CAPSS-311 CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs	
Name of Finished Product	TOPAMAX®	
Name of Active Ingredient(s)	topiramate	
Protocol No.: CAPSS-311 CR002869		
Title of Study: TOPAMAX® (Topiramate) Initiated as Monotherapy in Epilepsy (TIME): A Multicenter, Outpatient, Open-label, Study to Evaluate the Dosing, Effectiveness and Safety of TOPAMAX® as Monotherapy in the Treatment of Epilepsy in Clinical Practice		
Principal Investigator: Multicenter, 148 investigators		
Publication (Reference): None		
Study Period: 15 January 2006 – 04 August 2007 (first dose, last dose)		**Phase of Development:** IV
Objectives: The objective was to identify subject characteristics that were predictive of effective target, stabilized dosages of TOPAMAX® initiated as monotherapy in the treatment of epilepsy in clinical practice, as well as to evaluate the dosing, effectiveness, and safety of TOPAMAX® when administered as monotherapy. The study attempted to prove the hypothesis that subjects with a high baseline seizure frequency (>3 seizures in last 3 months prior to baseline) would be titrated to a higher stabilized effective TOPAMAX® dose, compared to subjects with a lower baseline seizure frequency.		
Methodology: This was a 24-week, multicenter, outpatient, open-label, single-arm study to evaluate the dosing, effectiveness, and safety of TOPAMAX® as monotherapy in the treatment of epilepsy in clinical practice. The study consisted of a screening/baseline phase of up to 7 days (Visit 1) followed by a 24-week treatment phase (Visits 2-3, a telephone contact, and Visit 4, or final visit). Subjects diagnosed with new-onset epilepsy or epilepsy relapse characterized by partial-onset (with or without secondary generalization) or primary generalized tonic-clonic seizures who were candidates for TOPAMAX® monotherapy and satisfied all the entry criteria would be entered into the study. Study medication treatment was titrated according to the schedule in the Package Insert starting at 50 mg/day and increasing to 400 mg/day or the subject's maximum tolerated dose. Changes to the schedule were based on a risk-benefit assessment of the subject's clinical condition by the investigator. Subjects that were not controlled on TOPAMAX® monotherapy despite dose optimization had to be discontinued from the study. Concomitant antiepileptic drug (AED) treatment was not allowed.		
Number of Subjects (planned and analyzed): Approximately 560 subjects who were identified by their physicians as candidates for initial antiepileptic monotherapy were planned, 407 subjects were enrolled; 390 subjects were in the safety population, 378 were in the intent-to treat (ITT) population, 244 were in the modified intent-to-treat (mITT) population and 213 were in the mITT population on TOPAMAX® monotherapy at the end of the trial.		
Diagnosis and Main Criteria for Inclusion: Qualified subjects were male or female, 10 years of age or older, > 25 kg body weight with a diagnosis of new-onset or epilepsy relapse characterized by partial-onset or primary generalized tonic-clonic seizures (> 2 lifetime unprovoked seizures or 1 lifetime unprovoked seizure and an electroencephalogram [EEG] demonstrating focal or generalized epileptiform EEG abnormalities) who had 1 or more seizures within the 3 months before study entry. Qualified subjects were not previously treated with an AED or if they had been previously or currently treated with an AED the duration of treatment had to be less than 6 weeks. Qualified subjects also had not previously received TOPAMAX® for the treatment of epilepsy at any time.		
Test Product, Dose and Mode of Administration, Batch No.: Commercial TOPAMAX® was provided in kits containing 25-mg, 50-mg, and 100-mg tablets at Visits 1 and 2. TOPAMAX® was self-administered twice daily in the morning and evening. The dose was titrated to the maximum tolerated dose with a target dose of 400 mg/day. The titration schedule was determined by the investigator, based on the labeled dosing recommendations. Starting at Visit 3, subjects received TOPAMAX® through their pharmacy via a prescription and a prescription card. Bulk lot numbers were 5KG335 (25 mg), 5JG281 (50 mg), and 5JG312 (100 mg). Packaging lot numbers were R13754 (kits 3001-3300) and R13760 (kits 3301-5100).		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		
Duration of Treatment: Treatment would be for 168 days (24 weeks), including titration.		

Criteria for Evaluation:

Efficacy: Seizure occurrence and seizure characteristics, as well as the daily dose of TOPAMAX® were recorded by subjects in diaries and transcribed to case report forms (CRFs). The dosing information was used to calculate the mean stabilized dose achieved for the last 28 days of treatment.

Safety: Safety and tolerability were assessed by adverse events (AEs) and clinical laboratory tests of liver function and electrolytes.

Statistical Methods: The primary efficacy analysis was performed on a mITT population comprising only subjects who were treated for at least 12 weeks, that had reached a stabilized dose during the last 28 days of the study, and were on TOPAMAX® monotherapy at the end of the trial. Two definitions of stabilized dose were used: the mean stabilized dose was the subject's mean dose over the last 28 days and the median stabilized dose was the subject's median dose over the same period. The primary efficacy outcome was the comparison of the mean stabilized dose in subjects on TOPAMAX® monotherapy at the end of the trial who reported > 3 seizures vs. subjects who reported 1 to 3 seizures during the 3 months before study entry, using analysis of variance (ANOVA). This analysis was also performed using the median stabilized dose. Inferential analyses were done on the means of the stabilized dose, using either definition. Sensitivity analyses that accounted for missing values were also done. In addition, a linear regression model was used, with stabilized dose as the dependent variable and baseline characteristics included in the model. The stabilized dose was compared in the 2 groups of subjects stratified by baseline seizure frequency using an analysis of covariance (ANCOVA) with baseline characteristics as the covariate. Other secondary analyses were performed using the ITT population, comprised of subjects who received 1 dose of study medication and had at least 1 post-baseline efficacy assessment. These analyses included number of subjects remaining seizure free from baseline to post-baseline visits, subjects remaining seizure-free throughout the trial, and reduction in seizure frequency. Kaplan-Meier estimates were made for time to achieve stabilized dose and the difference between the 2 groups was assessed by a log rank test. Safety variables were summarized for the safety population, comprised of all subjects who took at least 1 dose of study medication and had a safety assessment, using descriptive statistics. Adverse events were summarized by stratified group based on baseline seizure frequency. Laboratory summaries include shift tables.

SUMMARY - CONCLUSIONS

Due to slower than planned subject enrolment and recruitment, a total of 407 subjects were enrolled. Although the number of subjects in the analysis population used for the primary outcome was considerably smaller than that described for sample size in the statistical analysis plan, the primary outcome was statistically significant.

EFFICACY RESULTS: The results of the primary outcome assessment are shown in the following table. The mean stabilized TOPAMAX® monotherapy dose over the last 28 day of the study for the group of subjects with >3 seizures in the 3 months prior to baseline was significantly higher than that of subjects with 1-3 seizures during this same time frame. A sensitivity analysis using all subjects' data showed similar results in support of the primary outcome measure. Analyses using median stabilized dose produced similar results, as well.

Comparison of Mean Stabilized Dose in mg/day (mITT Population)

Stabilized Dose	TOPAMAX Treated Subjects with 1-3 Seizures in Last 3 Months Prior to Baseline N=166	TOPAMAX Treated Subjects with >3 Seizures in Last 3 Months Prior to Baseline N=78	p-value
n[a]	147	66	
Mean (SD)	190.57 (97.059)	239.12 (126.460)	0.0025
Median	200.00	200.00	
Min, Max	25.9, 600.0	50.0, 600.0	

Note: p-value from an ANOVA model with baseline seizure frequency as factor. Subjects who achieved a stabilized dose but were not on TOPAMAX® monotherapy at the end of the study were also excluded from this analysis.
[a] Excluded subjects not on TOPAMAX® monotherapy at the end of the study.

Secondary outcome results were as follows:

- A sensitivity analysis of the primary outcome using data from all subjects in the mITT population that was used for the primary outcome measure plus subjects in the ITT population with missing stabilized doses or with fewer than 12 weeks of treatment showed similar stabilized dose results that support the primary outcome measure.
- Analyses of the mean stabilized dose using the median over the last 28 days produced a similar association of stabilized dose and baseline seizure frequency.
- Analyses of the mean stabilized TOPAMAX® monotherapy dose on the subset of subjects who remained seizure free during the study demonstrated a between group difference in dosage that was directionally

different from the results of the primary analysis; the low baseline seizure frequency group had a higher mean stabilized dose than the high baseline seizure frequency group, but the difference did not reach statistical significance (p=0.0747).

- Based on simple linear regression analysis, baseline seizure frequency over the past 3 months and lifetime seizure count had statistically significant potential predictive relationship with the stabilized dose. Seizure frequency within 12 months prior to study entry, number of prior treatments, seizure etiology, (predominant) seizure type, and whether the subject was receiving an AED at the time TOPAMAX® was initiated did not have statistically significant predictive relationships with the stabilized dose.
- Regression analyses found that seizure frequency over the past 3 months at baseline (i.e., 1-3 seizures vs. >3 seizures) predicted a between group difference in mean stabilized daily dose of 51 mg using simple regression analysis or a difference of 43 mg using stepwise regression analysis.
- The use of lifetime seizure frequency as a covariate supports the results of the primary analysis in demonstrating a significant difference in stabilized dose based on baseline seizure frequency; this did not apply, however, to subjects who had complete seizure control during the study.
- Based on the Kaplan-Meier estimates of time to stabilized dose, the between group difference was statistically significant, demonstrating a median of 36 days for the group of subjects with 1-3 seizures and 53 days for the group of subjects with >3 seizures in the 3 months before baseline and indicating that subjects with a low seizure rate could on average be stabilized in a shorter time period of 5 weeks compared to an 8 weeks titration period for the high seizure frequency group.
- There were subjects in the group with high baseline seizure frequency who had a very high mean monthly seizure frequency and were especially refractory to therapy with TOPAMAX®.
- Subjects with high baseline seizure frequency are more refractory to becoming seizure free relative to subjects with low baseline seizure frequency.
- TOPAMAX® showed efficacy in seizure reduction over a range of different seizure types.

SAFETY RESULTS:

A summary of treatment-emergent AEs (TEAE) and serious treatment-emergent AEs (SAE) is presented in the following table:

Summary of Treatment-Emergent Adverse Events (Safety Population)

	TOPAMAX Treated Subjects with 1-3 Seizures in Last 3 Months Prior to Baseline N=259 n (%)	TOPAMAX Treated Subjects with >3 Seizures in Last 3 Months Prior to Baseline N=131 n (%)
Subjects with any TEAE	195 (75.3)	96 (73.3)
Subjects with any drug-related TEAE	161 (62.2)	79 (60.3)
Subjects who discontinued study medication due to TEAE	43 (16.6)	28 (21.4)
Subjects with any treatment-emergent SAE	12 (4.6)	8 (6.1)

Note: Drug-related TEAEs include events considered possibly, probably, or very likely related to study medication (or any AE with missing relationship).

Overall safety findings were:

- No deaths were reported during the study.
- The AEs and their incidence rates reported in this study are consistent with the known side effect profile and the product labeling for TOPAMAX®.
- The percentages of subjects with drug-related TEAEs were similar for both groups of subjects.
- The percentage of subjects experiencing SAEs was slightly higher for the group with a high baseline seizure frequency.
- Proportionally more subjects in the high baseline seizure frequency group discontinued due to TEAEs.
- Changes in liver function test results and electrolytes at endpoint were minor and similar in both groups. A modest lowering of serum bicarbonate levels, a known side effect of TOPAMAX®, was similarly observed in both treatment groups.

- Shift tables for liver function tests showed very few shifts from normal at baseline to abnormal (low or high) at endpoint and shifts were similar in both groups; shifts from normal to high chloride were observed in both groups; shifts from normal to low bicarbonate were observed in both groups but in a greater proportion of subjects in the high baseline seizure frequency group. Overall, few subjects had shifts in magnesium levels but a slightly greater proportion of subjects in the high baseline seizure frequency group had high magnesium shifts at endpoint.
- Subjects in both groups experienced statistically significant weight loss at all visits beginning at Day 28. There were no statistically significant differences in weight loss between the 2 groups. Body weight decreased by a mean of 2.8 kg in the low baseline seizure frequency group and 4.3 kg in the high baseline seizure frequency group.

CONCLUSIONS: Overall, the study proved the hypothesis that epilepsy subjects treated with TOPAMAX® monotherapy required different stabilized effective dosages of TOPAMAX®, based on their baseline seizure frequency.

Specifically:

- These data support the hypothesis that subjects with a lower baseline seizure frequency may require a lower daily TOPAMAX® monotherapy dose.
- Baseline seizure frequency over the previous 3 months was a significant predictor of the mean stabilized TOPAMAX® monotherapy dose.
- Subjects in the group with 1–3 seizures during the previous 3 months had a mean stabilized TOPAMAX® monotherapy dose of 191 mg/day and the group of subjects with >3 seizures during the previous 3 months had a mean stabilized TOPAMAX® monotherapy dose of 239 mg/day.
- The likelihood that subjects remain seizure-free during the titration and maintenance period is greater for subjects with low baseline seizure frequency compared to those with high baseline seizure frequency.
- Based on this study, a stabilized monotherapy dose of TOPAMAX® can be reached on average at 5 weeks for subjects with low baseline seizure frequency and on average at 8 weeks for subjects with high baseline seizure frequency.
- Most adverse events with TOPAMAX® therapy were mild to moderate in intensity.
- In this study, TOPAMAX® monotherapy demonstrated efficacy and was found to be safe in a variety of seizure types at different baseline seizure frequencies. The tolerability profile was consistent with product labeling for TOPAMAX®.

Issue Date of the Clinical Study Report: 03 July 2008

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