CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-USRA-10154600:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	TOPAMAX® (topiramate)	
Name of Active Ingredient	2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate	

Protocol No.: TOPMAT-PEP-3001

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Fixed Dose-Ranging Study to Assess the Safety, Tolerability, and Efficacy of Topiramate Oral Liquid and Sprinkle Formulations as an Adjunct to Concurrent Anticonvulsant Therapy for Infants (1 to 24 Months of Age, Inclusive) With Refractory Partial Onset Seizures, With Open-Label Extension

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Publication (Reference): None

Study Period: 30 September 2005 – 1 June 2007 | **Phase of Development:** 3

Objectives: The primary objective of the double-blind phase of the study was to compare the effectiveness of topiramate 5, 15, or 25 mg/kg per day (administered as either sprinkle capsules or oral liquid formulation) with that of placebo as an adjunct to concurrent anticonvulsant therapy in reducing daily partial-onset seizure (POS) rates in infants (1 to 24 months of age, inclusive) with refractory POS after 20 days of double-blind treatment. An additional objective was to evaluate the safety and tolerability of topiramate oral liquid and sprinkle formulations in infants with epilepsy at dosages up to 5, 15, and 25 mg/kg per day over 20 days of double-blind treatment.

Methodology: This was a randomized, double-blind, placebo-controlled, video electroencephalogram (vEEG) rater-blinded, parallel-group, 4-arm, fixed dose-ranging study to evaluate the tolerability, safety, and efficacy of topiramate as an adjunct to concurrent anticonvulsant therapy in infants, age 1 to 24 months, with refractory POS with or without secondary generalization. The study included 4 phases: a 3-day screening phase, a 20-day double-blind treatment phase (including uptitration and stabilization of dosage), a 1-year open-label extension phase (including a blinded taper of double-blind treatment and uptitration of open-label treatment), and a posttreatment phase (including a withdrawal taper). Following screening procedures, which was to include a 48-hour vEEG, eligible subjects were randomized (1:1:1:1) to topiramate (5, 15, or 25 mg/kg per day) or placebo, starting at an initial dosage of 3 mg/kg per day with gradual uptitration to the target dosage for the remainder of the 20-day treatment period. A single dosage reduction or pause in uptitration due to intolerability was allowed. Subject take-home records, containing information on seizure type and frequency, study drug intake, and adverse events, were kept throughout the double-blind phase, and a final 48-hour vEEG was to be performed the last 2 days of the treatment period. Physical and neurologic examinations, vital sign and anthropomorphic measurements, and evaluations of food and liquid intake, oligohidrosis, hyperthermia, and rash were regularly performed. Clinical laboratory tests, 12-lead electrocardiogram (ECG), renal ultrasound, and the Vineland Scales of Adaptive Behavior were performed at screening and the end of the double-blind phase. Adverse events and concomitant medications were continually monitored. At the end of the double-blind phase, subjects could enter the open-label phase or withdraw permanently from the study. This reports contains results from the double-blind treatment phase of the study; results from the open-label extension phase will be reported separately.

Number of Subjects (planned and analyzed): 120 subjects (30 per treatment arm) were planned, and 149 were randomized. Efficacy and safety were analyzed in 130 and 149 subjects, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects were 1 to 24 months of age with clinical or EEG evidence of POS (simple or complex), with or without secondary generalization, present at least 1 month prior to the first day of screening in subjects >6 months of age, or at least 2 weeks prior to the first day of screening in subjects ≤6 months of age. Subjects with at least 2 countable, electroclinical POS (with either EEG or clinical evidence of focal origin), based on the baseline vEEG during the screening phase, were allowed to enter the double-blind treatment phase of the study.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied in 25-mg sprinkle capsules (Batches D05LA1448, D05LD1534, D05LJ1658, D06LC1823, 4LG4303, 4NG685, 04JS25H, 5HG6398, 6LG379, 6NG612, 7AG645) and 30-mg/mL oral liquid (Batches 05C25/F017, 05H01/F017, 06D17/F017, 06E29/F017, 06F12/F017, 06H29/F017, 06K06/F017). The oral liquid was diluted with purified water to a concentration of 5 mg/mL prior to administration. Treatment was to be administered orally, twice daily, and

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subjects were to receive 5, 15, or 25 mg/kg per day.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied in sprinkle capsules (Batches PD1334, PD1402, PD1381, PD1720) and oral liquid (Batches 05D15/F020, 05K14/F020, 06E11/F020) matching topiramate. Treatment was to be administered orally, twice daily.

Duration of Treatment: Duration of double-blind therapy was to be 20 days.

Criteria for Evaluation:

Efficacy: The primary basis of efficacy for topiramate was a statistically significant ($p \leq 0.05$; analysis of covariance [ANCOVA] method) percentage reduction in POS seizure rate from baseline to end point (last non-missing observation on or prior to the end date) in the double-blind treatment phase as recorded on a vEEG of up to 48 hours in duration. Secondary efficacy end points included the percentage of treatment responders (≥50% reduction in seizure rate) for POS and all seizure types based on vEEG data, the percentage reduction in seizure rate for all seizure types based on vEEG data, and the percentage reduction in seizure rate for POS and all seizure types based on subject take-home records.

Safety: Safety was evaluated by treatment-emergent adverse events, clinical laboratory tests, vital sign and anthropometric measurements, physical and neurologic examinations, ECG findings, and evaluation of adequate food and liquid intake, oligohidrosis, hyperthermia, and rash.

Statistical Methods: The primary efficacy analysis compared each topiramate dosage group, from the highest (25 mg/kg per day) to the lowest dosage (5 mg/kg per day), with placebo using a step-down procedure at a 2-sided type-I error of 0.05. The null hypothesis for the higher tested dose must have been rejected before the next lower dose could be tested, and testing stopped when a dosage level was not significantly different from placebo to preserve the overall type-I error rate. The main analysis used an analysis of covariance (ANCOVA) on ranks of the percentage reduction in the modified intent-to-treat population, including age group (<6 months [180 days] vs ≥6 months [180 days] on Day 1) and treatment group as factors, and baseline POS seizure rate as a covariate. Additional analyses using the ANCOVA model were performed with additional factors of sex (male, female), baseline anti-epileptic drug category (inducer, noninducer), and number of anti-epileptic drugs (≤1, 2, >2). Three sensitivity analyses were also performed. The secondary efficacy end point on treatment responders was evaluated using a Mantel-Haenszel statistic stratified by age group. Other secondary end points were analyzed in the same manner as for the primary end point. Secondary end points were tested at a 0.05 significance level without adjustment for multiple comparisons.

Safety data were summarized descriptively. An exploratory analysis of treatment difference for the changes from baseline in ECG variables used an analysis of variance (ANOVA) model, with age at randomization (<180 days, ≥180 days) and treatment group as factors.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: The 25-mg/kg per day dosage was deemed to be the highest tolerable dosage and thus was first compared with placebo in the step-down procedure. The apparently greater median percent reduction in daily POS rate with topiramate 25 mg/kg per day than with placebo (20.40% vs 13.06%) during the double-blind phase was not statistically significant ($p=0.967$). Response was not related to the topiramate dosage (lower dosages were not formally tested). Similar results were obtained in alternate analyses ($p>0.2$ using 3 additional covariates and $p>0.7$ in 3 sensitivity analyses). Likewise, no treatment effect compared with placebo or indication of dose-related effect was observed in any of the secondary end points, whether based on vEEG or subject take-home log data. For all efficacy end points, response appeared similar in all treatment groups.

SAFETY RESULTS: Topiramate at dosages up to 25 mg/kg per day was generally well tolerated as add-on therapy in this group of infants with refractory POS, and there were no new or unexpected safety findings. The only death occurred at some time after treatment discontinuation. The few serious adverse events and events that led to premature discontinuation of study treatment were varied and occurred to a similar extent in both topiramate- and placebo-treated subjects. Dose adjustments of topiramate were infrequently needed, but most often for anorexia. Events with a greater incidence on topiramate than placebo (≥5% difference) included fever, vomiting, anorexia, diarrhea, infection viral, somnolence, upper respiratory tract infection, bronchitis, and nervousness. Most events were mild or moderate in intensity and considered by the investigator to be unrelated or of doubtful relation to study treatment.

Subjects With Adverse Events/Reactions (Double-Blind Phase)

	Placebo (N=37) n (%)	All topiramate (N=112) n (%)
One or more adverse events/reactions	19 (51)	91 (81)
One or more serious adverse events/reactions	3 (8)	9 (8)

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Deaths	0 (—)	0 (—)*
Treatment stopped due to adverse events/reactions	2 (5)	4 (4)

* One death on an unknown date after premature withdrawal of topiramate 5 m/kg per day was reported.

Consistent with the observed topiramate-associated anorexia were a smaller increase in body weight (1.26% to 1.76% vs 3.38%) and a higher incidence of decreased weight (6% vs 3%) on topiramate than placebo. A mean dose-related decrease in serum carbon dioxide was observed with topiramate, and 10 topiramate-treated subjects showed indications of metabolic acidosis (vs 0 on placebo). Compared with placebo, subjects on topiramate had more renal events (mainly changes on renal ultrasound with no reports of nephrolithiasis), indications of oligohidrosis (including possible secondary rash), and hepatic events (but no notable mean changes, shifts, or markedly abnormal values for liver function laboratory tests). Hyperammonemia and ocular events were rare with both treatments. No other clinically meaningful changes in safety variables, including laboratory variables other than carbon dioxide, vital signs, and ECG, were seen with topiramate treatment in these infants.

CONCLUSION: The 20-day double-blind treatment phase of this study was unable to show a significant treatment effect for topiramate oral liquid or sprinkle formulations at dosages of 25, 15, and 5 mg/kg per day compared with placebo as adjunct therapy on the reduction of daily POS rate in infants aged 1 to 24 months with refractory POS. No treatment effect was consistently seen in all alternate efficacy analyses and for all secondary end points. All topiramate dosages tested were generally well tolerated in these infants, with no new safety concerns. The safety profile for topiramate in infants was consistent with that previously seen in older children and adults.

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