNOPSIS

<u>NAME OF SPONSOR/COMPANY:</u> Johnson & Johnson Pharmaceutical Research & Development, L.L.C. <u>NAME OF FINISHED PRODUCT:</u> TOPAMAX [®] (topiramate) Tablets <u>NAME OF ACTIVE INGREDIENT(S):</u> 2,3:4,5-Di- <i>O</i> -isopropylidene- β -D-fructopyranose sulfamate	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
Protocol No.: CR003202 Title of Study: A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Topiramate on Electrophysiologic Parameters in Subjects With Diabetic Peripheral Polyneuropathy		
Coordinating Investigator: Roy Freeman, M.D. - Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Medical Center, Boston; MA		
Publication (Reference): None		
Study Initiation/Completion Dates: 5 July 2001 - 14 January 2003	Phase of development: 2	
Objectives: The objective of this study was to determine whether topiramate (200 mg/day) was non-inferior to placebo on clinical and electrophysiologic parameters in subjects with diabetic peripheral polyneuropathy. Study assessments included nerve conduction studies (NCS), a detailed, graded neurological examination, and, in selected centers, quantitative sensory testing (QST). This study also evaluated the safety of topiramate in this subject population.		
Methodology: This randomized, double-blind, placebo-controlled, parallel group, multicenter trial evaluated the effect of topiramate (200 mg/day) versus placebo on clinical and electrophysiologic parameters in subjects with diabetic peripheral polyneuropathy. The trial included 3 phases: baseline, double-blind, and taper. Eligibility was determined during the baseline phase that lasted up to 28 days. Eligible subjects must have had 2 sets of approved baseline NCS tests. All NCS tests were evaluated by a central reading center. Any NCS tests that failed to meet approval were returned to be redone. Baseline QST was also conducted at selected centers. At least 7 days before Visit 2, subjects must have been tapered off all background medications being used to treat neuropathic pain. During the baseline phase, all subjects were to have their diabetes controlled with a stable, therapeutic regimen of oral hypoglycemics or insulin, in combination or alone, or diet alone. At the end of the baseline phase, eligible subjects were randomized in equal proportions to receive either topiramate 200 mg/day or placebo. The 18-week double-blind phase included 2 periods: a 6-week titration period and a 12-week maintenance period. During the double-blind phase, subjects received periodic assessments of pain, vital signs, clinical laboratory values, body weight, and neurologic function. Adverse events were recorded throughout the study after initiation of the study medication. Subjects were considered to have completed the trial if they completed the double-blind phase, including 2 sets of final NCS and QST (if applicable) assessments.		
Number of Subjects (planned and analyzed): Seventy-two subjects with pain associated with diabetic peripheral polyneuropathy were to be enrolled in this trial. A total of 67 subjects were randomized; of these, 65 were included in the intent-to-treat population, 47 were included in the per-protocol population, and 67 were included in the safety population.		
Diagnosis and Main Criteria for Inclusion: Eligible patients were adults between 18 and 75 years of age with type 2 diabetes mellitus who had experienced pain that had been attributed by the investigator to diabetic peripheral polyneuropathy for at least 6 months before randomization. Eligible subjects were required to have rated their current pain as at least a 1 (mild pain) on the 0-4 Categorical Pain Scale at the time of randomization. Completion and approval of 2 sets of NCS tests before randomization was also required for inclusion.		
Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25-mg (batch numbers D00LE0441 and D99LK0224) and 100-mg (batch numbers D00LE0429 and D00LC0321) tablets in child-resistant bottles. All blinded medication was administered in a twice-a-day fashion except for the first week of titration medication, which consisted of a single evening dose each day.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as 25-mg (batch number D00LB0306) and 100-mg (batch numbers D99LF0135 and D00LC0322) tablets in child-resistant bottles.		
Duration of Treatment: The duration of double-blind therapy included a 6-week titration period and a 12-week maintenance period.		

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<p>Criteria for Evaluation:</p> <p>Efficacy: All efficacy assessments included comparison of the topiramate 200 mg/day treatment group to the placebo group. The primary efficacy endpoint was the change in peroneal motor nerve conduction velocity (NCV) from baseline to the end of the double-blind phase. Secondary efficacy endpoints included changes from baseline to the end of the double-blind phase in: 1) NCVs of the sural sensory and ulnar (motor and sensory) nerves; and 2) changes in amplitudes and latencies of the peroneal motor, sural sensory, and ulnar (motor and sensory) nerves. At selected centers, changes in sensory perception were measured using QST. For QST, the efficacy endpoints were the changes from baseline to the end of the double-blind phase in cooling and heat-pain detection thresholds. Clinical assessments of pain were conducted using a 100-mm Visual Analog Scale (VAS) and a 0-4 Categorical Pain Scale.</p> <p>Safety: The safety assessments included the incidence, type and severity of treatment-emergent adverse events (including abnormal findings in physical examinations); clinical laboratory analyte values (hematology, blood chemistry, and urinalysis); pretreatment to posttreatment changes in vital signs, HbA_{1c}, body weight and body mass index (BMI); rescue medication and diabetic medication usage; and graded neurologic examination findings.</p>																										
<p>Statistical Methods: The primary efficacy endpoint, the change in peroneal motor NCV from baseline to the end of the double-blind phase, was analyzed using a linear model with factors for treatment and analysis center, and baseline peroneal NCV as a covariate. The primary objective of the trial was to show that topiramate was non-inferior to placebo in the change in peroneal motor NCV. Confidence limit bounds were used to assess "non-inferiority" of topiramate using the non-inferiority margin of 3 m/s for the primary efficacy endpoint. The primary efficacy variable was analyzed for the per-protocol population (clinically evaluable population); however, a secondary analysis of the primary efficacy variable in the intent-to-treat population was also done. The per-protocol population consisted of subjects who were more compliant with the protocol as compared with subjects in the intent-to-treat population. The secondary nerve conduction assessments were analyzed using a linear model with treatment and analysis center as the 2 main factors, and baseline peroneal NCV as the covariate. Descriptive statistics were provided for all nerve conduction assessments at baseline, at the end of the double-blind phase, and for the changes from baseline to the end of the double-blind phase. For QST evaluations, descriptive summary statistics were provided for values at baseline, at the end of the double-blind phase, and for the changes from baseline to the end of the double-blind phase. For the VAS scores and Categorical Pain Scale scores, descriptive summary statistics were provided for values at baseline, over time, and at the end of the double-blind phase, as well as for changes from baseline over time.</p>																										
<p>SUMMARY - CONCLUSIONS</p> <p>EFFICACY RESULTS: Based on the primary efficacy analysis using a confidence interval approach, the non-inferiority claim was supported. The two-sided 95% confidence interval for the difference between topiramate and placebo for the change in peroneal motor nerve conduction velocity was (-1.30, 1.42). The lower limit of the confidence interval was above the non-inferiority bound of -3 thus supporting the claim that topiramate was non-inferior to placebo with respect to the change in peroneal nerve conduction velocity. The mean change in peroneal nerve NCV from baseline to final visit is shown in the table below.</p> <p style="text-align: center;">Peroneal Motor Nerve Conduction Velocity: Mean Change From Baseline to Final Visit (Study CR003202: Per Protocol Population)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Placebo</th> <th style="text-align: center;">Topiramate 200 mg/day</th> </tr> </thead> <tbody> <tr> <td>No. of subjects^a</td> <td style="text-align: center;">24</td> <td style="text-align: center;">23</td> </tr> <tr> <td>Baseline mean (SD), m/s</td> <td style="text-align: center;">40.3 (5.03)</td> <td style="text-align: center;">39.1 (4.56)</td> </tr> <tr> <td>Final visit mean (SD), m/s</td> <td style="text-align: center;">39.9 (4.78)</td> <td style="text-align: center;">39.0 (4.76)</td> </tr> <tr> <td>Mean (SD) change</td> <td style="text-align: center;">-0.4 (1.76)</td> <td style="text-align: center;">-0.1 (2.62)</td> </tr> <tr> <td>Mean (SE) change^b</td> <td style="text-align: center;">-0.2 (0.46)</td> <td style="text-align: center;">-0.1 (0.48)</td> </tr> <tr> <td>Difference</td> <td></td> <td style="text-align: center;">0.1</td> </tr> <tr> <td>95% CI</td> <td></td> <td style="text-align: center;">(-1.30, 1.42)</td> </tr> </tbody> </table> <p>^a The number of subjects for whom both baseline and final visit data were available. ^b Least squares mean</p>				Placebo	Topiramate 200 mg/day	No. of subjects ^a	24	23	Baseline mean (SD), m/s	40.3 (5.03)	39.1 (4.56)	Final visit mean (SD), m/s	39.9 (4.78)	39.0 (4.76)	Mean (SD) change	-0.4 (1.76)	-0.1 (2.62)	Mean (SE) change^b	-0.2 (0.46)	-0.1 (0.48)	Difference		0.1	95% CI		(-1.30, 1.42)
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<p>SUMMARY - CONCLUSIONS (continued)</p> <p>Results from secondary nerve measures evaluated also showed no evidence that topiramate was different from placebo in this population. QST measurements were potentially indicative that topiramate may be inhibiting sensory nerve degeneration or promoting sensory nerve growth in this population. There was no statistically significant difference in the mean change in VAS scores between the topiramate group and the placebo group ($p=0.354$). There was no correlation between an improvement in subject pain (i.e., reduction in mean VAS scores) and reduction in peroneal NCV.</p> <p>SAFETY RESULTS: Consistent with previous clinical experience, the most common adverse events were related to the central and peripheral nervous system or were psychiatric in nature. Of these, those occurring more frequently in the topiramate treatment group versus the placebo group included paresthesia, anorexia, somnolence, dizziness, difficulty with concentration and attention, and confusion. The incidence of headache was higher in the placebo group compared with the topiramate treatment group. In other body systems, commonly reported adverse events occurring more frequently in the topiramate treatment group compared with placebo included: weight decrease, taste perversion, and abnormal vision.</p> <p>One subject in each treatment group experienced serious adverse events. The serious adverse event (urinary tract infection) experienced by the topiramate-treated (200 mg/day) subject resulted in a temporary interruption of therapy and was considered moderate in severity, of doubtful relationship to topiramate, and resolved in 8 eight days. The serious adverse events experienced by the placebo-treated subject (fatigue and palpitations) resulted in withdrawal of the subject from the study. Three months after discontinuation of therapy, this subject died from a myocardial infarction following spinal surgery. There were no other deaths during this trial. Adverse events most commonly ($\geq 2\%$) leading to discontinuation of subjects in the topiramate group included difficulty with concentration and attention, dizziness, emotional lability, mood problems, nervousness, fatigue, gastrointestinal disorder, taste perversion, and abnormal vision.</p> <p>There were no clinically important changes in clinical laboratory tests of liver or renal function, HbA_{1c} levels, or abnormalities in vital sign measurements or neurologic examinations. Consistent with the activity of topiramate as a carbonic anhydrase inhibitor, there was a mean decrease in bicarbonate levels with a concomitant increase in chloride levels in the topiramate treatment group. Both treatment groups demonstrated a mean decrease in serum glucose levels. Subjects in the topiramate treatment group experienced a greater mean decrease in weight compared with subjects in the placebo group (decreases of 4.1 and 0.3 kg, respectively).</p> <p>CONCLUSION: Topiramate 200 mg/day was shown to be non-inferior to placebo with respect to the change from baseline in the peroneal motor NCV. Measurements of nerve function in the peroneal motor nerve (amplitude and latency) and other secondary nerves did not change substantially over time in topiramate-treated subjects. Taken together, topiramate treatment does not appear to be associated with enhanced deterioration of nerve function in subjects with diabetic peripheral polyneuropathy. Topiramate 200 mg/day had a generally acceptable tolerability profile and no unexpected adverse events were observed during this study.</p> <p>Date of the report: 11 SEPTEMBER 2003</p>		

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