2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Depakote® ER	**Volume:**	
Name of Active Ingredient: Divalproex sodium (ABT-711)	**Page:**	
Title of Study: The Safety and Efficacy of Divalproex Sodium Extended-Release Tablets in Migraine Prophylaxis: A Double-Blind, Placebo-Controlled Study in Adolescents		
Investigator: Multicenter study		
Study Sites: Thirty-eight (38) sites in the United States randomized subjects.		
Publications: Not applicable.		
Studied Period (Years): Date of first screening procedure: 28 April 2003 Date first subject dosed: 13 June 2003 Date last subject completed dosing: 06 June 2006 Date of last study procedure: 07 June 2006	**Phase of Development:** 3	
Objectives: The objective of this study was to compare the safety and efficacy of Depakote ER to placebo in the prophylactic treatment of migraine headache in adolescents.		
Methodology: Study M02-488 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in the United States. Potential subjects were to be screened at approximately 37 centers in the United States and approximately 300 adolescent subjects (i.e., 75 per treatment group) with a history of migraine were to be randomized. The maximum duration of subject participation in this study was 16 weeks and included a 4-week Baseline Phase and a 12-week double-blind Experimental Phase (2-week dose titration period and a 10-week maintenance dose period). Eligibility for enrollment in the Baseline Phase of this study was determined by results of Screening Visit procedures, which were conducted within two weeks prior to the Baseline Phase, completion of a washout period, and satisfaction of the appropriate inclusion and exclusion criteria. Subjects who received prophylactic antimigraine medication upon screening underwent a washout period equivalent to ≥ 5 half-lives of the respective prophylactic antimigraine medication. Eligible subjects who did not receive prophylactic antimigraine medication or did not receive prophylactic migraine medication for a period of time equivalent to ≥ 5 half lives proceeded directly to the Baseline Phase of the study. In these cases, the Screening and baseline (Day -28) visits could be combined, however, continuing participation in the Baseline Phase was contingent upon acceptable laboratory and electrocardiogram (ECG) results.		

Methodology (Continued):

At the onset of the Baseline Phase, each subject received a Headache and Medication Diary (e.g., number of headaches, functional ability/disability for migraine headaches, associated symptoms, use of symptomatic medication) in which they recorded all headache activity and related medication use during their participation in this study. Subjects were allowed to use particular symptomatic medication. Providing all other entry criteria continued to be met, subjects who completed the Baseline Phase, experienced the protocol specified number of migraine headaches, and demonstrated Headache and Medication Diary compliance were randomized to receive either 250 mg, 500 mg, or 1000 mg Depakote ER or matching placebo in a 1:1:1:1 ratio during the Experimental Phase. The Experimental Phase of this study consisted of two periods, beginning on Study Day 1: a 2-week dose titration period and a 10-week maintenance period.

During the Experimental Phase, efficacy was assessed using data recorded by subjects in the Headache and Medication diary and the PedMIDAS questionnaire that assessed quality-of-life issues related to migraines. The primary efficacy variable was the Experimental Phase reduction from baseline (Baseline Phase) in 4-week migraine headache rate. Safety was also assessed by adverse event (AE) monitoring, laboratory tests, vital signs, and ECGs.

Blood samples for measurement of serum trough concentrations of total valproate were collected on Study Days 29, 57, and 85 (or upon premature discontinuation) at approximately 24 hours (± 3 hours) after the last dose of study medication. An unblinded, qualified designee at the central laboratory who was not involved with clinical procedures of the study was to contact Abbott in the event that a subject who had received active study medication had a serum valproate level ≥ 180 mcg/ml.

Number of Subjects (Planned and Analyzed):

		Depakote ER		
	Placebo	**250 mg**	**500 mg**	**1000 mg**
Planned	75	75	75	75
Randomized	73	83	74	75
Treated	73	82	74	75
Intent-to-Treat	71	81	74	73
Completed	67	74	62	62

Diagnosis and Main Criteria for Inclusion:

Males and females between the ages of 12 and 17 at the time of randomization who had migraine headaches diagnosed according to the International Headache Society (IHS) diagnostic criteria occurring at an average frequency of at least three, but no more than 12, migraine headaches per month during the three months prior to screening, were eligible for the Baseline Phase. Subjects who had at least three, but no more than 12, migraine headaches diagnosed according to the IHS diagnostic criteria during the 4-week Baseline Phase of the study were eligible for the Experimental Phase of the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Depakote ER (divalproex sodium extended-release) 250 mg tablets; oral administration.

Bulk lot numbers: 01-492-AR, 09-533-AR, 25-577-AR

Duration of Treatment: 12 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Placebo, identical in appearance to Depakote ER tablets, oral administration.

Bulk lot numbers: 81-066-4R, 05-091-4R, 25-098-4R

Criteria for Evaluation

Efficacy:

The primary efficacy variable that was used for comparing the prophylactic treatment effects of Depakote ER and placebo was the Experimental Phase reduction from baseline (i.e., the Baseline Phase) in 4-week migraine headache rate.

The principal secondary variables were: the Experimental Phase reduction from baseline in 4-week migraine headache rate for the last four weeks of the Experimental Phase; the Experimental Phase percent reduction from baseline in 4-week migraine headache rates, assessing both actual values and the proportion of subjects with at least a 50% reduction; and Experimental Phase reduction from baseline in the number of migraine headache days per four weeks and for the last four weeks.

Other secondary efficacy variables included the proportion of migraine headache-free subjects or those with at least a 75% reduction in migraine headache rate during the Experimental Phase and Experimental Phase changes from baseline in the following variables: PedMIDAS scores, average functional ability/disability rating for migraine headaches, 4-week rates of migraine headaches with particular associated symptoms, proportion of migraine headaches treated with particular symptomatic medications (e.g., triptans), average amount (e.g., number of doses) of the symptomatic medications used per migraine headache treated with that medication, Experimental Phase reduction from baseline in 4-week headache rate for all headaches, and Experimental Phase reduction from baseline in 4-week headache rate of headaches that subjects self-reported in the diary to be typical of a migraine.

Safety:

Adverse events, physical examinations, routine laboratory data, vital signs, and ECGs were assessed throughout the course of this study.

Statistical Methods

Efficacy: Efficacy analyses were performed on the intent-to-treat-dataset, which included all subjects who received at least one dose of randomized study drug and provided at least one headache evaluation during the Experimental Phase. Treatment differences for the primary efficacy variable were assessed by a one-way ANOVA of rank-transformed data. The 4-week migraine headache rate for all subjects in the intent-to-treat dataset was ranked from smallest to largest, with the smallest observation having rank 1, the second smallest having rank 2, and so on. Average ranks were assigned in cases of ties. The comparisons of interest were each Depakote ER dose compared to placebo; these comparisons were evaluated by contrasts within the ANOVA framework.

The following supportive analyses were conducted on the primary efficacy variable of Experimental Phase reduction from baseline in 4-week migraine headache rate: (1) one-way ANOVA model on the raw data (untransformed) with treatment as the main effect; (2) the van Elteren method of combining Wilcoxon test results from independent strata; and, (3) two-way ANOVA model including factors for center and treatment.

Statistical Methods

Efficacy (Continued):

The proportions of subjects who were migraine headache-free or achieved at least a 50% or 75% reduction in 4-week migraine headache rates were analyzed using the Fisher's exact test.

For primary and principal secondary variables, the analyses described above were also performed separately for each 28-day period of the Experimental Phase. In these analyses, the last observation carry-forward (LOCF) method was employed for subjects who prematurely discontinued before entering a 28-day period.

The methods described above were used to analyze changes from baseline in the average functional ability rating for each migraine headache, the proportion of migraine headaches treated with particular classes of symptomatic medications and the average amount of particular symptomatic medications used per migraine headache treated with that medication. These analyses were restricted to subjects with at least one migraine headache during the Experimental Phase. Analyses of 4-week rates of migraine headaches with particular associated symptoms were restricted to subjects who exhibited the particular symptom with a migraine headache during the Baseline or Experimental Phases; these analyses were performed using a one-way ANOVA.

Safety: Subjects who received at least one dose of randomized study medication were assessed for safety. Adverse events were coded using the MedDRA dictionary.

Treatment-emergent AEs were summarized by system organ class (SOC) and preferred term. Treatment emergent AEs were those that begin or worsen after the first dose of randomized study drug. Each Depakote ER treatment group was compared to the placebo group by Fisher's exact test for the proportions of subjects who reported:

- any adverse event
- at least one AE in each SOC
- a particular treatment-emergent AE

Differences between each Depakote ER dose group and the placebo group in laboratory data were analyzed by one-way ANOVA with treatment as the main effect. The primary analysis was the change from baseline to final evaluation for each variable. Change from baseline to minimum and maximum values during the Experimental Phase for each variable were also analyzed. Laboratory values meeting criteria for potentially clinically significant values were identified. Laboratory values outside the reference range were flagged in the data listings.

Differences between each Depakote ER dose group and the placebo group in vital signs, height and weight for mean change from baseline to the final evaluation were also assessed by one-way ANOVA. Vital sign values meeting criteria for potentially clinically significant values were identified.

Summary/Conclusions

Efficacy Results:

The primary efficacy variable, the Experimental Phase reduction from baseline in 4-week migraine headache rate, did not demonstrate a statistically significant treatment difference between any Depakote ER dose group and the placebo group. Likewise, evidence for efficacy was lacking for any Depakote ER dose group when compared to placebo on other efficacy measures.

There were no statistically significant differences between any Depakote ER dose group and placebo for reductions from baseline in the number of doses of symptomatic medications used per migraine headache or in the proportion of migraine headaches treated with any symptomatic medication class.

In this study of adolescents with migraine headaches, Depakote ER did not differentiate from placebo in the prophylactic treatment of migraine headaches.

Summary/Conclusions

Safety Results:

Three hundred and five (305) subjects were randomly assigned to Depakote ER 250 mg, Depakote ER 500 mg, Depakote ER 1000 mg, or placebo, and 304 took study drug. In subjects assigned to Depakote ER, the mean maximum daily dose was 4.3 mg/kg, 8.5 mg/kg, and 16.9 mg/kg in the 250 mg, 500 mg, and 1000 mg groups, respectively.

There were no statistically significant differences in the proportion of subjects who reported any AE between any Depakote ER dose group and placebo: placebo (58%), Depakote ER 250 mg (65%), Depakote ER 500 mg (72%), and Depakote ER 1000 mg (64%). In addition, there were no statistically significant differences for any Depakote ER dose group compared to placebo for any individual AEs. No subjects died during the study. One subject who received Depakote ER 250 mg and one subject who received Depakote ER 1000 mg experienced an AE that met the regulatory definition of serious. Both SAEs were classified as not related to study drug by the subject's investigator: hypersensitivity (i.e., allergic reaction to an allergy shot) in the Depakote ER 250 mg-treated subject, and pneumonia in the Depakote ER 1000 mg-treated subject (prior to the initiation of study drug). One (1%) placebo subject, two (2%) Depakote ER 250 mg subjects, and seven (9%) Depakote ER 1000 mg subjects prematurely discontinued from the study due to treatment emergent AEs.

In the assessment of laboratory parameters during the study, few statistically significant differences were observed between a Depakote ER dose group and the placebo group based on mean change from baseline to final values for hematology and chemistry values. Treatment differences in laboratory variables were generally small, with the exception of platelets for which a notable (dose-related) decrease was observed. Increases in ammonia levels were observed in both Depakote ER and placebo-treated subjects. In interpreting this finding, it is worthwhile noting that venous instead of the more reliable arterial blood was used to measure ammonia levels, leading to large variability in the results.

Overall, Depakote ER therapy was well tolerated in adolescents aged 12 to 17 years.

Conclusions:

In this study of adolescents with migraine headaches, Depakote ER did not differentiate from placebo in the prophylactic treatment of migraine headaches. Depakote ER therapy was generally well tolerated in adolescents aged 12 to 17 years.