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 Long-Term Study to Evaluate the Safety of Depakote Extended Release Tablets in the Treatment of Mania Associated with Bipolar Disorder in Children and Adolescents	
Investigator: Multicenter; Coordinating Investigator: Scott Segal, MD	
Study Sites: Seventeen (17) investigative sites enrolled subjects into this study.	
Publications: None	
Studied Period (Years): First Subject First Visit: 05 July 2004 Last Subject Last Visit: 19 May 2006	**Phase of Development:** 3

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

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

This study was conducted as a six-month extension study to Study M01-342, "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."

Only subjects who either completed Study M01-342 or prematurely discontinued due to ineffectiveness were eligible to participate in this study. Subjects must have met all inclusion criteria and none of the exclusion criteria to be enrolled into the study. Up to 150 subjects were to be enrolled in the study at approximately 20 study sites. The duration of the study was approximately six months, with study visits at Screening, if applicable, Day 1, and Months 1, 2, 3, and 6. Subjects were instructed to take Depakote ER once daily at approximately the same time each day.

For subjects transitioning from Study M01-342 into Study M02-555 with no interruption in study medication, the blinded study medication from Study M01-342 was reduced by approximately 50% on Day 1 of Study M02-555. After 3-4 days, the dose of blinded study medication from Study M01-342 could be reduced again at the investigator's discretion, and was to be stopped altogether by the end of the first week of this study. M02-555 study medication (Depakote ER) was initiated once daily at a target dose of 15 mg/kg/day, not to exceed a total of 750 mg/day, on Day 1 and should have approximately equaled the dose reduction of blinded study medication. Subsequently, the dose could be increased as needed at the discretion of the investigator to achieve an optimal clinical response and/or a serum valproate level within the range of 80-125 mcg/mL, with a maximum allowable dose of 35 mg/kg/day.

Methodology (Continued):

For subjects transitioning from Study M01-342 into Study M02-555 who had an interruption in study medication and were not currently taking valproate, M02-555 study medication (Depakote ER) was 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 and/or a serum valproate level within the range of 80-125 mcg/mL, with a maximum allowable dose of 35 mg/kg/day.

For subjects transitioning from Study M01-342 into Study M02-555 who had an interruption in study medication and were currently taking valproate, the investigator had the subject continue on an equivalent dose using M02-555 study medication (Depakote ER) in order to maintain a satisfactory clinical response. The dose could be adjusted as needed at the discretion of the investigator to achieve an optimal clinical response and/or a serum valproate level within the range of 80-125 mcg/mL, with a maximum allowable dose of 35 mg/kg/day.

Safety was assessed by adverse event (AE) collection, laboratory tests, vital signs, and electrocardiograms (ECGs). Efficacy was assessed using the Young Mania Rating Scale (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 collected at the Month 1 and Month 6 visits, approximately 24 hours (± 3 hours) after the last dose of study medication. Additional blood samples for measurement of serum trough concentrations of total valproate were obtained at the discretion of the investigator.

Number of Subjects (Planned and Analyzed): Depakote ER

Planned - Up to 150

Enrolled - 66

Completed - 26

Diagnosis and Main Criteria for Inclusion:

Subject was randomized into Study M01-342 and either completed the study or prematurely discontinued due to ineffectiveness.

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 - 19-674-S2 / 13-134-S2

500 mg – 13-135-S2 / 05-000596

Duration of Treatment: Six (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, routine laboratory tests, and vital signs.

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 in Study M02-555.

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 overall and by treatment group assignment in Study M01-342. The percentage of subjects with > 50% improvement from baseline to the final evaluation and to each evaluation and with YMRS score < 12 at the final evaluation and at each evaluation was also summarized overall and by treatment group assignment in Study M01-342.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs were summarized by body system and MedDRA term.

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 and vital signs variables was summarized. For subjects treated with Depakote ER in Study M01-342, baseline was the last evaluation obtained before the first dose of Depakote ER in that study. For subjects treated with placebo in Study M01-342, baseline was the last evaluation obtained prior to the first dose of Depakote ER in Study M02-555. Laboratory values and vital signs values meeting predefined criteria for potentially clinically significant values were identified.

Summary/Conclusions

Efficacy Results: In this open-label study of children and adolescents with a diagnosis of bipolar disorder, only small mean improvements in efficacy assessments were observed over the six months of the study.

Safety Results: Sixty-six (66) subjects were treated with Depakote ER. Twenty subjects (30%) had at least six months (i.e., 180 days) exposure to Depakote ER. The overall mean duration of Depakote ER exposure was 116.8 days for the cumulative dataset (i.e., the sum of the exposure in M01-342 and M02-555 for those subjects assigned to Depakote ER in Study M01-342 whose gap between studies was seven days or less, and total Depakote ER exposure accrued from Study M02-555 only for all other subjects).

The mean maximum Depakote ER daily dose for the entire exposure period was 28.3 mg/kg (1523 mg) and the mean modal Depakote ER daily dose was 25.7 mg/kg (1383 mg) for the cumulative dataset.

Safety Results (Continued):

The most commonly experienced (≥ 5%) treatment-emergent AEs in the cumulative dataset were headache (17%), vomiting (9%), upper abdominal pain (6%), dyspepsia (6%), nausea (6%), pharyngolaryngeal pain (6%), streptococcal pharyngitis (5%), upper respiratory tract infection (5%), and increased weight (5%).

The median serum valproate concentrations at the Month 1, Month 6, and final visits were 78.0 mcg/mL, 83.5 mcg/mL, and 78.0 mcg/mL, respectively.

No subjects died. One subject had an SAE of hallucination that started nine days after the last dose of study drug. Five subjects prematurely discontinued study drug due to a treatment-emergent AE, including alopecia (n=2), obesity (n=1), decreased platelet count (n=1), and increased ammonia (n=1).

For laboratory parameters that demonstrated a statistically significant treatment difference in the preceding double-blind, randomized study (M01-342), mean changes from baseline to the final visit in this extension study were generally of the same order of magnitude and in the same direction of change as those observed in the Depakote ER treatment group of Study M01-342.

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 18.63 mcmol/L (mean baseline value was 43.05 mcmol/L). Eleven subjects had a very high ammonia level(s) (≥ 90 mcmol/L). One subject 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 BMI were 3.1 kg and 0.6 kg/m^2, respectively. Mean height increased 2.4 cm.

Overall, Depakote ER therapy was well tolerated by children and adolescents aged 10 to 17 years.

Conclusions:

This was a Phase 3, open-label, multicenter, long-term, outpatient study, which was conducted to evaluate the long-term safety and efficacy of Depakote ER in the treatment of bipolar I disorder, manic or mixed, in children and adolescents ages 10-17 years. This study was conducted as a six-month extension study to double-blind Study M01-342 in which a treatment effect vs. placebo was not observed during the 28-day study for the primary efficacy variable of mean change from baseline to final evaluation for the YMRS. In the current study, only small mean improvements in efficacy assessments were observed over the six months of treatment with Depakote ER.

The most commonly experienced (≥ 5%) treatment-emergent AEs in the cumulative dataset were headache (17%), vomiting (9%), upper abdominal pain (6%), dyspepsia (6%), nausea (6%), pharyngolaryngeal pain (6%), streptococcal pharyngitis (5%), upper respiratory tract infection (5%), and increased weight (5%).

No subjects died. One subject had an SAE of hallucination that started nine days after the last dose of study drug. Five subjects prematurely discontinued their participation in the study due to a treatment-emergent AE, including alopecia (n=2), obesity (n=1), decreased platelet count (n=1), and ammonia increased (n=1).

Conclusion (Continued):

Safety monitoring included the assessments of changes in hematology, chemistry, and vital signs values. The safety profile observed for Depakote ER in this study was similar to that observed in Study M01-342, as well as in the previous studies of adults with bipolar disorder, with one exception. In both Study M01-342 and in this study, increases in ammonia levels were observed among 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 18.63 mcmol/L (mean baseline value was 43.05 mcmol/L). Eleven subjects had a very high ammonia level(s) (≥ 90 mcmol/L). None of the subjects that had very high ammonia levels was symptomatic. One subject 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.

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. Only small mean improvements in efficacy assessments were observed.