SYNOPSIS

Name of Sponsor/Company:	Ortho-McNeil Pharmaceutical, Inc.	
Name of Finished Product:	TOPAMAX® (topiramate)	
Name of Active Ingredient(s):	RWJ-17021-0000 (2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate)	

Protocol No.: CR002659

Title of Study: A Comparison of the Efficacy and Safety of Topiramate Versus Placebo in the Treatment of Essential Tremor

Coordinating Investigator: Multicenter Study

Publication (Reference): None

Study Period: 19 October 2001 to 04 November 2003 | **Phase of development:** 3

Objectives: The objective of this study was to evaluate the efficacy and safety of topiramate versus placebo in the treatment of essential tremor.

Methodology: This was a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel study. Subjects with essential tremor (as defined by the Tremor Investigational Group criteria) were to be randomized equally to 1 of 2 treatment groups (topiramate or placebo). The study was composed of 4 phases: screening, double-blind, washout, and open-label extension. Only the data collected through the end of the double-blind phase are included in this report.

Eligibility was assessed during the screening phase, which lasted up to 21 days. Subjects who successfully completed the screening phase were randomized into the double-blind phase. The double-blind phase consisted of 2 periods each lasting 12 weeks: a titration period and a maintenance period. During the titration period, subjects were to titrate up to a maximum of 400 mg/day of study medication or their maximum tolerated dose, whichever was lower. Study medication, consisting of either 25 mg or 100 mg topiramate, or matching placebo in identically-appearing tablets, was titrated at the investigator's discretion according to the protocol-defined titration schedule. Upward titration of the study medication was stopped if the subject had complete resolution of their tremor. During the maintenance period, the dose of study medication was to remain constant. Clinical study visits were to occur on Day 1 (Visit 2), Day 28 (Visit 3), Day 56 (Visit 4), Day 84 (Visit 5), Day 112 (Visit 6), Day 140 (Visit 7) and Day 168 (Visit 8). After completing the double-blind phase of the study, subjects were tapered off of the study medication and entered a 2-week washout period. Subjects were considered to have completed the double-blind phase of the study if they completed the Maintenance Period through Visit 8. Discontinued subjects were not replaced.

Number of Subjects (planned and analyzed): Two hundred subjects were planned, 223 were randomized, 208 were evaluated for efficacy in the Intent-to-Treat (ITT) population (all randomized subjects who took study medication and for whom a post-randomization, on-treatment efficacy assessment was available), and 221 were evaluated for safety.

Diagnosis and Main Criteria for Inclusion: The study was to be conducted on subjects between 18 and 80 years of age with current manifestations of essential tremor symptoms based on the Tremor Investigational Group criteria for definite or probable essential tremor. Subjects were to have a dominant upper extremity posture or action intention tremor of 2 (moderate) to 4 (severe) in Part A (Tremor Location/Severity Rating) of the TRS at Visit 2. Subjects were to be taking no more than 1 concomitant tremor medication.

Test Product, Dose and Mode of Administration, Batch No.: The test product consisted of either 25 mg (batch numbers R10598, R11287, or R12118) or 100 mg topiramate (batch numbers R10600, R11289, or R12119) and was orally administered.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was provided in identically-appearing 25 mg tablets (batch numbers R10599, R11288, or R12120) and 100 mg tablets (batch numbers R10601, R11290, or R12121) and was orally administered.

Duration of Treatment: The planned duration of double-blind treatment was 24 weeks.

Criteria for Evaluation:

Efficacy: Efficacy was assessed using a 3-part Clinical Rating Scale for Tremor (TRS) consisting of Part A (tremor location/severity rating), Part B (specific motor tasks/function rating) and Part C (functional disabilities relating from tremor rating); the SF-36 Health Survey; and a 5-point subjects' and investigators' global assessment of study

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medication consisting of very good, good, no change, poor and very poor.

A normalization procedure was applied to the three subscales of the TRS in order to give subscales equal weight in the overall TRS score. The primary efficacy variable was the final overall normalized restricted TRS score, defined as the sum of the normalized, restricted Part A score, the normalized Part B score and normalized Part C score divided by 3, with a range from 0 to 100. The restricted Part A score included only 4 items (posture holding for the right and left upper extremity, and action and intention for the right and left upper extremity) of the 22 items in the unrestricted Part A subscale.

Secondary efficacy variables included the final normalized restricted Part A, normalized Part B and normalized Part C subscale scores; the final overall normalized unrestricted TRS score; the final overall unadjusted (without normalization) restricted TRS score and unadjusted subcategory scores; the SF-36 Health Survey scores and the subjects' and investigators' global assessment of study medication.

Safety: Safety evaluations included a complete medical history, physical examinations, neurological examination (including mental status, cranial nerves, reflexes and coordination, and motor and sensory examinations), vital sign and electrocardiogram measurements, hematology and chemistry clinical laboratory tests and monitoring of adverse events.

Statistical Methods: The primary and secondary TRS scores and the SF-36 Health Survey scales were analyzed using an analysis of covariance, with treatment and center as qualitative factors, and the baseline score as a covariate. The subjects' and investigators' global assessments were analyzed with the Cochran-Mantel Haenszel test, with treatment as a between group factor and stratified by center. All statistical tests were conducted at the two-sided, 5% significance level.

SUMMARY - CONCLUSIONS

Of the 223 subjects randomized into the study, 117 received topiramate and 106 received placebo. Seventy-three subjects (62.4%) in the topiramate group and 83 subjects (78.3%) in the placebo group completed the study. Of the 208 subjects included in the ITT population, 115 (55.3%) were male and 93 (44.7%) were female. The subjects ranged in age from 17 to 80 years (mean age 62.0 years). The majority of subjects were white (190 subjects, 91.3%).

EFFICACY RESULTS:

Topiramate was statistically superior compared to placebo for the primary efficacy variable, the final overall normalized restricted TRS score ($p<0.001$).

Topiramate was statistically superior to placebo for the majority of secondary efficacy variables. Among the TRS secondary efficacy variables, topiramate was statistically superior to placebo for the normalized Part B subscale ($p<0.001$) and the normalized Part C subscale ($p=0.001$). For the normalized, restricted Part A subscale, the mean change from baseline was numerically greater for the topiramate group compared to the placebo group with the difference approaching statistical significance ($p=0.061$). The results for the unadjusted and unrestricted TRS efficacy variables mirrored those of the normalized TRS variables. Results for completed subjects were similar to the results for the Intent-to-Treat population with the exception that the difference in mean change from baseline for the normalized restricted Part A subscale was statistically significant.

Topiramate was also statistically superior to placebo for subjects' and investigators' global assessment ($p<0.001$ for both). There was no consistent difference in the pattern between topiramate and placebo for the SF-36 subscale scores. On all but 1 of the quality of life subscales of the SF-36 there was no statistically significant difference between topiramate and placebo.

SAFETY RESULTS:

One hundred and nine subjects (94.0%) in the topiramate group and 81 subjects (77.1%) in the placebo group experienced adverse events. The most commonly reported adverse events in the topiramate group were paraesthesia (28.4%), weight decrease (22.4%), upper respiratory tract infection (19.0%) and taste perversion (19.0%). The most commonly reported adverse events in the placebo group were upper respiratory tract infection (14.3%) and dizziness (11.4%).

The majority of adverse events were mild to moderate in severity. Twenty-eight subjects (24.1%) in the topiramate group and 8 subjects (7.6%) in the placebo group experienced adverse events that were marked in severity.

Five subjects (4.3%) in the topiramate group and 8 subjects (7.6%) in the placebo group experienced serious adverse events. All of the serious adverse events in the topiramate group were considered by the investigator to be unrelated or of doubtful relationship to study medication. A larger proportion of subjects in the topiramate group (31.9%) than in the placebo group (9.5%) discontinued treatment due to an adverse event. The most common treatment limiting

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adverse events in the topiramate group were paraesthesia (5.2%), nausea (2.6%), difficulty with concentration/attention (2.6%), and somnolence (2.6%). In the placebo group there were no adverse events for which more than 1 subject discontinued the study.

There were no clinically relevant mean changes from baseline in hematology or chemistry laboratory tests or in vital signs in either group. There was a small mean decrease in body weight and BMI that was significantly greater for the topiramate group (-4.23% for both) than for the placebo group (-0.72% and -0.70%, respectively) ($p<0.001$ for both).

No clinically meaningful trends were observed for changes in EKGs, physical examinations, or neurological exams.

CONCLUSION:

The results of this study demonstrate that topiramate is significantly more effective than placebo in the treatment of essential tremor, as measured by final overall normalized restricted TRS scores, as well as subjects' and investigators' global assessments. Topiramate was well tolerated by subjects experiencing essential tremor.

Date of the report:

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