



## 2.0 Synopsis

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Depakote <sup>®</sup> ER	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Divalproex sodium	<b>Page:</b>	
<b>Title of Study:</b> The Safety of Divalproex Sodium Extended Release Tablets in Migraine Prophylaxis: An Open-Label Extension Study in Adolescents		
<b>Investigator:</b> Multicenter; Coordinating Investigator: Ann Pakalnis, MD		
<b>Study Sites:</b> Twenty-six (26) investigative sites enrolled subjects into this study.		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> <b>Date of First Subject Screening Visit:</b> 06 July 2004 <b>Date of First Subject Dosed:</b> 06 July 2004 <b>Date Last Subject Completed Dosing:</b> 20 February 2007 <b>Date of Last Subject Procedure:</b> 21 February 2007	<b>Phase of Development:</b> 3	
<b>Objective:</b> The primary objective of this study was to evaluate the long-term safety of Depakote ER for migraine headache prophylaxis in adolescents.		
<b>Methodology:</b> <p>This was a Phase 3, open-label, multicenter, 12-month extension study of Depakote ER in subjects who either completed or prematurely discontinued due to ineffectiveness from Study M02-488, "The Safety and Efficacy of Divalproex Sodium Extended-Release Tablets in Migraine Prophylaxis: A Double-Blind, Placebo-Controlled Study in Adolescents."</p> <p>In order to be eligible for study enrollment, subjects were to meet all inclusion criteria and none of the exclusion criteria. Up to 300 subjects were expected to participate in the study. Study visits were conducted at Days 1 and 15 and Months 1, 2, 3, 6, 9, and 12. Subjects were instructed to take Depakote ER once daily at approximately the same time each day and to swallow the medication whole without cutting or chewing it.</p> <p>Subjects were given Depakote ER 500 mg once daily for 15 days and then increased to 1000 mg once daily. The investigators could adjust the dose at any time, not to exceed 1000 mg per day and not to be less than 250 mg per day, to maintain a satisfactory clinical response.</p> <p>Safety was assessed by adverse event (AE) collection, laboratory tests, physical examinations, brief neurological examinations, vital signs, and electrocardiograms. At each visit (except Month 12), subjects received a Headache and Medication Diary in which they recorded all headache activity and related medication use during their participation in this study. Four-week migraine headache rate, derived from data recorded in the Headache and Medication Diary, was used to assess efficacy.</p>		



<p><b>Methodology (Continued):</b></p> <p>Blood samples for measurement of serum trough concentrations of total valproate were collected, via venipuncture, at the Month 1, 2, 3, 6, 9, and 12 visits, approximately 24 hours (<math>\pm</math> 3 hours) after study drug dosing.</p>
<p><b>Number of Subjects (Planned and Analyzed): Depakote ER</b></p> <p>Planned - Up to 300; Enrolled - 114; Treated - 112; Completed - 63</p>
<p><b>Diagnosis and Main Criteria for Inclusion:</b></p> <p>Subject was randomized into Study M02-488 and either completed the study or prematurely discontinued due to ineffectiveness.</p>
<p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b></p> <p>Depakote ER (divalproex sodium extended-release) 250 mg tablets: oral administration. <b>Lot numbers:</b> 96561AA21, 15832AA21, 30213AA22</p> <p><b>Duration of Treatment:</b> 12 months</p>
<p><b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b></p> <p>None</p>
<p><b>Criteria for Evaluation:</b></p> <p><b>Efficacy:</b></p> <p>Efficacy was assessed using 4-week migraine headache rate.</p> <p><b>Safety:</b></p> <p>The following safety parameters were summarized: AEs, routine laboratory tests, and vital signs.</p>
<p><b>Statistical Methods</b></p> <p><b>Efficacy:</b></p> <p>Four-week migraine headache rates were summarized over time during the study, both overall and by treatment assignment in Study M02-488. Migraine headaches separated by less than a 48-hour headache-free interval were combined and considered as a single migraine headache. The 4-week migraine headache rates were calculated as the total number of migraine headaches during the particular time interval multiplied by the ratio of 28 days to the actual number of days in that time interval.</p> <p>For a subject whose headache diary was considered unreliable during a particular interval, the subject's 4-week migraine headache rate during that unreliable interval was assumed to be equivalent to the subject's 4-week migraine headache rate during the remaining portion of the period of interest.</p> <p><b>Safety:</b></p> <p>Depakote ER doses and exposure were summarized. The number of subjects with at least six months (i.e., 180 days) and the number of subjects with at least 12 months (i.e., 365 days) of exposure to Depakote ER were reported. For those subjects assigned to Depakote ER in Study M02-488 whose gap between studies was seven days or less, total Depakote ER exposure was the sum of the exposure in the two studies. For all other subjects, total Depakote ER exposure accrued from Study M02-554 only.</p>



### **Safety (Continued):**

Adverse events were coded using MedDRA<sup>®</sup> (Medical Dictionary for Regulatory Activities). Treatment-emergent AEs were summarized by system organ class and preferred term. A treatment-emergent AE was defined as any AE that began or worsened after the first dose of Depakote ER, whether in Study M02-488 or Study M02-554.

The prevalence and incidence of each treatment-emergent AE were summarized over time. The prevalence rate for a given time interval was calculated as the number of subjects with a first reported occurrence or with a repeated occurrence (or continuation) of an AE divided by the number of subjects who entered the time interval. The incidence rate for a given time interval was calculated as the number of subjects with a first reported occurrence of an AE divided by the number of subjects who entered the time interval and who had not experienced the AE during any of the previous intervals.

The mean change from baseline in laboratory and vital sign variables was summarized. For subjects treated with Depakote ER in Study M02-488, baseline was the last evaluation obtained before the first dose of Depakote ER taken in that study. For subjects treated with placebo in Study M02-488, baseline was the last evaluation obtained prior to the first dose of Depakote ER in Study M02-554. Laboratory results and vital sign measurements meeting predefined criteria for potentially clinically significant values were identified.

### **Summary/Conclusions**

#### **Population and Exposure:**

One hundred and twelve (112) subjects were treated with Depakote ER. The study population was 54% female and 70% white. The mean age of subjects was 14.6 years, with 24% between the ages of 12 and 13, 47% between the ages of 14 and 15, and 29% between the ages of 16 and 18 years.

A total of 83 subjects (74%) had at least six months (i.e., 180 days) of exposure to Depakote ER, and 53 subjects (47%) had at least 12 months (i.e., 365 days) of exposure to Depakote ER. The overall mean duration of Depakote ER exposure was 300 days for the cumulative dataset (i.e., the sum of the exposure in Studies M02-488 and M02-554 for those subjects assigned to Depakote ER in Study M02-488 whose gap between studies was seven days or less, and total Depakote ER exposure accrued from Study M02-554 only for all other subjects).

The mean maximum Depakote ER daily dose for the entire exposure period was 926 mg (15.4 mg/kg), and the mean modal Depakote ER daily dose was 741 mg (12.5 mg/kg) for the cumulative dataset.

#### **Efficacy Results:**

In this open-label study of adolescents with migraine headache, the median (mean) 4-week migraine headache rate was 1.1 (1.4) over the 12-month study and 1.0 (1.2) for the final 4-week period. The 4-week median and mean migraine headache rates improved between the first (2.0, 2.1) and the fourth (1.0, 1.4) 28-day period, with the effect persisting for the entire 12-month duration of the study. The most commonly used symptomatic medications for the treatment of migraine headaches were NSAIDs and acetaminophen, which were used for an average of 33.4% and 35.3% of migraine headaches, respectively.

#### **Safety Results:**

The most commonly experienced treatment-emergent AEs in the cumulative dataset were weight increased (15%), nausea (14%), somnolence (12%), upper respiratory tract infection (11%), ammonia increased (8%), and sinusitis (8%).



---

**Safety Results (Continued):**

No subjects died. Five study subjects (4%) had one or more SAEs. One subject had an SAE of hyperammonaemia that was classified as possibly related to study drug and four subjects had SAEs of schizophreniform disorder; peptic ulcer; depressive symptom, intentional self-injury, skin laceration, suicidal ideation; and abortion induced that were classified as either probably not or not related to study drug.

Fifteen subjects prematurely discontinued study drug due to an AE. The AEs that led to premature discontinuation for two or more subjects included weight gain (n=3), somnolence (n=2), and nausea (n=2).

In general, laboratory results in this study were consistent with those observed in Study M02-488.

In this study, increases in ammonia levels were observed in some subjects treated with Depakote ER. The mean increase of ammonia from baseline to final evaluation was 19.2 mcmol/L (mean baseline value was 39.3 mcmol/L). Twenty-six (26) subjects had at least one very high ammonia level ( $\geq 90$  mcmol/L) during the study, and in all but six, these increases were transitory. With one exception, none of these subjects were symptomatic. In interpreting this finding, it is worthwhile noting that venous instead of the more reliable arterial blood was used to measure ammonia levels, contributing to large variability in the results. These data appear to be consistent with reports of hyperammonaemia associated with valproate therapy that are described in the Depakote ER label.

Mean changes from baseline to final values for body weight and height were 4.1 kg and 2.5 cm, respectively. Mean body mass index (BMI) increased 0.8 kg/m<sup>2</sup>.

Overall, Depakote ER therapy was generally well tolerated by children and adolescents aged 12 to 18 years.

**Conclusions:**

In this 12-month, open-label safety study of children and adolescents with a diagnosis of migraine headache, Depakote ER was generally well tolerated. Migraine headache rates decreased early in the study, with the effect persisting for the duration of the trial.

---