

## SYNOPSIS

<p><u>NAME OF SPONSOR/COMPANY:</u> Johnson &amp; Johnson Pharmaceutical Research &amp; Development, L.L.C.</p> <p><u>NAME OF FINISHED PRODUCT:</u> TOPAMAX<sup>®</sup> (topiramate)</p> <p><u>NAME OF ACTIVE INGREDIENT(S):</u> 2,3:4,5-Di-<i>O</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><b>Protocol No. And Title of Study:</b> A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Two Doses of Topiramate for the Treatment of Acute Manic or Mixed Episodes in Subjects With Bipolar I Disorder With an Optional Open-Label Extension (Protocol CR002248)</p>		
<p><b>Investigators:</b> Pauline S. Powers, M.D., 3515 East Fletcher Ave., Tampa, FL 33613 USA</p>		
<p><b>Study Center(s):</b> 40 study centers (all in the United States)</p>		
<p><b>Publication (Reference):</b> None</p>		
<p><b>Study Initiation/Completion Dates:</b> 03 October 2000 to 21 June 2002 (Double-Blind Phase) and 16 October 2002 (Open-Label Phase)</p>		<p><b>Phase of development:</b> 3</p>
<p><b>Objectives:</b> To determine the safety and efficacy of 2 doses of topiramate versus placebo in the treatment of acute manic or mixed episodes in subjects with Bipolar I Disorder as defined by DSM-IV criteria.</p>		
<p><b>Methodology:</b> This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 study that evaluated 2 doses of topiramate (400 and 600 mg/day) and placebo in subjects ≥16 years of age who presented for hospitalization with an acute manic or mixed episode of Bipolar I Disorder as defined by DSM-IV criteria. The trial consisted of 3 phases: screening (of variable duration, depending upon the washout required for previous psychotropic medications), double-blind treatment (84 days, subdivided into titration and stabilization), and double-blind taper. Entry into an open-label extension phase was optional. Upon enrollment in the double-blind phase, each subject received study medication (topiramate target daily dosage of 400 mg, 600 mg, or placebo) twice daily in a blinded fashion for up to 84 days. Subjects who completed the study through at least Day 1 and subsequently discontinued for lack of efficacy were permitted to enter the open-label extension. Efficacy was evaluated by using psychometric measures. Safety assessment was based on reported adverse events, rehospitalizations, clinical laboratory tests, vital sign measurements, physical examinations, and electrocardiogram (ECG) findings. In addition, plasma topiramate concentrations were measured periodically.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> Planned enrollment was 312 subjects (104 per treatment group). A total of 314 subjects (100 placebo, 112 topiramate 400 mg, and 102 topiramate 600 mg) were randomly assigned to treatment. A total of 308 subjects (99 placebo, 108 topiramate 400 mg, and 101 topiramate 600 mg) comprised the intent-to-treat (ITT) population and were evaluated for efficacy. A total of 313 subjects (100 placebo, 112 topiramate 400 mg, and 101 topiramate 600 mg) were included in the safety analyses. The open-label phase included 141 subjects (51 placebo, 48 topiramate 400 mg, and 42 topiramate 600 mg).</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were eligible to participate if they were 16 years of age or older, had a diagnosis of Bipolar I Disorder confirmed by the Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID-I), had at least 1 previous manic or mixed episode, and had a Young Mania Rating Score (YMRS) score of ≥20 at screening and randomization.</p>		
<p><b>Test Product, Dose and Mode of Administration, Batch No.:</b> Topiramate was supplied as 50-mg (Batch D99LL0247/FD 17021-000-AR-22) or 100-mg (Batch D99LJ0214/FD 17021-000-AK-22) tablets. Each dose was administered orally.</p>		
<p><b>Duration of Treatment:</b> 84 days</p>		

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<p><b>Reference Therapy, Dose and Mode of Administration, Batch No.:</b> Placebo to match topiramate in appearance was supplied as 50-mg (Batch D99LK0223/ FD 17021-000-ARX-22) or 100-mg (Batch D99LF0135/ FD 17021-000-AKX-22) tablets. Each dose was administered orally.</p>		
<p><b>Criteria for Evaluation:</b></p> <p><u>Efficacy:</u> The change from baseline in the YMRS score at Day 21 was the primary efficacy endpoint. The secondary efficacy endpoints were the Day 21 Clinical Global Impression Change (CGI-C) score and the Day 21 change from baseline in the Global Assessment Scale (GAS) score. The Day 21 tertiary efficacy endpoints were the proportion of DSM-IV responders; the changes from baseline in the Brief Psychiatric Rating Scale (BPRS) score, the BPRS psychosis subscale score, the Montgomery-Åsberg Depression Rating Scale (MADRS) score, the MADRS suicidality item score, and the YMRS manic syndrome subscale score; and the proportion of subjects who switched into depression. Tertiary endpoints also included the change from baseline to Day 84 in the YMRS score, the CGI-C, the GAS score, and all of the corresponding Day 21 tertiary endpoints as listed above. Since the clinical development program for Bipolar I Disorder was terminated prematurely, only the primary efficacy variable, YMRS, is summarized.</p> <p><u>Body weight:</u> The percent change in body weight at Day 21 and Day 84 were assessed.</p> <p><u>Safety:</u> Safety evaluations were based on reports of treatment-emergent adverse events and changes from baseline in clinical laboratory analyte values (hematology, blood chemistry, urinalysis), vital sign measurements (blood pressure and pulse rate), ECG, and physical examination findings.</p>		
<p><b>Statistical Methods:</b></p> <p><u>Efficacy:</u> The change from baseline in the YMRS score at Day 21 was the primary efficacy endpoint. Analysis of covariance (ANCOVA) was used to compare the YMRS change from baseline at Day 21 between treatment groups. The ANCOVA model for assessing the significance of treatment effect included factors for baseline value, treatment, and (pooled) study center. Treatment groups compared were: placebo group with each of the topiramate groups. The comparison of topiramate 600 mg versus placebo based on the primary endpoint was to be done only if topiramate 400 mg was significantly (<math>p \leq 0.05</math>, 2-sided) superior to placebo as specified in the protocol. However, because of negative efficacy results, all comparisons between groups were done in order to explore all possibilities of positive efficacy. The comparisons between topiramate and placebo treatments were made using least square means within the ANCOVA model. The SAS PROC GLM procedure type III sums of squares were used for statistical tests. The 95% confidence intervals for the difference between LSMEANS of topiramate groups and placebo were provided. Confidence intervals for between-group differences were computed based on the mean square error from the ANCOVA.</p> <p><u>Body weight:</u> Body weight was analyzed based on the ITT population using the last observation carried forward (LOCF) data. Summary statistics (mean, standard deviation, median and range) were provided for Days 21 and 84. The percent change from baseline was analyzed using the same ANCOVA model as used for the YMRS data.</p> <p><u>Safety:</u> The nature and frequency of adverse events as well changes in clinical laboratory values, ECGs, and vital signs were summarized. Serious adverse events and adverse events that led to discontinuation of a subject were also summarized.</p>		

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<p><b>SUMMARY – CONCLUSIONS</b></p> <p><b>EFFICACY RESULTS:</b> The primary efficacy endpoint was the change in YMRS score from baseline to Day 21. The mean change in YMRS score from baseline to Day 21 for the placebo group was -7.7, and for the topiramate 400-mg and 600-mg groups this mean change was -8.2 and -7.9, respectively. The results of the ANCOVA showed that the changes from baseline to Day 21 for each of the topiramate groups was not statistically different compared with these changes from baseline for the placebo group.</p> <p>Body Weight: There was almost no change in body weight from baseline to Day 21 and Day 84 in the placebo group (mean change for both periods was -0.2%). In the topiramate 400-mg and 600-mg groups, the mean change in body weight from baseline to Day 21 was -2.3% and -1.4%, respectively, and the mean change in body weight from baseline to Day 84 for these 2 groups were -3.2% and -2.3%, respectively. These decreases were statistically different compared with the percent change from baseline to Day 21 and Day 84 for the placebo group.</p> <p><b>SAFETY RESULTS:</b> In the placebo, topiramate 400-mg, and topiramate 600-mg groups, 85%, 79%, and 85% of subjects, respectively, reported a treatment-emergent adverse event during the double-blind period. Common treatment-emergent adverse events that occurred more frequently in one of the topiramate groups than in placebo-treated subjects were generally central and peripheral nervous system-related, and included paraesthesia, dizziness, and hypoesthesia. For each of the 3 treatment groups, the maximum severity for most treatment-emergent adverse events was mild or moderate. For most treatment-emergent adverse events, investigators assessed the relationship to study drug to be no greater than possibly related. There were no deaths reported in this study, and there was a low incidence of serious adverse events in each of the treatment groups during double-blind treatment. Except for 1 report of renal calculus in the topiramate 600-mg group, the serious adverse events reported during the double-blind phase of the study were at most considered possibly related to study drug. In the topiramate 400-mg and 600-mg groups, 17 (15%) and 11 (11%) subjects, respectively, discontinued double-blind treatment due to an adverse event, while 5 (5%) subjects discontinued treatment due to an adverse event in the placebo group. In the topiramate groups, the adverse events that were most likely to result in the discontinuation of therapy were paraesthesia, suicide attempt, headache, nausea, anorexia, abdominal pain, insomnia, and difficulty with concentration/attention. As was seen during double-blind treatment, adverse events that were most commonly reported during open-label treatment were related to the central and peripheral nervous systems, and included paraesthesia and headache. No clinically relevant changes from baseline to final visit were observed for any mean hematology values, serum chemistry values, or hepatic function tests for any of the treatment groups for either phase of the study. There were no clinically significant mean changes from baseline over time in vital sign measurements and ECG findings for each of the treatment groups during both phases of the study.</p> <p><b>CONCLUSION:</b> Changes in YMRS score from baseline to Day 21 for each of the topiramate groups were not statistically different compared with these same changes for the placebo group. During double-blind treatment, there were statistically significant decreases in body weight from baseline to Day 21 in both topiramate groups compared with the placebo group. There were no deaths reported in this study, and there was a low incidence of serious adverse events in each of the treatment groups during double-blind and open-label treatment. The most frequently reported adverse events reported during double-blind treatment were central and peripheral nervous system-related, and, of these, the adverse events that occurred more frequently in one of the topiramate groups than in placebo-treated subjects were paraesthesia, dizziness, and hypoesthesia. For most treatment-emergent adverse events, investigators assessed the relationship to study drug to be no greater than possibly related. As was seen during double-blind treatment, adverse events that were most commonly reported during open-label treatment were central and peripheral nervous system-related and included paraesthesia and headache.</p> <p>Date of the report: 01 October 2003</p>		

**Disclaimer**

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