SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho –McNeil Janssen Scientific Affairs, LLC. previously Ortho-McNeil Pharmaceutical, Inc. NAME OF FINISHED PRODUCT: TOPAMAX® NAME OF ACTIVE INGREDIENT(S): topiramate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CAPSS-272 CR004663

Title of Study: A Double-Blind Trial Comparing the Efficacy, Tolerability and Safety of Monotherapy Topiramate versus Phenytoin in Subjects with Seizures Indicative of New Onset Epilepsy

Coordinating Investigator: None.

Publication (Reference): None to date.

Study Initiation/Completion Dates: 11 August 2004 / 30 July 2007	**Phase of development:** IIIB

Objectives: The objective of this study was to evaluate the efficacy, tolerability, and safety of topiramate versus phenytoin sodium extended release (phenytoin) in subjects with seizures indicative of new onset epilepsy (or epilepsy relapse in subjects who were not receiving anti-epileptic drug [AED] treatment), and who required rapid initiation of oral AED therapy.

Methodology: This was a multicenter, randomized, double-blind, parallel group, comparative study. The study consisted of a Screening Phase of up to 7 days, a Double-Blind Phase of 4 weeks, and an optional Open-Label Extension Phase of 12 weeks. The procedures and results of the Open-Label Extension Phase will be presented in a separate clinical study report.

Subjects who completed the Screening Phase and met the eligibility (inclusion/exclusion) criteria were randomized and entered the Double-Blind Phase. The Double-Blind Phase consisted of a 1-day initiation period followed by a Maintenance Period. All subjects remained under observation in the study sites during the Initiation Period until the last initiation dose of study drug was administered (a minimum of 4 hours). Subjects were randomized to topiramate or phenytoin in a 1:1 ratio. The target initiation dose of topiramate on Day 1 was 100 mg followed by a maintenance dose of 100 mg/day. The target initiation dose of phenytoin was 1,000 mg followed by a maintenance dose of 300 mg/day. During the first week of the Maintenance Period (Days 2 through 7), doses of topiramate and phenytoin could have been adjusted based on subject tolerability. After Day 8, subjects had to tolerate a dose of at least 75 mg/day of topiramate or 200 mg/day of phenytoin to remain in the study. Subjects who completed the Double-Blind Phase, or who discontinued because of a complex partial or generalized tonic-clonic (GTC) seizure, could have entered the Open-Label Extension Phase. Subjects who did not enter the Open-Label Extension Phase had Visit 4/Final Visit procedures performed and had study drug tapered with concurrent initiation of alternate therapy. A final visit (Visit 4T) was conducted after the conversion to alternate therapy was complete.

The primary efficacy variable was the time to the first complex partial or GTC seizure. Seizure data were recorded daily during the Screening and Double-Blind Phases. Safety was assessed by vital signs, physical examinations, brief neurological examinations, clinical laboratory tests, and evaluation of adverse events (AEs). Additionally, blood was drawn for AED level determination and a complete medical history was obtained at screening.

Number of Subjects (planned and analyzed): A total of 55 sites were initiated in the United States (US); 43 of the 55 sites enrolled subjects. Approximately 262 subjects were expected to be enrolled. At the end of the Double-Blind Phase, 261 subjects had been randomized: 133 received topiramate and 128 received phenytoin. Of those, 259 were included in the Safety Population and 254 were included in the Intent-to-Treat population.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women 12 to 65 years old (inclusive), weighed $\geq$ 50 kg, had a diagnosis of new onset epilepsy or a relapse of epilepsy after stopping AED therapy in the past. Subjects had to be candidates for a rapid initiation of AED therapy. At the time of enrollment, subjects had to have experienced at least 1 but no more than 20 unprovoked complex partial or GTC seizures (primary or secondarily generalized) within the past 3 months.

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NAME OF FINISHED PRODUCT: TOPAMAX®	Volume:	
NAME OF ACTIVE INGREDIENT(S): topiramate	Page:	

Test Product, Dose and Mode of Administration, Batch No.: Study drug was 25 mg topiramate tablets (Batch numbers: 3KG0866 and 4NG4614; Package lot numbers R12585, R12586, R12790, R12791, R12788, R12789, R13706, R13707, R13565 and R13566). The target initiation dose of topiramate on Day 1 was 100 mg (given as 3 doses of 50 mg, 25 mg, and 25 mg, respectively, at 2-hour intervals), followed by a maintenance dose of 100 mg/day (50 mg twice daily [BID]). During the first week of the Maintenance Period (Days 2 through 7), doses could have been adjusted based on subject tolerability. After Day 8, subjects had to tolerate a dose of at least 75 mg/day of topiramate to remain in the study.

Matching placebo tablets (Batch number PD1104; Package lot numbers R12586, R12791, R12788, R12789, R13707, and R13566) were also supplied.

Reference Therapy, Dose and Mode of Administration, Batch No.: Reference therapy was 100 mg extended release phenytoin sodium capsules (Batch number PD1111, PD1332, and PD1712, Package lot numbers R12586, R12791, R12789, R13707, and R13566). The target initiation dose of phenytoin was 1,000 mg (given as 3 doses of 400 mg, 300 mg and 300 mg, respectively, at 2-hour intervals), followed by a maintenance dose of 300 mg/day (given as 1 dose of 300 mg). During the first week of the Maintenance Period (Days 2 through 7), doses could have been adjusted based on subject tolerability. After Day 8, subjects had to tolerate a dose of at least 200 mg/day of phenytoin to remain in the study.

Matching placebo capsules (Batch numbers PD1110 and PD1711, Package lot numbers R12585, R12586, R12790, R12791, R12788, R12789, R13706, R13707, R13565, and R13566) were also supplied.

Duration of Treatment: 4 week

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the time to the first seizure (complex partial or GTC seizure) over a 28-day period. The date, description, and duration of any seizure experienced during the trial were recorded in a seizure diary. The information could have been recorded by the subject or by an observer who witnessed the event. Seizure data were reviewed and classified by the investigator.

Safety: Safety and tolerability evaluations included AEs, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, physical and neurological examinations, and AED concentrations.

Statistical Methods: The primary efficacy variable, time to first seizure (complex partial or GTC seizure) over the first 28-day of treatment, was analyzed by a Wald's chi-square test. The null hypothesis of the primary analysis was H_0: $\lambda_T/\lambda_S > 2.275$, where λ_T and λ_S represent the hazards for the topiramate and phenytoin groups respectively. Topiramate was to be considered as effective as phenytoin if the null hypothesis was rejected at the one-sided alpha = 0.05 level.

A secondary efficacy endpoint was the proportion of subjects who were seizure-free at Day 28. The proportions were calculated using Kaplan-Meier estimates for the ITT Population for each treatment group. Two-sided 90% and 95% confidence intervals (CI) of the difference of cumulative seizure-free rates at Day 28 were constructed. Cox proportional hazard models were used for assessment of the effect of covariates, such as, sex, age, baseline weight, baseline seizure type, and duration since first diagnosis of epilepsy. Kaplan-Meier estimates and Cox proportional hazard model were also used to analyze the time to first seizure by exiting seizure type. In addition, Kaplan-Meier estimates for the cumulative rate of time to discontinuation were obtained. A log-rank test was performed to compare the two study completion survival functions. All statistical tests were conducted at the two-sided, 0.05 significance level, unless otherwise specified.

The number and percentage of subjects reporting treatment-emergent AEs were tabulated by Double-Blind treatment group. The frequency of AEs was summarized for all events and for the most common AEs. The number of subjects reporting AEs was tabulated by relationship to study drug as well as by the intensity of the AE.

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NAME OF ACTIVE INGREDIENT(S): topiramate	Page:	

Summaries and listings were provided for subjects reporting serious adverse events (SAEs) and for subjects withdrawing due to an AE.

Summary statistics were calculated by visit for clinical laboratory tests. The incidence of treatment-emergent, markedly abnormal laboratory values was summarized.

Summary statistics were calculated for each on-study drug visit for vital signs measurements. The number and percent of subjects with treatment-emergent, markedly abnormal vital signs were summarized by Double-Blind treatment. The number and percent of subjects with normal or abnormal physical and neurological examination results were summarized by Double-Blind treatment at baseline and the final visit. The number and percent of subjects reporting concomitant medication use were summarized by Double-Blind treatment group.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The primary efficacy variable, time to first seizure (GTC or complex partial seizure) after rapid initiation of monotherapy at the doses studied over the first 28 days of treatment, was analyzed by a Wald chi-square test. The test failed to reject ($p = 0.3661$) the non-inferiority null hypothesis $H_0:\lambda_T/\lambda_S > 2.275$, therefore, non-inferiority of topiramate to phenytoin was not established. The secondary efficacy analyses for time to first seizure by exiting seizure type (GTC and complex partial seizure) support the results of the primary efficacy analysis.

The proportion of subjects who experienced any seizure type (GTC or complex partial seizure) was higher in the topiramate group (18.8%) compared with the phenytoin group (11.1%). Results were similar for either GTC or complex partial seizures.

Although the non-inferiority of topiramate to phenytoin was not established at the protocol-defined non-inferiority limit and the proportion of subjects who experienced any seizure was higher in the topiramate group compared with the phenytoin group, the overall retention rate at the end of Double-Blind Phase of the study was significantly higher for the topiramate group compared with the phenytoin group (89.4% and 80.3%, respectively, $p = 0.0469$)

SAFETY RESULTS:

Overall, both topiramate and phenytoin were well tolerated in this population. The incidences of AEs considered related to study drug were similar in each treatment group (56.8%, topiramate, 55.9%, phenytoin). A total of 7 subjects experienced 8 SAEs, 4 of which led to withdrawal from the Double-Blind Phase. The most common treatment-related AEs (occurring in at least 5% of subjects in either treatment group) were dizziness and somnolence (which occurred more frequently in the phenytoin group) and paraesthesia (which occurred more frequently in the topiramate group). None of these common AEs were unexpected based on the prescribing information for both of the study drugs.

Of note, approximately twice as many subjects who received phenytoin (13.4%) discontinued from the Double-Blind Phase due to AEs compared with subjects who received topiramate (6.8%). The only adverse event leading to discontinuation that occurred in >5% of the subjects in either group was rash. For subjects receiving phenytoin, 10 subjects experienced rash/macro-papular rash and 2 subjects experienced pruritus leading to withdrawal; none of these AEs were unexpected based on the prescribing information for phenytoin. No subjects in the topiramate group withdrew due to these skin-related AEs.

Mean changes from baseline in clinical laboratory evaluations and vital signs were small and generally similar in each treatment group. No markedly abnormal clinical laboratory values occurred in more than 5.0% of subjects in either treatment group, and none were recorded as AEs. Only 1 abnormal vital sign (mild rapid heartbeat in a subject taking phenytoin) was reported as an AE. The only physical examination findings reported in more than 5% of subjects in either treatment group at the Final Visit of the Double-Blind Phase occurred in the phenytoin group (general appearance, 6.6%; skin, 9.8%), which is consistent with the incidence of skin-related AEs in the phenytoin group.

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CONCLUSION:

The primary analysis of time to first seizure (GTC or complex partial seizure) after rapid initiation of monotherapy at the doses studied over the first 28 days of treatment did not establish non-inferiority of topiramate to phenytoin. The overall retention rate during the Double-Blind Phase was significantly higher for the topiramate group compared with the phenytoin group. Additionally, the rate of withdrawal due to AEs was higher in the phenytoin group. Overall, the safety results for each study medication was consistent with the medication's safety profiles in its prescribing information.

Date of the report: 20 May 2008 (Draft 2)

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