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	**Page:**	

Title of Study: An Open-Label Study to Evaluate the Safety of Depakote® ER in the Treatment of Mania Associated with Bipolar I Disorder in Children and Adolescents

Investigator: Multicenter; Coordinating Investigator: Melissa DelBello, MD

Study Sites: Thirty-two (32) investigative sites enrolled subjects into this study.

Publications: None

Studied Period (Years):	**Phase of Development:** 3
Date of First Screening Period: 21 February 2005	
Date First Subject Dosed: 25 February 2005	
Date Last Subject Completed Dosing: 26 October 2006	
Date of Last Subject Procedure: 27 October 2006	

Objectives: The objective of this study was to evaluate the long-term safety of Depakote ER in the treatment of bipolar I disorder, manic or mixed episode, in children and adolescents.

Methodology: This was a Phase 3, six-month, open-label, multicenter, outpatient study to evaluate the long-term safety of Depakote ER in the treatment of bipolar I disorder, manic or mixed episode, in children and adolescents ages 10-17 years.

Subjects with a current clinical diagnosis of bipolar I disorder, manic or mixed episode, according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR) criteria using the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) were to be enrolled in the study at approximately 30-40 U.S. study sites. Enough subjects were to be enrolled (approximately 200-250) to ensure that approximately 75 subjects would complete the six-months of treatment. Subjects were outpatients in a manic or mixed episode with a Young Mania Rating Scale (YMRS) score of greater than or equal to 16 at Screening and at Day 1. The duration of the study was approximately seven months, with a 1-14 day Screening Period; a six-month Treatment Period with required study visits at Day 1, Months 1, 2, 3 and 6; and an optional taper period, not exceeding two weeks, added at the investigator's discretion. Interim visits were scheduled at the discretion of the investigator. The Screening Period may have exceeded two weeks if required to allow adequate time for the washout of prohibited medications (at least five elimination half-lives) or the repeat of laboratory tests.

Methodology (Continued):

Depakote ER was to be initiated once daily at a target dose of 15 mg/kg/day, not to exceed a total of 750 mg/day on Day 1. The dose could be increased as needed at the discretion of the investigator to achieve an optimal clinical response with a maximum allowable dose of 35 mg/kg/day. Subjects were instructed to take Depakote ER once daily at approximately the same time each day.

Safety was assessed by adverse event (AE) collection, both spontaneous reports and responses elicited by the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, laboratory tests, vital signs, and electrocardiograms (ECGs). In addition, the Wechsler Abbreviated Scale of Intelligence (WASI) and the Behavior Assessment System for Children (BASC) assessed neurocognitive and behavioral status, respectively.

Efficacy was assessed by using the YMRS, the Children's Global Assessment Scale (C-GAS), the Clinical Global Impression Scale (CGI) Part 1 (Severity) and the Children's Depression Rating Scale-Revised (CDRS-R). In addition, the Caregiver Strain Questionnaire (CGSQ) was utilized.

Blood samples for measurement of serum trough concentrations of total valproate were to be collected at the visits for Months 1, 2, 3 and Month 6, approximately 24 hours ($\pm$ 3 hours) after the last dose of study medication. Additional blood samples for measurement of serum trough concentrations of total valproate could be obtained at the discretion of the investigator.

Number of Subjects (Planned and Analyzed): Depakote ER:

Planned -   200-250

Enrolled -   227

Treated -   226

Completed -   109

Diagnosis and Main Criteria for Inclusion:

Male and female outpatients between the ages of 10 and 17 at the time enrollment, who had a current psychiatric diagnosis of bipolar I disorder, manic or mixed episode, based on DSM-IV-TR criteria using the K-SADS-PL with a YMRS score $\geq$ 16 during Screening and at Day 1.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:
Depakote ER (divalproex sodium extended-release) 250 mg and 500 mg tablets: oral administration.

Lot Numbers:

250 mg - 22-801-S2 and 05-001184
500 mg - 22-802-S2 and 05-001185

Duration of Treatment: 6 months

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

None

Criteria for Evaluation

Efficacy: Efficacy was assessed using the YMRS, the C-GAS, the CGI Part 1 (Severity), the CDRS-R, and the CGSQ.

Safety: The following safety parameters were summarized: AEs (both spontaneous reports and responses elicited by the UKU Side Effect Rating Scale), routine laboratory tests, vital signs, BASC, and WASI.

Statistical Methods

Efficacy: Rating scale scores for a subject were obtained for YMRS, CGI-Severity, C-GAS, CDRS-R, and CGSQ. Baseline for efficacy measures was the last assessment prior to the first dose of Depakote ER.

Mean change from baseline to the final evaluation and to each evaluation for the YMRS, CGI-Severity, C-GAS, CDRS-R, and CGSQ were summarized. The percentage of subjects with ≥ 50% improvement from baseline to the final evaluation and to each evaluation and with a YMRS score < 12 at the final evaluation and at each evaluation was also summarized.

Safety: Depakote ER doses and exposure were summarized. The number of subjects with six months (i.e., 180 days) or more exposure to Depakote ER was reported.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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.

The prevalence and incidence of each treatment-emergent AE was summarized over time. The prevalence rate for a given time interval was calculated as the sum of 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 sum of 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 values and vital signs variables was summarized.

Baseline was the last evaluation obtained prior to the first dose of Depakote ER. Laboratory values and vital signs values meeting predefined criteria for potentially clinically significant values were identified.

For the UKU Side Effect Rating Scale, the percentage of subjects with each individual side effect and the percentage of subjects with at least one of the individual side effects were summarized at each scheduled time point.

For the WASI and BASC, mean scores at baseline and at the final visit, as well as the mean change from baseline to the final visit, were summarized.

Summary/Conclusions

Efficacy Results: In this open-label study of children and adolescents with a diagnosis of bipolar disorder, mean improvements as assessed by each efficacy measurement were observed following one month of Depakote ER treatment, and continued to improve over the six-month study. Based on the LOCF analysis at Month 6, there was a 12.4 decrease in YMRS Total score from a baseline score of 25.0, with 56% of subjects having at least 50% improvement in their YMRS Total score.

Safety Results: Two hundred twenty-six (226) subjects were treated with Depakote ER. Ninety-nine subjects (44%) had at least six months (i.e., 180 days) exposure to Depakote ER. The overall mean duration of Depakote ER exposure was 124.4 days.

The mean maximum Depakote ER daily dose was 22.1 mg/kg (1272 mg), and the mean modal Depakote ER daily dose was 19.5 mg/kg (1131 mg).

The most commonly experienced ($\geq$ 5%) treatment-emergent AEs were increased weight (16%), nausea (9%), increased appetite (8%), fatigue (6%), insomnia (6%), tremor (6%), upper abdominal pain (5%), somnolence (5%), and nasopharyngitis (5%).

No subjects died. Seven subjects (3%) experienced treatment-emergent SAEs during the study. One SAE of aggression was classified by the investigator as possibly related to study drug. All other SAEs were classified as probably not or not related to study drug. Twenty-eight (28) subjects (12%) prematurely discontinued study drug due to an AE. Increased weight (7 subjects, 3%) was the only AE that resulted in premature discontinuation of study drug for more than two subjects.

For laboratory parameters, mean changes from baseline to the final value were generally consistent with results seen in previous studies of Depakote and Depakote ER in both adults and children.

In this study, increases in ammonia levels were observed in subjects treated with Depakote ER. 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. The mean increase of ammonia from baseline to final evaluation was 11.71 mcmol/L (mean baseline value was 39.16 mcmol/L). Twenty-seven subjects had a very high ammonia level(s) ($\geq$ 90 mcmol/L). No subjects discontinued study drug prematurely due to a high ammonia level. These data appear to be consistent with reports of hyperammonemia 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 +2.95 kg and +1.74 cm. BMI increased 0.63 kg/m^2.

No increase of neurologic, movement-related side effects, as assessed using the UKU, was observed during six-month treatment with Depakote ER. Parents' ratings on the BASC indicated small improvements in their child's adaptive and problem behaviors from baseline to the final visit. Small improvements from baseline to the final visit were observed for all sub-test T-scores and IQ scores of the WASI.

Overall, Depakote ER therapy over a period of six months was generally well tolerated by children and adolescents aged 10 to 17 years.

Conclusions: This was a Phase 3, six-month, open-label, multicenter, outpatient study conducted in the U.S. to evaluate the long-term safety and efficacy of Depakote ER in the treatment of bipolar I disorder, manic or mixed episode, in children and adolescents ages 10-17 years. Two-hundred twenty-six (226) subjects were treated with Depakote ER. Ninety-nine subjects (44%) had at least six months (i.e., 180 days) exposure to Depakote ER.

Mean improvements, as assessed by each efficacy measurement, were observed following one month of Depakote ER treatment, and continued to improve over the six-month study. Based on the LOCF analysis at Month 6, there was a 12.4 decrease in YMRS Total score from a baseline score of 25.0, with 56% of subjects having at least 50% improvement in their YMRS Total score.

The most commonly experienced ($\geq 5\%$) treatment-emergent AEs were increased weight (16%), nausea (9%), increased appetite (8%), fatigue (6%), insomnia (6%), tremor (6%), upper abdominal pain (5%), somnolence (5%), and nasopharyngitis (5%).

No subjects died. Seven subjects (3%) experienced treatment-emergent SAEs during the study. One SAE of aggression was classified by the investigator as possibly related to study drug. All other SAEs were classified as probably not or not related to study drug. Twenty-eight (28) subjects (12%) prematurely discontinued study drug due to an AE. Increased weight (7 subjects, 3%) was the only AE that resulted in premature discontinuation of study drug for more than two subjects.

The safety profile observed for Depakote ER in this study was similar to that observed in other pediatric studies of bipolar disorder, as well as in previous studies of adults with bipolar disorder. Increases in ammonia levels were observed among subjects treated with Depakote ER in this study and in previous pediatric studies of bipolar disorder. Ammonia levels were not measured in previous studies of Depakote or Depakote ER in adults. 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. These data appear to be consistent with reports of hyperammonemia associated with valproate therapy that are described in the Depakote ER label.

The UKU results show that Depakote ER was not associated with an increase in movement-related side effects over the six-month treatment period. Parents' ratings on the BASC indicated small improvements in their child's adaptive and problem behaviors from baseline to the final visit. Small improvements from baseline to the final visit were observed for all sub-test T-scores and IQ scores of the WASI.

In summary, in this six-month, open-label safety study of children and adolescents with a diagnosis of bipolar disorder, manic or mixed episode, Depakote ER was generally well-tolerated. Mean improvements in YMRS and other efficacy measures were observed.