SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho–McNeil Janssen Scientific Affairs, LLC. previously Ortho-McNeil Pharmaceutical, Inc NAME OF FINISHED PRODUCT: Topiramate NAME OF ACTIVE INGREDIENT(S): Topiramate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR002872 **Title of Study:** A Pilot Study of Topiramate in Childhood Absence Epilepsy		
Study Initiation/Completion Dates: 15 April 2005 (first subject screened); 20 October 2006 (last subject, last follow-up visit)		**Phase of development:** II
Objectives: The objectives of this study were to evaluate the antiepileptic effect of topiramate monotherapy in childhood absence epilepsy (CAE) and to determine the dose of topiramate associated with a therapeutic response.		
Methodology: This open-label, single-arm, multicenter, pilot study had 3 phases: a Screening Phase followed by a Treatment Phase, including Titration and Maintenance Periods, and an optional post-study treatment Taper Phase. Subjects for this study were children aged 4 to 9 years weighing ≥15 kg with a diagnosis of CAE in general good health with normal neurological examination and normal intelligence, and naïve to antiepileptic drug treatment, other than having taken and discontinued use of ethosuximide, lamotrigine, or valproate due to problems with tolerability. Subjects for whom informed consent was obtained and who met eligibility criteria entered the 3- to 11-week Titration Period. Topiramate sprinkle capsules (Topamax®) were administered orally starting at a dose of 15 mg/day (subjects weighing 15-24 kg) or 25 mg/day (≥25 kg) and titrated upward at weekly intervals, depending on response, to a maximum of the lesser of 9 mg/kg/day or 400 mg/day. When biweekly seizure assessments indicated subjects were free of absence seizures on hyperventilation (HV) a confirmatory 30-minute electroencephalographic (EEG) evaluation with hyperventilation and photic stimulation was performed. If subjects displayed no signs of seizure activity during this EEG, they entered the Maintenance Period and continued taking the last attained dose for 12 weeks. At the end of the Maintenance Period, subjects entered the Taper Phase (approximately 1 week) and had a follow-up visit at the end of taper. The duration of treatment was variable, depending on titration and taper, could be up to a maximum of approximately 24 weeks. A total of 12 subjects were enrolled prior to early termination of the study by the sponsor due to lack of demonstrated therapeutic response in these subjects (25 subjects were planned). All 12 subjects were analyzed for safety and 10 subjects were analyzed for efficacy.		
Criteria for Evaluation: Efficacy: The primary efficacy outcome was the proportion of subjects who became seizure-free, confirmed by a 30-minute EEG with two trials of 3 to 5 minutes of HV and one trial of photic stimulation performed at the end of the Maintenance Period. The secondary efficacy outcome was the change in number of electrographic or electroclinical seizures per hour from pretreatment to the final 30-minute EEG and change in duration per hour of spike wave. Safety: Safety was assessed based on incidence and severity of treatment-emergent adverse events (AEs) and changes from prestudy to poststudy in physical examination findings, vital sign measurements, and clinical laboratory assay values performed during scheduled study visits.		

SYNOPSIS (CONTINUED)

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SUMMARY - CONCLUSIONS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: This study was terminated early due to lack of lack of demonstrated therapeutic response. A total of 12 subjects were enrolled at 5 centers in the U.S. All 12 subjects were included in the safety population and 10 subjects with sufficient follow up data in the ITT population. Four subjects (33.3%) completed the study. Six discontinued during the Titration Period (50.0%) and 2 discontinued during the Maintenance Period (16.7%). The most common reason for discontinuation was lack of efficacy (6 subjects, 50.0%). Subjects ranged in age from 4.8 to 9.1 years, with a mean age of 6.9 years. The majority of subjects were female (7 [58.3%] and white (8 [66.7%]). The mean number of years since epilepsy diagnosis was 0.8 years with a standard deviation of 1.51 years. The average number of absence seizures in the 30 days prior to baseline was 5.8 per day with a standard deviation of 2.95.

EFFICACY RESULTS: Due to study termination only selected efficacy variables were analyzed. The study results presented and analyses conducted were difficult to interpret due to the limited amount of data resulting from the high rate of premature discontinuation. Due to missing data some of the analyses pre-specified in the statistical analysis plan were abbreviated and the data were analyzed on a more descriptive basis.

- There was no improvement in the mean number of electroclinical seizures per hour from baseline to the final 30-minute EEG in the ITT population (9.2 and 11.6 respectively, with a mean change from baseline of 2.4).
  - Overall, reductions in number of electrographic or electroclinical seizures per hour were noted sporadically through the Titration Phase (Day 36, 50 and 78), though none of the reductions were significant ($P>0.05$).
  - A comparison of EEGs on a subject by subject basis showed no clear sign of a consistent response during treatment with topiramate. Some subjects had complete electrographic seizure resolution, some responded to treatment but continued to have seizures and some had an increased number of electrographic seizures.
- During two 1-hour daily observation periods during the 7 days prior to study visits the average reduction from baseline in the daily seizure count ranged from 0.5 to 2.1 seizures per hour.
  - The mean reduction in seizure count was statistically significant at Day 22 (Visit T2) and Day 36 (Visit T3) ($P=0.0391$ and 0.0156, respectively) and approached statistical significance on Days 50, 64 and 92 ($P=0.0625$ at each time point).
  - At each study visit the percentage of days with seizures during the 7-day observation period prior was decreased from the baseline percentage of 90 (68% at Day 22, 38% at Day 36, 50% at Day 50, 52% at Day 64, 62% at Day 78, 46% at Day 92 and 70% at the final visit).
  - Possible trends towards improvement were noted, but due in part to the small number of subjects, the efficacy observations did not reach statistical significance.
- The mean daily dose of topiramate was 104 mg/day and the mean duration of exposure was 96 days.

SAFETY RESULTS: All 12 subjects were analyzed for safety. A total of 8 subjects had AEs, most commonly fever (3 subjects), fatigue, somnolence, otitis media, rhinitis, and urinary incontinence (each in 2 subjects). Four subjects had AEs that were considered possibly or probably related to treatment, including fatigue and fever (each in 2 subjects), and anorexia, difficulty with concentration/attention, mood problems, nervousness, somnolence, sweating decreased, and urinary incontinence (each in 1 subject). Most AEs were of mild severity. No subjects experienced severe AEs and none had serious AEs or discontinued the study due to AEs. No subjects died.

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CONCLUSION: Secondary efficacy analyses indicated that at the Final Visit there were no statistically significant reductions in the number of electrographic or electroclinical seizures or duration of spike wave discharges recorded during a 30-minute EEG, nor was there a significant improvement in seizure frequency and number of days with seizures. A possible trend towards improvement was seen but could not be confirmed due in part to the limited number of subjects and evaluations. An antiepileptic effect of topiramate monotherapy in CAE was not determined in this study and therefore a dose associated with a therapeutic response could not be determined. Topiramate was safe in children 4 to 9 years of age, and adverse events - when they occurred - were generally mild in severity.

Date of the report: 07 December 2007

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