SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: TOPAMAX® (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. And Title of Study: A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Topiramate in Subjects With Acute Manic or Mixed Episodes of Bipolar I Disorder With an Optional Open-Label Extension (Protocol CR003232)		
Investigators: Jose Daniel Toledo Arenas, M.D., Central Military Hospital, Bogota, Colombia		
Study Center(s): 36 study centers - (in Eastern Europe, South Africa, Latin America, and India)		
Publication (Reference): None		
Study Initiation/Completion Dates: 17 July 2001 to 29 August 2002 (Double-Blind Phase) and 30 September 2002 (Open-Label Phase)		**Phase of development:** 3
Objectives: The primary objective of this study was to determine the safety and efficacy of topiramate 400 mg/day versus placebo in the treatment of subjects with acute manic or mixed episodes of Bipolar I Disorder diagnosed by DSM-IV criteria. A secondary objective was to compare the safety and efficacy of topiramate to lithium (1500 mg/day).		
Methodology: This was a randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter Phase 3 study that evaluated topiramate 400 mg/day, lithium 1500 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 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, was administered twice daily (b.i.d.), once in the morning and once in the evening, with placebo administered at the noon dose to maintain the blind; lithium (target daily dosage of 1500 mg) and placebo were administered three times daily (t.i.d.). Subjects randomized to placebo received topiramate (target daily dosage of 150 mg) beginning on Day 22. Subjects who completed the study through at least Day 21 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.		
Number of Subjects (planned and analyzed): Planned enrollment was 312 subjects (104 per treatment group). A total of 342 subjects (112 placebo/TPM, 116 topiramate 400 mg, and 114 lithium 1500 mg) were randomly assigned to treatment. A total of 341 subjects (112 placebo/TPM, 115 topiramate 400 mg, and 114 lithium 1500 mg) comprised the intent-to-treat (ITT) population and were evaluated for efficacy. A total of 342 subjects (112 placebo/TPM, 116 topiramate 400 mg, and 114 lithium 1500 mg) were included in the safety analysis. The open-label phase included 175 subjects (61 placebo/TPM, 55 topiramate 400 mg, and 59 lithium 1500 mg).		
Diagnosis and Main Criteria for Inclusion: 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) of ≥20 at screening and randomization.		

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Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as a capsule containing two 25-mg tablets (Batch R10889/GFI 17021-000-B-019) of topiramate. Each dose was administered orally.

Duration of Treatment: 84 days

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as matching capsules (Batch R10891/GFI 90000-000-B-016X). Lithium was supplied as identical-appearing over-encapsulated capsules containing 300 mg (Batch R10061/GFI 17021-000-B-020 and Batch R10890/GFI 17021-000-B-020) of lithium. Each dose was administered orally.

Criteria for Evaluation:

Efficacy: 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, 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 score, 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.

Body weight: The percent change in body weight at Day 21 and Day 84 was assessed.

Safety: 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), ECGs, and physical examination findings.

Statistical Methods:

Efficacy: The change from baseline in the YMRS score at Day 21 was the primary efficacy endpoint and was analyzed based on the ITT population using the last observation carried forward (LOCF) data. 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/TPM group with the topiramate 400-mg and lithium 1500-mg groups and the topiramate 400-mg group with the lithium 1500-mg group. The comparisons between placebo treatment and topiramate and lithium treatments were made using least square means (LSMEANS) 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 the placebo group and the topiramate 400-mg and lithium 1500-mg groups and between the topiramate 400-mg group and the lithium 1500-mg group were provided. Confidence intervals for between-group differences were computed based on the mean square error from the ANCOVA.

Body weight: Body weight was analyzed based on the ITT population using the 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.

Safety: The nature and frequency of adverse events, as well as 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.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The mean changes in YMRS score from baseline to Day 21 for the placebo/TPM and topiramate 400-mg groups were –8.4 and –8.2, respectively. The mean change in YMRS score from baseline to Day 21 for the lithium 1500-mg group was –13.8. The results of the ANCOVA showed that the change in YMRS score from baseline to Day 21 for the lithium 1500-mg group, but not for the topiramate 400-mg group, was statistically different compared with the change from baseline to Day 21 for the placebo/TPM group.

Body Weight: The mean percent change in body weight from baseline to Day 21 for the placebo/TPM group was -1.0%. Treatment with 400 mg/day topiramate resulted in a larger mean decrease in body weight from baseline to Day 21 (-2.1%). In contrast, treatment with 1500 mg/day lithium resulted in a slight mean increase in body weight from baseline to Day 21 (0.3%). The results of the ANCOVA showed that the changes in body weight from baseline to Day 21 for the topiramate 400-mg group and for the lithium 1500-mg group were statistically different compared with the percent change from baseline to Day 21 for the placebo/TPM group.

SAFETY RESULTS: In the placebo/TPM, topiramate 400-mg, and lithium 1500-mg groups, 63%, 67%, and 70% of subjects, respectively, reported a treatment-emergent adverse event during the double-blind period. Some of the more frequently reported treatment-emergent adverse events were related to the central (CNS) and peripheral nervous systems and included headache and dizziness, which were reported with a similar frequency across the 3 treatment groups. Other frequently reported adverse events included those related to gastrointestinal system disorders. For most treatment-emergent adverse events, the maximum severity was mild or moderate and 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 related to the CNS and peripheral nervous systems. There were 3 deaths in the open-label phase of this study. A death attributed to anemia was considered unrelated to study drug and 2 deaths by suicide were considered either doubtfully or possibly related to study drug. In addition, there was a low incidence of serious adverse events in each of the treatment groups during double-blind and open-label treatment. In the placebo/TPM, topiramate 400-mg, and lithium 1500-mg groups, 4 (4%), 5 (4%) and 14 (12%) subjects, respectively, discontinued double-blind treatment due to an adverse event. Almost half of the adverse events that led to discontinuation across the 3 treatment groups were psychiatric in nature or related to the CNS and peripheral nervous systems. During the open-label phase of the study, when all subjects received topiramate, 3 (5%), 6 (11%), and 1 (2%) subject in the placebo/TPM, topiramate 400-mg, and lithium 1500-mg groups, respectively, discontinued due to an adverse event. No noteworthy or clinically relevant changes from baseline to final visit were observed for any mean hematology or 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 or ECG findings for any of the treatment groups during either phase of the study.

CONCLUSION: The mean decreases in YMRS score from baseline to Day 21 and Day 84 for the lithium 1500-mg group, but not for the topiramate 400-mg group, were statistically different compared with the mean decreases from baseline to Day 21 and Day 84 for the placebo/TPM group. There were decreases in mean body weight from baseline to Day 21 and Day 84 in the topiramate 400-mg group which were statistically different compared with the decreases in weight from baseline to Day 21 and Day 84 in the placebo/TPM group. Some of the more frequently reported treatment-emergent adverse events in each of the treatment groups during double-blind and open-label treatment were related to the CNS and peripheral nervous systems, and included headache, dizziness, and paraesthesia. During both phases of the study, most treatment-emergent adverse events were assessed to be no greater than possibly related to study drug. There was a low incidence of serious adverse events in each of the treatment groups during double-blind and open-label treatment.

Date of the report: 02 DECEMBER 2003

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