



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: A Double-Blind, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Depakote ER for the Treatment of Mania Associated with Bipolar Disorder in Children and Adolescents		
Investigators: Multicenter; Coordinating Investigator: Scott Segal, M.D.		
Study Sites: Twenty-four (24) investigative sites randomized subjects in this study.		
Publications: None		
Studied Period (Years): Date of first screening procedure: 01 April 2003 Date first subject dosed: 08 April 2003 Date last subject completed dosing: 20 November 2005 Date of last study procedure: 22 November 2005	Phase of Development: 3	
Objective: The objective of this study was to compare the safety and efficacy of Depakote ER to placebo in the treatment of bipolar I disorder, manic or mixed episode, in children and adolescents.		
Methodology: <p>This was a Phase 3, randomized, placebo-controlled, double-blind, parallel-group, multicenter study designed to evaluate the safety and efficacy of Depakote ER compared to placebo in the treatment of bipolar I disorder, manic or mixed episode, in children and adolescents ages 10-17 years. In order to be randomized in the study, subjects were required to meet all inclusion criteria and none of the exclusion criteria.</p> <p>Approximately 150 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 Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) were to be enrolled in the study at approximately 20 study sites. Subjects were outpatients in a manic or mixed episode with a YMRS score of greater than or equal to 20 at screening and baseline. Subjects were randomized in a 1:1 ratio to receive active study medication (250 mg and/or 500 mg tablets of Depakote ER) or matching placebo tablets.</p> <p>The initial dose of study medication was targeted at 15 mg/kg/day (not to exceed a total of 750 mg/day). During the study, the dosage was to be increased in 250 mg increments at 1-3 day intervals at the discretion of the investigator to achieve maximum clinical effect and/or a serum valproate level within the range of 80-125 mcg/mL, with a maximum allowable dose of 35 mg/kg/day. In addition, all subjects and their families (or legal representatives) were to receive psychoeducation relative to their diagnosis during their participation in the study.</p>		



Methodology (Continued):

The duration of the study was approximately six weeks, including a screening period lasting 3-14 days, a 4-week treatment period, and an optional one-week taper period. Note: the screening period could exceed two weeks if required to allow adequate time (at least five elimination half-lives) for the washout of prohibited medications.

During the treatment period, efficacy was assessed using the Young Mania Rating Scale (YMRS), the Children's Global Assessment Scale (C-GAS), the Clinical Global Impression Scale (CGI) Parts I and II (Severity and Improvement), the Children's Depression Rating Scale-Revised (CDRS-R), and the Overt Aggression Scale-Modified (OAS-M). In addition, the ADHD Rating Scale-IV: Home Version and the Caregiver Strain Questionnaire (CGSQ) were utilized. The primary efficacy variable was the change in YMRS score from baseline (last observation prior to taking randomized study medication) to final evaluation (last observation carried forward at Day 28). Safety was also assessed by adverse event (AE) collection, laboratory tests, vital signs, and ECGs.

Blood samples for measurement of serum trough concentrations of valproate were collected on Study Days 7, 14, and 28, at approximately 24 hours (± 3 hours) after the last dose of study medication. Additional trough samples were to be obtained at approximately 24 hours (± 3 hours) after the last dose of study medication on any day that it became necessary to prematurely discontinue a subject from further participation in the study.

During the course of the study, an independent Data Monitoring Committee (DMC) reviewed and interpreted safety data from the study on a regular basis. After each safety review, the DMC made recommendations to Abbott regarding continuing, modifying, or terminating the trial.

Number of Subjects (Planned and Analyzed):

	Placebo	Depakote ER
Planned	75	75
Randomized	74	76
Intent-to-Treat	70	74
Completed	60	56

Diagnosis and Main Criteria for Inclusion: Males and females between the ages of 10 and 17 at the time of randomization, who had a current psychiatric diagnosis of bipolar I disorder, manic or mixed episode, based on the WASH-U-KSADS interview and DSM-IV-TR criteria and an outpatient in a current manic or mixed episode with an YMRS score ≥ 20 during screening/washout and at the time of randomization.

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 - 0672 / 01-492-AR, 1002 / 09-533-AR

500 mg - 0830 / 05-090-AR, 1002 / 05-090-4R

Duration of Treatment: 28 days



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

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

Lot Numbers:

250 mg placebo - 0672 / 81-066-4R, 1002 / 05-091-4R 500 mg placebo - 0830 / 05-092-4R, 1002 / 05-092-4R

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change from baseline to the final evaluation for the YMRS score for the intent-to-treat dataset. The final evaluation was the last observation carried forward (LOCF) at 28 days. The intent-to-treat dataset included all randomized subjects who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one follow-up visit.

The secondary efficacy variables were the C-GAS, the CGI Parts I and II (Severity and Improvement), the CDRS-R, the OAS-M, the CGSQ, and the ADHD Rating Scale-IV: Home Version. The percent of subjects with > 50% improvement from baseline to final evaluation on YMRS score and percent of subjects with YMRS score < 12 at the final evaluation were also assessed.

Safety: The following safety parameters were summarized and analyzed for significance between treatment differences in changes from baseline (where appropriate): AEs, routine laboratory parameters, and vital signs.

Statistical Methods:

Efficacy: Treatment group differences for the change from baseline to final evaluation for YMRS (*i.e.*, primary efficacy variable) were evaluated by a two-way ANOVA with factors for treatment and study center. Treatment differences in the percent of subjects with > 50% improvement from baseline to final evaluation on YMRS score and percent of subjects with YMRS score < 12 at final evaluation were assessed by a Cochran-Mantel- Haenszel test with study centers as strata.

Treatment differences in the mean change from baseline to the final evaluation for the C-GAS, CGI, CDRS-R, OAS-M, ADHD Rating Scale IV: Home Version and CGSQ scores were assessed by a two-way ANOVA as described in the previous section. Treatment differences for the CGI improvement score were evaluated by the CMH test for equal row means with study centers as strata.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs were tabulated by system organ class and MedDRA term. Comparisons between treatment groups were made using Fisher's exact test for the proportion of subjects with a particular treatment-emergent AE.

Treatment group differences in laboratory data were analyzed using one-way ANOVA with treatment as the main effect. The primary analysis was on the change from baseline to the final evaluation for each variable. In addition, laboratory values were categorized as low, normal, or high based on the normal range for individual laboratories. Values that were low or high were flagged in the data listings. Laboratory values meeting predefined criteria for potentially clinically significant values were identified.

Treatment group differences in vital signs data (mean change from baseline to the final evaluation) were assessed by one-way ANOVA. Vital signs values meeting the predefined criteria for potentially clinically significant values were identified.



Summary/Conclusions:

Efficacy Results: The primary efficacy variable, mean change from baseline to final evaluation in YMRS total score, did not demonstrate a statistically significant treatment difference between the Depakote ER group and the placebo group. Likewise, Depakote ER generally did not show evidence of efficacy when compared to placebo on other efficacy measures.

In this study of children and adolescents with a diagnosis of Bipolar Disorder, Depakote ER did not produce a statistically significant clinical benefit when compared to placebo.

Safety Results: Among Depakote ER-treated subjects, the mean maximum Depakote ER daily dose was 1457 mg and the mean modal daily dose was 1286 mg.

The overall incidence and severity of AEs observed during this study was not statistically significant between subjects that received Depakote ER (67%) and those that received placebo (59%). In addition, there were no statistically significant treatment differences for individual AEs. Overall, gastrointestinal disorders were more commonly reported in the Depakote ER group (33%) than in the placebo group (15%), $p = 0.013$.

Serious adverse events (SAE) were observed in two subjects receiving Depakote ER and one subject receiving placebo. In two of these subjects, the SAEs were classified as possibly related to study drug by the investigator: suicidal ideation in a placebo subject, and increased ammonia/disorientation in a Depakote ER subject. Three placebo subjects and four Depakote ER subjects prematurely discontinued from the study due to treatment-emergent AEs.

In the assessment of laboratory parameters during the study, a statistically significant decrease from baseline was observed in platelet count, white blood cells, total protein, albumin, total bilirubin, AST/SGOT, ALT/SGPT, calcium and cholesterol. A statistically significant increase from baseline was observed in monocytes, BUN, potassium and ammonia in the Depakote ER group compared to the placebo group. In this study, increases in ammonia levels were observed in subjects randomized to both Depakote ER and to placebo. 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. Nevertheless, a higher increase in ammonia levels was observed in the Depakote ER group (18.63 ± 25.72 mcmmol/L) compared to the placebo group (2.12 ± 22.21 mcmmol/L). Potentially clinically significant ammonia levels (≥ 90 mcmmol/L) were reported in two subjects receiving placebo and three subjects receiving Depakote ER. One subject with a high ammonia level in the Depakote ER group was symptomatic (disoriented) requiring hospitalization. These data appear to be consistent with reports of hyperammonemia associated with valproate therapy, which are described in the Depakote label.

Overall, Depakote ER therapy was well tolerated in children and adolescents aged 10 to 17 years. The increased incidence of gastrointestinal events reported during the study was consistent with the Depakote ER label.



Conclusions: This was a Phase 3, randomized, placebo-controlled, double-blind, parallel-group, multicenter study designed to evaluate the safety and efficacy of Depakote ER compared to placebo in the treatment of bipolar I disorder, manic or mixed episode in children and adolescents ages 10-17 years. The primary efficacy variable, the change from baseline to the final evaluation (*i.e.*, LOCF at 28 days) for YMRS, did not demonstrate a statistically significant treatment difference. Likewise, Depakote ER therapy did not result in statistically significant clinical benefits in psychopathology, as measured by secondary endpoints. No factors have been identified that could explain the lack of differentiation between Depakote ER and placebo.

In this study of children and adolescents with a diagnosis of Bipolar Disorder, Depakote ER did not produce a statistically significant clinical benefit when compared to placebo.

Adverse events were generally mild or moderate in severity. One placebo subject and two Depakote ER subjects experienced at least one SAE. Three placebo subjects and four Depakote ER subjects prematurely discontinued study drug due to treatment-emergent AEs.

Safety monitoring included the assessment of changes in hematology, blood chemistry, and vital signs values. The safety profile observed for Depakote ER in this study was similar to that observed in previous studies of adults with bipolar disorder, with one exception. In this study, increases in ammonia levels were observed in subjects randomized to both Depakote and to placebo. 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. Nevertheless, a higher increase in ammonia levels was observed in the Depakote ER group (18.63 ± 25.72 mcmmol/L) compared to the placebo group (2.12 ± 22.21 mcmmol/L). Potentially clinically significant ammonia levels (≥ 90 mcmmol/L) were reported in two subjects receiving placebo and three subjects receiving Depakote ER. One subject with a high ammonia level in the Depakote ER group was symptomatic (disoriented) requiring hospitalization. Although ammonia levels have not previously been assessed in Abbott-sponsored Depakote or Depakote ER studies, these data appear to be consistent with reports of hyperammonemia associated with valproate therapy, which are described in the Depakote ER label.

In summary, in this study of children and adolescents with a diagnosis of Bipolar Disorder, manic or mixed episode, Depakote ER did not produce a statistically significant clinical benefit when compared to placebo. Overall, Depakote ER was well tolerated.
