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-ß-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 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 CR003199)

Investigators: Carlos A. Morra, M.D., Sanatorio "Prof. León Morra," Córdoba, Argentina

Study Center(s): 59 study centers (in Eastern and Western Europe, Argentina, India, Israel, and Australia)

Publication (Reference): None

Study Initiation/Completion Dates: 19 January 2001 to 12 September 2002 (Double-blind Phase) and 8 October 2002 (Open-label Phase)	**Phase of development:** 3

Objectives: 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. A secondary objective was to compare the safety and efficacy of topiramate and lithium.

Methodology: This was a randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter Phase 3 study that evaluated 2 dosages of topiramate (200 and 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 200 or 400 mg, lithium target daily dosage of 1500 mg, or placebo) three times daily in a blinded fashion for up to 84 days. Subjects assigned to the placebo group were transitioned to lithium in a blinded fashion after 21 days. 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 standard 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 drug concentrations were measured periodically.

Number of Subjects (planned and analyzed): Planned enrollment was 416 subjects (104 per treatment group). A total of 444 subjects (111 placebo/lithium, 110 topiramate 200 mg, 110 topiramate 400 mg, and 113 lithium 1500 mg) were randomly assigned to treatment and evaluated for safety. A total of 439 subjects (111 placebo/lithium, 108 topiramate 200 mg, 107 topiramate 400 mg, and 113 lithium 1500 mg) comprised the intent-to-treat (ITT) population and were evaluated for efficacy. A total of 442 subjects (111 placebo/lithium, 109 topiramate 200 mg, 109 topiramate 400 mg, and 113 lithium 1500 mg) were included in the safety analyses. The open-label phase included 232 subjects (64 placebo/lithium, 48 topiratmate 200 mg, 56 topiramate 400 mg, and 64 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 Scale (YMRS) score of ≥20 at screening and randomization.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as capsules containing two 25 mg tablets (Batch 901 007). Each dose was administered orally.

Duration of Treatment: 84 days

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Reference Therapy, Dose and Mode of Administration, Batch No.: Lithium was supplied as overencapsulated 300 mg capsules (Batch 903 007). Placebo capsules (Batch 902 007) matched the topiramate and lithium capsules in appearance. 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, 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 fro Bipolar 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), ECG, and physical examination findings.

Statistical Methods:

Efficacy: 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/lithium versus topiramate 200 mg, topiramate 400 mg, and lithium 1500 mg, as well as lithium 1500 mg versus topiramate 200 mg and 400 mg. Comparisons between topiramate 200 mg versus placebo/lithium, based on the primary endpoint was done only if topiramate 400 mg was significantly (two-sided, $p \leq 0.05$) superior to placebo/lithium. The comparisons between topiramate and placebo/lithium 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.

Body weight: Body weight was analyzed based on the ITT population using the last observation carried forward (LOCF) data. Summary statistics (mean, SD, median, and range) were provided for Days 21 and 84 LOCF. The percent change from baseline was analyzed using the same ANCOVA model as for YMRS.

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.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Subjects in each of the topiramate 200 mg and 400 mg treatment groups experienced smaller mean decreases from baseline in YMRS scores to the Day 21 visit (less improvement in symptoms) than either the placebo/lithium or lithium 1500 mg groups. The topiramate treatment groups were not statistically significantly different from placebo.

SAFETY RESULTS: Common treatment-emergent adverse events that occurred more frequently in one or both of the topiramate groups than in the placebo/lithium and lithium 1500 mg groups were associated with the central and peripheral nervous systems (paraesthesia, headache), or were psychiatric (anorexia, insomnia) or metabolic (acidosis, weight decrease) in nature. Subjects in the lithium 1500 mg group had higher incidences of tremor (15%), nausea (12%), diarrhea (16%), and thirst (6%) than the other three treatment groups. During the open-label phase of the study when all subjects received topiramate, common treatment-emergent adverse events that occurred more frequently in the placebo/lithium and the lithium 1500 mg groups were associated with the central and peripheral nervous systems, with the exception of paraesthesia in the topiramate 400 mg group, which occurred in 11% of subjects. Paraesthesia occurred in 17% of the lithium 1500 mg group and 9% of the placebo group.

Three subjects died during the study, all while receiving topiramate (1 during the double-blind phase and 2 during the open-label phase). Two of the three cases were suicides, and in each case, the investigators considered the deaths to be unrelated or of doubtful relationship to the study drugs.

Most of the serious adverse events reported by topiramate subjects during the double-blind and open-label phases of the study were considered to be unrelated or of doubtful relationship to the study drug. These events included delirium, difficulty with concentration and memory, neurosis, injury, metabolic acidosis, and attempted suicide. The only serious events reported among topiramate subjects that were considered drug-related were delirium (very likely related) and psychosis (possibly related).

Fourteen subjects in each of the placebo/lithium and topiramate 400 mg groups discontinued from the double-blind phase because of adverse events, compared with 16 subjects taking lithium 1500 mg and 9 who received topiramate 200 mg. Adverse events that most often resulted in discontinuation across the treatment groups were: nausea, diarrhea, parasthesia, tremor, headache and anorexia; most were considered at least possibly related to treatment. During the open-label phase, when all subjects received topiramate, 9% of placebo/lithium subjects, 6% of topiramate 200 mg, and 5% of subjects in each of the lithium 1500 mg and topiramate 400 mg groups discontinued because of adverse events. The only events among topiramate subjects that were considered drug-related and resulted in discontinuation were diarrhea and metabolic acidosis.

Post-baseline changes in bicarbonate levels were noted across the four treatment groups, but more subjects in the two topiramate groups experienced markedly abnormal values. Additionally, 2 subjects receiving topiramate 400 mg and 1 receiving topiramate 200 mg had increased chloride values, consistent with the carbonic anhydrase inhibitory activity of the drug. None of the topiramate subjects experienced any increases in liver function test values, while 6 subjects receiving lithium 1500 mg had increased ALT values, 2 had increased AST values, and 1 had increased values for alkaline phosphatase. One placebo/lithium subject had an increased level of AST.

CONCLUSION: In this randomized, double-blind, placebo-controlled, 12-week study with an open-label extension, subjects in each of the two topiramate dose groups experienced smaller mean decreases in YMRS scores at Day 21 and Day 84 (less improvement in symptoms), and the mean changes at Day 84 were statistically significantly smaller in the two topiramate groups than in either the placebo/lithium group or the lithium 1500 mg/day groups. Both topiramate groups experienced greater mean percent reductions in body weight than subjects in the other treatment groups, and by the Day 84 final assessment visit, mean percent reductions from baseline in body weight in both topiramate groups were statistically significantly different from placebo. Common treatment-emergent adverse events among topiramate subjects were related to the central and peripheral nervous systems, or were psychiatric or metabolic in nature.

Date of the report: 06 AUGUST 2003

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