CLINICAL STUDY REPORT SYNOPSIS

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

Protocol No.: CR002245

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Topiramate for the Prophylaxis of Migraine in Pediatric Subjects 12 to 17 Years of Age

Coordinating Investigator: Paul K. Winner, D.O. - Premiere Research Institute/Palm Beach Neurology, West Palm Beach, FL; U.S.A

Publication (Reference): None

Study Period: Date of First Study Related Procedure: 10-Aug-2005 Date of Last Observation for Last Subject: 29-Nov-2006	**Phase of Development:** 3

Objectives: The primary objective of the study was to compare the effectiveness of topiramate 50 or 100 mg/day with that of placebo in the prevention of migraine attacks in subjects 12 to 17 years of age after 16 weeks of double-blind treatment. Additional objectives were to evaluate the safety and tolerability of topiramate migraine prophylaxis, document topiramate exposure by estimated trough plasma concentrations, and explore the effect of topiramate on the physical, emotional, social, home, and school functioning in subjects 12 to 17 years of age receiving topiramate 50 or 100 mg/day double-blinded treatment over 16 weeks.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, fixed dose-ranging study to evaluate the tolerability, safety, and efficacy of topiramate as prophylaxis in pediatric subjects, age 12 to 17 years with episodic migraine headaches with or without aura. The study included 3 phases: a ≤9-week pretreatment phase (including screening, a 4-week washout period if needed, with a 2-week taper of disallowed prophylactic migraine medications and 2-week observation period, and a 4-week medication-free, prospective baseline period), a 16-week double-blind treatment phase (including titration and maintenance to target dose), and a posttreatment phase (including a 2-week withdrawal taper and a follow-up visit 4 weeks after the last treatment visit). Subjects with 3 to 12 migraine attacks during the baseline period (but no more than 14 migraine or non-migraine headache days) were allowed to enter the double-blind treatment phase of the study. The efficacy measurements were based on information from headache and medication records maintained by the subjects during the prospective baseline period, the double-blind phase, and the post-treatment phase. The Pediatric Quality of Life Inventory (PedsQL) and Pediatric Migraine Disability Assessment (PedMIDAS) were recorded during screening, before study drug administration at the beginning of the double-blind phase, the double-blind phase and the post-treatment phase. The primary and secondary efficacy variables are presented below. Safety was evaluated based on treatment-emergent adverse events, clinical laboratory tests, vital sign and anthropometric (body weight and height) measurements, physical and neurologic examinations, Cambridge Neuropsychological Test Automated Battery, Profile of Mood States, and monitoring for signs of renal or urinary disturbances, visual or ocular disturbances, oligohidrosis, heat intolerance, rash, depression, or suicidal ideation.

Number of Subjects (planned and analyzed): 102 subjects (34 per treatment arm) planned and 103 subjects analyzed for efficacy and safety, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects were 12 to 17 years of age diagnosed with migraine, with or without aura, as defined by the proposed IHS classification of Pediatric Migraine; Subjects with 3 to 12 migraine attacks during the baseline period (but no more than 14 migraine or non-migraine headache days) were allowed to enter the double-blind treatment phase of the study.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25-mg tablets (Batches D06LC1819, D05LB1475) administered orally twice daily.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as matching tablets (Batch D03LK1145) administered orally twice daily.

Duration of Treatment: Duration of double-blind therapy was 16 weeks.

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Criteria for Evaluation:

Efficacy: The efficacy of topiramate was based primarily on percent reduction from the prospective baseline period to the last 12 weeks of the double-blind phase in the monthly migraine attack rate using the 48-hour rule for definition of a migraine attack. The secondary efficacy variables (prospective baseline period to the last 12 weeks of the double-blind phase) included the following: percent reduction in the monthly migraine day rate, monthly headache day rate, monthly migraine attack rate (using the 24-hour rule), monthly migraine day with rescue medication rate, percent reduction in monthly migraine attack rate (using the 48-hour rule) from the prospective baseline period to the last 4 weeks of the double-blind phase as well as and responder rate, where a responder was defined as a subject with 50% or greater reduction for the primary endpoint. Other efficacy analyses (prospective baseline period to the last 12 weeks of the double-blind phase) included the following: change in monthly rates for each headache type, average migraine attack severity, monthly migraine attack duration, and monthly rate for days of migraine rescue medication use, and (prospective baseline period to the last post-baseline observation in the double-blind treatment phase) subject-reported outcomes (PedMIDAS and PedsQL). An evaluation of headache rebound after the discontinuation of the study medication was also performed

Safety: Safety was evaluated based on treatment-emergent adverse events, clinical laboratory tests, vital sign and anthropometric (body weight and height) measurements, physical and neurologic examinations, Cambridge Neuropsychological Test Automated Battery, Profile of Mood States, signs of renal or urinary disturbances, visual or ocular disturbances, oligohidrosis, heat intolerance, rash, depression, suicidal ideation, or metabolic acidosis.

Statistical Methods: The primary efficacy variable (percent reduction from the prospective baseline period to the last 12 weeks of the double-blind phase in the monthly migraine attack rate) was analyzed using an ANCOVA model on ranks that included subjects' stratified age at baseline (i.e., 12 to 14 or 15 to 17 years old), treatment group, and analysis center as factors and monthly migraine attack rate during prospective baseline period as a covariate. There were 2 null hypotheses related to the 2 topiramate treatment groups, specifically that there would be no differences between placebo and the topiramate treatment groups in the ranks of the primary endpoint. This study was to be considered positive if at least 1 null hypothesis could be rejected. The Hochberg's procedure was used to adjust for multiple comparisons of the 2 topiramate treatment groups versus placebo, with an overall 2-sided Type I error rate of 0.05. The secondary efficacy parameters (except responder rate) were analyzed by the same ANCOVA model on ranks as for the primary endpoint, using the corresponding baseline variable in the model but without multiplicity adjustments. The association between treatment and responder rate was analyzed using the Cochran-Mantel-Haenszel pairwise tests between each treatment group and placebo controlling for the analysis center effect. The other headache-associated and safety data were to be descriptively summarized.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Subjects treated with topiramate 100-mg per day had a significantly greater percent reduction in monthly migraine attack rate (48 hour rule) compared to subjects randomized to placebo; this treatment effect was not observed in the 50-mg per day topiramate group. The majority of the secondary analyses supported the primary analysis results. Statistical significance of the 100-mg per day topiramate group relative to placebo was achieved in monthly migraine day rate, monthly headache day rate, monthly migraine attack rate (24-hour rule), and monthly migraine attack rate (48-hour rule) over last 4 weeks. Statistical significance was not reached for the monthly migraine day with rescue medication rate. For all efficacy endpoints a higher treatment effect was observed in the last 4 weeks as compared to the last 12 weeks of the double-blind phase. The median change in migraine attack severity from baseline to the last 12 weeks of double-blind treatment was comparable for the 2 topiramate-treated study groups (–0.25 and –0.28 for 100- and 50-mg per day topiramate-treated subjects respectively), vs. –0.20 in the placebo. Median change in migraine attack duration for the same period was marked in the 100-mg per day topiramate group vs. the 50-mg per day topiramate and placebo groups, (-1.78, -0.88 and -0.90, respectively). There was a significantly higher responder rate for the 100-mg per day topiramate group relative to placebo (83% vs. 45%). Cumulative response rates for topiramate and placebo treated groups show that 100-mg per day topiramate-treated subjects had a consistently higher response rate than subjects treated with 50-mg per day topiramate or placebo, based on any definition of "responder", rather than restricting to the commonly accepted 50% reduction criteria. Descriptive results for PedMIDAS total score and rating scale did not show clear differentiation between the topiramate groups and placebo. The largest improvement in the PedsQL physical health summary score and school functioning subscale was observed in the 100-mg dose group.

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SAFETY RESULTS: No unexpected or unusual safety issues arose during this study; overall, topiramate was well tolerated; both the qualitative nature and frequency of side effects (reported as well as measured) were similar to what has been noted in children, adolescents and adult subjects treated with topiramate for a variety of indications, including the pivotal migraine trials. Evaluations of special safety events (including rash, ocular, renal and hepatic events, oligohidrosis/hyperthermia, hyperammonemia/encephalopathy, metabolic acidosis, weight loss, depression/suicide, and suicide-related events) did not reveal any unexpected findings; events were either absent, not clinically relevant, considered by the investigator to be unrelated to topiramate treatment, or consistent with the known safety profile of topiramate. No deaths occurred during this study; there were 2 serious adverse events in subjects treated with topiramate (back pain and injury). These were considered of doubtful relationship to study treatment. There were no clinically important changes in clinical lab tests of liver function, renal function, serum ammonia, hematologic parameters or in vital signs. No major treatment differences were observed between topiramate and placebo groups in CANTAB measurements. Descriptive results suggest some topiramate-related improvements in visual memory and simple attention tests. Despite increased latency of response in topiramate groups, overall accuracy was comparable to placebo in discrimination and sustained attention tests. These findings are likely not clinically important; few adverse events reported were related to neurocognitive functioning, including psychomotor slowing, word finding and other language difficulties, and attention problems. Mood states were unaffected by treatment, as evidenced by the consistent lack of change or reduction in symptoms on all of the POMS subscales.

CONCLUSION: Topiramate was effective in the prevention of migraine in adolescents 12 to 17 years of age, as assessed by the percent reduction from prospective baseline to the last 12 weeks of double-blind phase in the monthly migraine attack rate (using 48-Hour Rule), when compared to placebo. The results of this study demonstrated that topiramate at a dose of 100-mg daily was effective in migraine prophylaxis whereas treatment with topiramate 50-mg daily did not separate from placebo. Both topiramate doses were well tolerated and demonstrated a safety profile consistent with that of previous indications, including migraine prophylaxis in adults.

Issue Date of the Clinical Study Report: 20 August 2007

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