Janssen Research & Development

Clinical Study Report Synopsis
[Protocol TOPMAT-PDMD-006; Phase 3]

RWJ-17021-000 (Topiramate)

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- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

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, 21-Day Study of the Safety and Efficacy of Topiramate for the Treatment of Acute Manic or Mixed Episodes in Subjects With Bipolar I Disorder With an Optional Open-Label Extension – (Protocol TOPMAT-PDMD-006)		
Investigators: [redacted] M.D. - [redacted] USA		
Study Center(s): 11 study centers - (all in the United States)		
Publication (Reference): None		
Study Initiation/Completion Dates: 08 December 2000 to 03 May 2002 (Double-Blind Phase) and 30 September 2002 (Open-Label Phase)		**Phase of development:** 3
Objectives: To determine the safety and efficacy 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.		
Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 study that evaluated topiramate (400 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: a screening phase (of variable duration, depending upon the washout required for previous psychotropic medications), a double-blind treatment phase (21 days, subdivided into titration and stabilization) followed by a double-blind taper phase for subjects not entering open-label treatment (Days 22 to 35), and an optional open-label extension phase. Upon enrollment in the double-blind phase, each subject received study medication (topiramate target dose of 400 mg/day or placebo) twice daily in a blinded fashion for up to 21 days. Subjects who completed the study through Day 21 were permitted to enter the open-label phase. 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 208 subjects (104 per treatment group). A total of 215 subjects (106 placebo and 109 topiramate) were randomly assigned to treatment and were evaluated for safety. A total of 213 subjects (106 placebo, 107 topiramate 400 mg) comprised the intent-to-treat population and were evaluated for efficacy. The open-label phase included 106 subjects (62 placebo, 44 topiramate 400 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.		
Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 50-mg (Batch D99LL0247) or 100-mg (Batch D99LJ0214) tablets. Each dose was administered orally.		
Duration of Treatment: 21 days		

SYNOPSIS (Continued)

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Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match topiramate was supplied as 50-mg (Batch D99LK0223) or 100-mg (Batch D99LF0135) tablets. 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. 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 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 treatment, (pooled) study center, and baseline as a covariate. The placebo and topiramate 400-mg groups were compared. The comparison between placebo and topiramate treatments was made using least square means (LSMEANS) within the ANCOVA model. The SAS PROC GLM procedure type III sums of squares was used for statistical tests. The 95% confidence intervals for the difference between LSMEANS of the placebo and topiramate 400-mg groups 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 Day 21. 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.

SYNOPSIS (Continued)

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The mean changes in YMRS score from baseline to Day 21 for the placebo and topiramate 400-mg groups were –6.4 and –5.1, respectively. The results of the ANCOVA showed that the change in YMRS score for each of the 2 treatment groups were not statistically different.

Body Weight: The mean percent change in body weight from baseline to Day 21 for the placebo group was –0.1%. Treatment with 400 mg/day topiramate resulted in a larger mean decrease in body weight from baseline to Day 21 (-1.9%). The results of the ANCOVA showed that these changes in body weight for each of the 2 treatment groups were statistically different.

SAFETY RESULTS: In the placebo and topiramate 400-mg groups, 75% and 70% of subjects, respectively, reported a treatment-emergent adverse event during the double-blind period. The results of the tapering period were included in the double-blind data for all subjects, whether or not they were entering the open-label phase of the study. Thus, the placebo group includes subjects who received either topiramate or placebo during the double-blind taper period. Treatment-emergent adverse events that occurred at the greatest incidence during the double-blind phase were associated with central and peripheral nervous system disorders and gastrointestinal system disorders. Headache was reported by more subjects in the placebo group (26%) than in the topiramate 400-mg group (18%), whereas paraesthesia was reported by fewer subjects in the placebo group (8%) than in the topiramate 400-mg group (17%). Many of the common treatment-emergent adverse events (i.e., those occurring in ≥5% of subjects) were gastrointestinal in nature. Most of these were reported by less than 10% of subjects in each treatment group, and there was a similar percentage of subjects in each treatment group that reported many of the adverse events in this body system. 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. Common treatment-emergent adverse events during the open-label phase were associated with the central and peripheral nervous systems or respiratory system and included headache, paraesthesia, and upper respiratory tract infection, each reported by more than 10 subjects. 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 and topiramate 400-mg groups, 10 (9%) and 6 (6%) subjects, respectively, discontinued double-blind treatment due to an adverse event. Adverse events leading to discontinuation of study drug treatment were often psychiatric in nature or related to the central and peripheral nervous systems. Open-label treatment was discontinued due to an adverse event by 8 (13%) and 5 (11%) subjects in the placebo and topiramate 400-mg groups, respectively. No noteworthy or clinically relevant changes from baseline to final visit were observed for any mean hematology or chemistry values or hepatic function tests for either 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 either of the treatment groups during either phase of the study.

CONCLUSION: The mean decrease in YMRS score from baseline to Day 21 for the topiramate 400-mg group and placebo group were not statistically different. The topiramate 400-mg group experienced a statistically significant greater mean reduction in body weight at Day 21 compared with the placebo group.

Common treatment-emergent adverse events among topiramate-treated subjects were related to the central and peripheral nervous systems or were gastrointestinal in nature. The reporting of central and peripheral nervous system-related adverse events during topiramate treatment is consistent with the adverse events described in the current product label.

Date of the report: 13 January 2004