

SYNOPSIS

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| NAME OF SPONSOR/COMPANY: Ortho-McNeil Neurologics, Inc. | | |
| NAME OF FINISHED PRODUCT: TOPAMAX [®] (topiramate) | | |
| NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-Di- <i>O</i> -isopropylidene- β -D-fructopyranose sulfamate | | |
| Protocol No.: CR002653 Title of Study: Topiramate Versus Placebo as Add-On Treatment in Subjects with Bipolar Disorder in the Outpatient Setting | | |
| Coordinating Investigator: Multicenter Study | | |
| Publication (Reference): None | | |
| Study Period: 25 October 2001 to 06 October 2003 | | Phase of development: 3b |
| Objectives: The primary objective of this study was to evaluate the efficacy and safety of topiramate versus placebo as an add-on therapy in an outpatient setting in subjects with bipolar I disorder. | | |
| Methodology: This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of topiramate, titrated to 400 mg/day, versus placebo as add-on therapy to lithium or valproate for the treatment of bipolar I disorder in an outpatient setting. The study included 2 phases: screening/washout and double-blind treatment. After screening and washout of prohibited medications, eligible subjects were randomized to topiramate or placebo in a 1:1 ratio. Following the baseline visit, subjects returned to the treatment center weekly for efficacy and safety assessments for the duration of the 8-week titration period. During this period, subjects in the topiramate treatment group were titrated from 25 mg/day during Week 1 to 400 mg/day or the maximum tolerated dose, whichever was lower; subjects in the placebo treatment group received matching placebo. Following the titration period, subjects entered a 4-week continuation period, where they remained on a stable dose of topiramate or matching placebo, depending on treatment group. They returned to the study center for efficacy and safety assessments every 2 weeks during this period (Days 70 and 84). Following this period, subjects were tapered off study medication. Their achieved dose was decreased by approximately 30% every 3 days for 1 week. Subjects then returned to the study center for a follow-up visit (Day 91) to assess safety. | | |
| Number of Subjects (planned and analyzed): The original planned analysis was based on 200 randomized subjects (100 subjects per treatment group). As a result of higher-than-expected rates of premature discontinuation, an amendment to the protocol (17 September 2002) increased the randomized sample for the planned analysis to 260 subjects (130 subjects per treatment group). Two hundred eighty-seven subjects (143 in the topiramate treatment group and 144 in the placebo treatment group) were randomized, took at least 1 dose of study medication, and were assessed for safety. For efficacy analyses, 278 subjects (136 in the topiramate treatment group and 142 in the placebo treatment group) were included in the Intent-to-Treat (ITT) population (who took at least 1 dose of study medication and provided at least 1 post-baseline efficacy evaluation), and 229 subjects (110 in the topiramate treatment group and 119 in the placebo treatment group) were included in the ITT Per-Protocol population (ITT population excluding those who did not initiate lithium/valproate within 30 days prior to enrollment). | | |
| Diagnosis and Main Criteria for Inclusion: Eligible subjects were 18 to 70 years old; had successfully completed the screening procedures; had a diagnosis of bipolar I disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and supported by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); had been taking a mood stabilizer (lithium or valproate) for at least 6 weeks prior to study entry; and had a Young Mania Rating Scale (YMRS) score ≥ 18 at Visits 1 and 2. | | |
| Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25-mg tablets (batch R12213, R11795, and R11211) and 100-mg tablets (batch R12214, R11796, and R11213). | | |
| Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo was inert, identical in appearance to topiramate, and supplied as 25-mg (batch R12215, R11797, and R11212) and 100-mg tablets (batch R12216, R11798, and R11214). | | |
| Duration of Treatment: Double-blind treatment continued for 84 days (56-day titration period and 28-day continuation period), with 7 days of follow-up to taper subjects off study medication. | | |

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change from baseline to final visit in the YMRS total score. Secondary efficacy variables included YMRS responder analysis, the change from baseline to final visit in the Clinical Global Impressions (CGI) scale, Global Assessment Scale (GAS), Brief Psychiatric Rating Scale (BPRS), and Montgomery-Åsberg Depression Rating Scale (MADRS), and the rate of discontinuation due to efficacy failure (defined as the need for psychiatric hospitalization, new antipsychotic drug intervention, or an increase in the subject's stable dose of antipsychotic therapy taken throughout the study; suicidal or homicidal intervention; and/or inadequate clinical response despite adequate exposure to study and rescue medication).

Safety: Safety was assessed by physical examinations, including vital signs (sitting blood pressure, resting pulse, oral temperature, and weight), clinical laboratory tests (hematology, chemistry, and urinalysis), thyroid function tests, serum pregnancy tests, and the evaluation of adverse events (AEs).

Statistical Methods: The primary analysis compared changes from baseline to the final visit in the YMRS total scores using the ITT population. For subjects who withdrew early, the last available post-baseline observation carried forward (LOCF). The final visit corresponded to the Week 12 (Day 84) data in the LOCF dataset. Analysis for the YMRS total score was performed for both the absolute change and the percent change from baseline to the endpoint visit using an analysis of covariance (ANCOVA) model with treatment and center as independent factors and the baseline value as covariate. The analysis was also performed on the ITT Per Protocol and Completer populations.

Analysis of the secondary efficacy variables was done on the ITT, ITT-Per Protocol, and Completer populations. Changes from baseline to the endpoint visit for the CGI-S, CGI-C, MADRS, BPRS, and GAS scores was analyzed using the ANCOVA model described above. Treatment response (responder/not responder) at endpoint was analyzed using a logistic regression including treatment, center, and baseline YMRS in the model.

SUMMARY – CONCLUSIONS

A total of 287 subjects were randomized in this study, 144 to placebo and 143 to topiramate. One hundred seventy-seven (61.7%) completed the study, and 110 (38.3%) discontinued early. The subjects ranged in age from 18 to 70 years (mean age of 40.0 years). The majority of subjects were female (162 subjects, 56.4%) and white (241 subjects, 84.0%). In general, key demographic and subject characteristics were comparable across treatment groups.

EFFICACY RESULTS:

In the primary analysis, the least-square (LS) mean YMRS score improved between baseline and endpoint for both treatment groups in the ITT population (-10.0 and -9.8 for the placebo and topiramate treatment groups, respectively; a negative change score represents improvement); however, no statistically significant difference was demonstrated between topiramate and placebo. In secondary analyses involving the CGI-S, CGI-C, MADRS, BPRS, GAS, and YMRS responder criteria, subjects taking topiramate did not differ significantly from those taking placebo with the exception of an isolated difference on the BPRS change from baseline score at endpoint in the Completer population. These analyses were completed without adjusting for the inflated error rate that occurs with multiple comparisons, and thus an isolated difference between groups on a single measure is not interpretable. A statistically significant difference ($p=0.008$) in the percent change from baseline in MADRS scores in the Completer population (-21.8% and 13.3% for the placebo and topiramate treatment groups, respectively) was demonstrated in favor of placebo. The positive value of the mean change from baseline for placebo could be attributed to 1 or more high outliers (range -100 to 850).

In the ITT population, adjunctive treatment with topiramate was determined not to be associated with worsening of mania or induction of depression. Similar proportions of subjects in the topiramate and placebo groups experienced a 10% or greater increase in YMRS score from baseline (8.8% versus 8.5%, $p = 1.000$), a 20% or greater increase in YMRS score from baseline (4.4% versus 5.6%, $p = .786$), or a MADRS score of ≥ 18 and an increase from baseline in MADRS score ≥ 4 points on 2 consecutive visits or at the final visit (24.1% versus 20.9%, $p = .563$).

SYNOPSIS (CONTINUED)

SAFETY RESULTS:

Topiramate was generally safe and well tolerated. The incidence of AEs was similar between treatment groups: 120 (83.9%) subjects in the placebo treatment group and 122 subjects (85.3%) in the topiramate treatment group had at least 1 AE. The incidence of AEs related to study drug was somewhat greater in the topiramate group, with 105 (73.4%) in the topiramate treatment group and 89 (62.2%) subjects in the placebo treatment group having AEs considered possibly, probably, or very likely related to study drug.

Ten (7.0%) and 20 (14.0%) subjects in the placebo and topiramate treatment groups, respectively, discontinued early because of AEs. Five (3.5%) subjects in each treatment group had at least 1 serious adverse event (SAE). Only 1 (0.7%) subject in the topiramate treatment group had an SAE considered possibly related to study drug. No subjects died during the study.

The body system with the highest incidence of AEs was psychiatric disorders. The most frequently occurring AE was headache, reported by 37 (25.9%) subjects in the placebo treatment group and 34 (23.8%) subjects in the topiramate treatment group. Other frequently occurring AEs, reported by at least 10% of subjects in either the placebo or the topiramate treatment groups, included paraesthesia (3.5% placebo, 23.1% topiramate), upper respiratory tract infection (11.2% placebo, 17.5% topiramate), diarrhea (8.4% placebo, 16.8% topiramate), somnolence (16.1% placebo, 15.4% topiramate), nausea (11.9% placebo, 15.4% topiramate), anorexia (5.6% placebo, 13.3% topiramate), insomnia (11.2% placebo, 11.9% topiramate), difficulty with memory (7.0% placebo, 11.2% topiramate), and dizziness (10.5% placebo, 10.5% topiramate).

No remarkable trends in laboratory parameters, vital signs, body weight, and physical examinations from baseline to endpoint were identified. Body mass index decreased from baseline to endpoint in the topiramate treatment group, but increased slightly in the placebo treatment group.

DRUG CONCENTRATION RESULTS:

For subjects receiving lithium during the study, serum lithium levels at Day 42 were the same for both treatment groups: 0.7 (SD 0.3) mEq/L and 0.7 (SD 0.2) mEq/L for the placebo and topiramate treatment groups, respectively. For the remaining subjects at Day 84, there was little difference between the treatment groups in serum lithium levels: 0.8 (SD 0.1) mEq/L and 0.7 (SD 0.3) mEq/L for the placebo and topiramate treatment groups, respectively. For subjects receiving valproate during the study, there was little difference in serum valproate levels at Day 42 between the treatment groups: 60.0 (SD 24.2) µg/mL and 58.5 (SD 18.8) µg/mL for the placebo and topiramate treatment groups, respectively. For the remaining subjects at Day 84, there was again little difference between treatment groups in serum valproate levels: 53.4 (SD 28.7) µg/mL and 51.7 (17.8) µg/mL for the placebo and topiramate treatment groups, respectively. Five subjects had levels <2.00 at Day 42, while 6 subjects had levels <2.00 at Day 84. Of these, the data suggests that 4 subjects had potential non-compliance at Day 42 and Day 84, 1 subject had potential non-compliance at Day 42, and 2 subjects had potential non-compliance at Day 84.

CONCLUSION:

Within the context of this 12-week, multicenter, double-blind, randomized, placebo-controlled trial in outpatients with inadequately controlled bipolar I disorder, topiramate (at a mean dose of approximately 250 mg/day), when added on to valproate or lithium, failed to show statistically significant separation from placebo in both the primary outcome (YMRS) and a variety of secondary measures (BPRS, CGI-C, CGI-S, MADRS, GAS, YMRS responder criteria). However, adjunctive topiramate did not worsen manic symptoms or induce depression compared with placebo subjects.

Adjunctive topiramate was relatively well tolerated with over 60% of subjects completing the study and approximately 15% of subjects on topiramate discontinuing due to AEs. The profile of AEs was similar to that seen with other trials of topiramate.

Date of the report: 21 January 2005

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