SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (the sponsor) 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.: PRI/TOP-INT-28 (CR003259) **Title of Study:** A Randomized, Double-Blind, Parallel Group, Monotherapy Study to Compare the Safety and Efficacy of Two Doses of Topiramate in the Treatment of Newly Diagnosed or Recurrent Epilepsy.		
Coordinating/Principal Investigator: Santiago Arroyo, M.D., Ph.D.		
Publication (Reference): None		
Study Initiation/Completion Dates: 18 November 1998 - 26 February 2002		**Phase of development:** 3
Objectives: The objective of this study was to compare the safety and efficacy of 2 doses of topiramate (TPM) as monotherapy in pediatric and adult subjects with newly diagnosed (within 3 months) epilepsy characterized by partial-onset or generalized seizures, or with recurrent epilepsy while off of antiepileptic drugs (AEDs).		
Methodology: This randomized, double-blind, parallel-group study compared the safety and efficacy of 2 doses of topiramate, 50 mg/day (TPM 50) and 400 mg/day (TPM 400) administered as monotherapy in subjects with a new diagnosis of epilepsy (made within 3 months) or with recurrent epilepsy. The trial included 4 phases: baseline, open-treatment, double-blind, and long-term extension. Only the data collected through the end of the double-blind phase are included in this report. During the 3-month retrospective baseline, subjects were to have either 1 or 2 documented partial onset (POS) or generalized (GEN) seizures. To ascertain tolerability and to allow for discontinuation of any baseline AEDs therapy, eligible subjects received TPM 25 during a 7-day open treatment phase. Between screening (up to 14 days before study entry) and randomization, subjects were to have no more than 1 seizure. Subjects who experienced significant tolerability problems during the open-treatment phase were not eligible for randomization. At the end of open treatment, eligible subjects were randomly assigned to either TPM 50 or TPM 400. AEDs, if any, were tapered off prior to randomization. The double-blind phase comprised 2 periods: titration (up to 42 days) and stabilization (of variable duration); subjects who experienced significant tolerability problems during the first 21 days of the double-blind phase were withdrawn from the study. Subjects remained in the double-blind phase until i) the first POS or GEN seizure, ii) double-blind phase termination (6 months after the last subject was randomized), or iii) withdrawal for protocol-specified reasons (adverse events, subject choice, or lost to follow-up). The efficacy assessment was based on between-group difference in time to first seizure during the double-blind phase. Safety evaluations were based on treatment-emergent adverse events, clinical laboratory tests, measurements of vital signs and body weight, physical and neurologic examinations in all subjects, as well as visual field examinations at pre-selected sites in subjects 12 years and older.		
Number of Subjects (planned and analyzed): Sample size calculation was based on the assumption of a constant ratio of hazard rates (0.525) for the time to first seizure. Since the power of log-rank test used in primary efficacy analysis is driven by the number of treatment failures, i.e. subjects who experience a first seizure, it was calculated that the number of first seizures needed to achieve sufficient power to demonstrate the between-group difference was 108. The estimated sample size required to yield 108 first seizures was 500 to 560 subjects. Subject enrollment therefore continued until 108 subjects experienced a first POS or GEN seizure during the double-blind phase. A total of 487 subjects were enrolled; of those, 16 withdrew during the open treatment phase. Of the 471 subjects randomized, 470 had at least 1 study visit after randomization and were included in the intent-to-treat analysis.		
Diagnosis and Main Criteria for Inclusion: Eligible subjects weighed at least 25 kg and had, within 3 months of Visit 1, either a new diagnosis of epilepsy (partial-onset or generalized) or recurrent epilepsy while not taking AEDs. For entry into the open-treatment phase of the trial, subjects were required to have at least 1, and no more than 2, well-documented partial-onset or generalized seizures during the 3-month retrospective baseline phase.		

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Test Product, Dose and Mode of Administration, Batch No.: TPM was supplied in tablets (25-mg, batches D99LF0139, D99LK0224, D00LB0305, and D00LM0570; 50-mg, batches D99LG0148, D99LL0247, and D01LA0603; and 100-mg, batches D99LF0138, D99LK0226, D99LF0139, and D00LC0321). TPM was administered in 2 divided doses.

Duration of Treatment: Prior to randomization, subjects received TPM 25 for 7 days in the open-treatment phase. Duration of double-blind therapy was variable for individual subjects (median duration, 266 days; range, 9 to 786 days). Subjects received double-blind treatment until i) the first POS or GEN seizure, ii) study termination (6 months after the last subject was randomized), or iii) withdrawal for protocol-specified reasons.

Criteria for Evaluation:

Efficacy: Efficacy assessment was based on the comparison between TPM 400 and TPM 50 with respect to time to the first POS or GEN seizure during the double-blind phase (excluding taper).

Safety: Safety was evaluated on the basis of treatment-emergent adverse events, clinical laboratory tests, measurements of vital signs and body weight, and physical examination findings in all subjects, as well as visual field examination results in subjects 12 years and older at selected sites.

Statistical Methods: Primary efficacy analysis was based on a survival analysis of the difference between TPM 400 and TPM 50 with respect to time to first POS or GEN seizure during the double-blind phase (excluding taper). Kaplan-Meier (KM) estimates were calculated for time to first seizure. Statistical significance of the treatment effect was tested by the log-rank test. To examine onset of effect and efficacy of lower doses of topiramate, the primary endpoint was analyzed using truncation of the follow-up period at various times during the study, starting on Day 14. The treatment groups were compared with respect to time to first seizure at each of these time points using a 2-sided log-rank test. Consistency of the treatment effects with respect to demographic/baseline characteristics (sex, age, baseline weight, geographic region, baseline AED use, baseline seizure type, and time since diagnosis) was assessed using Cox's proportional hazards model. Efficacy was also examined as a function of plasma TPM concentration data obtained on or after Day 36 across 3 TPM concentration strata (<2 μg/mL, 2 to <10 μg/mL, and ≥10 μg/mL). KM estimates for time to first seizure by TPM concentration strata were obtained.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS: Mean (SD) TPM plasma concentrations, determined from the samples obtained on Day 127, were 1.89 (0.97) μg/mL for the subjects in TPM 50 group and 11.71 (5.32) μg/mL in TPM 400 group.

EFFICACY RESULTS: Comparison of the KM survival curves of time to first seizure favored TPM 400 over TPM 50 (p=0.0002; 2-sided log-rank test). The separation between the 2 groups in favor of the higher dose group occurred early in the titration phase and was statistically significant as early as after 2 weeks post randomization (p = 0.046; 2-sided log-rank test), when, by following the weekly titration schedule, the subjects in the higher dose group achieved the maximum TPM dose of 100 mg/day. The separation between the groups continued to increase for the duration of the double-blind phase; between-group comparisons using truncation of the follow-up duration on Day 14 favored TPM 100 over TPM 25 (p = 0.046; 2-sided log-rank test); on Day 21 (at the end of the third week, when the dose was titrated upwards in both groups), this comparison showed a trend for significance (p= 0.071; 2-sided log-rank test) in favor of TPM 150 vs. TPM 50. The pointwise comparisons were significant at all other time points examined for the remainder of the study.

SYNOPSIS (CONTINUED)

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EFFICACY RESULTS (CONT.): The higher dose group was superior to the lower dose group with respect to the estimated proportion of subjects who remained seizure-free for a minimum of 6 months (82.9% vs. 71.4%; p = 0.005, t-test), and a minimum of 1 year of therapy (75.7% vs. 58.8%, p = 0.001, t-test). Based on the Cox proportional hazards model, the ratio of hazard rates for the time to first seizure obtained in the study (0.516) was consistent with the estimated hazard ratio of 0.525 used in calculation of the sample size. The results of subgroup analyses with respect to time to first seizure were consistent across the demographic/baseline strata, indicating that efficacy was not affected by these characteristics. Supportive of these analyses, the treatment effects were also consistent across these subgroups based on the Cox proportional hazards model. Adjustment of the model for each of the covariates did not affect the comparison between TPM dose groups; none of the interactions were statistically significant (p≥0.1.96; Cox proportional hazards model).

SAFETY RESULTS: The median duration of therapy for all subjects in the intent-to-treat population was approximately 9 months; some subjects received double-blind TPM treatment for over 2 years. The most common treatment-emergent adverse events reported in both treatment groups were neuropsychiatric in nature; many occurred at a less than 10% incidence at either dosage. Some neuropsychiatric events were reported at similar rates in both groups, e.g., dizziness, fatigue, difficulty with concentration/attention, and insomnia. Common adverse events in other body systems that occurred at similar rates in both groups included, among others, upper respiratory tract infection, nausea, injury, abdominal pain, diarrhea, viral infection, and dyspepsia. The incidence of headache was lower in TPM 400 group than in TPM 50 group. The most common among the events with at least twice the incidence in TPM 400 group, compared to TPM 50 group, were paresthesia, anorexia, weight decrease, difficulty with memory, mood problems, and cognitive problems. No deaths were reported during the double-blind phase of the study. At least 1 serious adverse event was reported for 14 subjects (6%) in TPM 400 group and for 10 subjects (4%) in TPM 50 group, including only 2 pediatric subjects. Most of the serious adverse events were considered by the investigators to be of either doubtful or no relationship to topiramate therapy and resolved as of the final study visit. Six subjects discontinued the study therapy due to the serious adverse events. No consistent pattern of adverse events or clinically remarkable new event was observed in either of the treatment groups. Notably, only 44 subjects (19%) in TPM 400 group and 16 subjects (7%) in TPM 50 group experienced adverse events that resulted in permanent discontinuation of therapy. Reduction of topiramate dosage or temporary interruption of treatment due to adverse events was implemented in 56 subjects (24%) in TPM 400 group and 20 subjects (9%) in TPM 50 group. Neuropsychiatric adverse events were most likely to contribute to either discontinuation of topiramate therapy or dosage reductions/temporary interruption of treatment in both groups. Most of these events were reported at a higher incidence in subjects assigned to TPM 400 group, compared to those assigned to TPM 50 group. Most of the subjects who experienced dose reductions or temporary interruptions of study treatment completed the study per protocol. There were no clinically important changes or abnormalities in vital sign measurements or in laboratory tests of liver function, renal function, and hematologic parameters.

CONCLUSION: The results of the present study demonstrate that monotherapy with topiramate 400 mg/day was superior to topiramate 50 mg/day with respect to efficacy in preventing the occurrence of seizures among adults and children (6 years of age and older) with newly diagnosed or recurrent epilepsy. The higher dose group separated from the lower dose group with regard to the primary efficacy endpoint after 2 weeks of double-blind treatment, at the dose of 100 mg/day. Topiramate monotherapy also demonstrated efficacy with respect to the seizure freedom for at least 6 months and at least 1 year of treatment. The overall distribution of adverse events observed in the study was consistent with the previous add-on clinical experience in epilepsy, although the incidence rates appeared to be lower for monotherapy. No unexpected or unusual safety issues arose in this study.

Date of the report: 20 AUGUST 2002

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