CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-168

Statistical Review(s)

Statistical Review and Evaluation

NDA #:	21-168
Sponsor:	Abbott Laboratory
Drug:	Depakote ER
Indication:	Migraine
Reviewer:	Kallappa M. Koti
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1. INTRODUCTION

Divalproex sodium, which has been commercially available in the United States since 1983, is a stable coordination complex comprised of sodium valproate and valproic acid in a 1:1 molar ratio. Depakote delayed-release (DR) tablets are an enteric-coated form of divalproex sodium. Depakote DR is registered for use in the treatment of complex partial seizures and manic episodes associated with bipolar disorder. It is also used for prophylactic treatment of migraine headache.

Divalproex sodium extended-release (Depakote ER) tablets, an extended-release formulation of Depakote, was developed to enable a reduction in dosing frequency for the treatment of patients with migraine headache. The objective of Study M98-845 was to evaluate the efficacy and safety of Depakote ER tablets as compared to placebo in the prophylactic monotherapy treatment of subjects with migraine headache.

2. OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

Study M98-845 was a Phase III, double-blind, randomized, multicenter, placebo-controlled, parallel-group study. It was a 17-week study consisted of three phases: a 4-week Baseline Phase, a 12-week, double-blind, Experimental Phase, and a 1-week, double-blind, Termination Phase. Subjects who were compliant in maintaining a headache diary and experienced at least two migraine headache attacks (separated by a headache-free interval of at least 24 hours) during the 4-week Baseline Phase were eligible for randomization into the Experimental Phase.

The eligibility of subjects for inclusion into study, as well as subsequent enrollment into the Baseline Phase, was to be assessed at the Screening Visit. Eligible subjects who were receiving or who had recently received prophylactic anti-migraine medications were to complete a washout period equivalent to at least five half-lives of these medications. Upon successful completion of the washout period, eligible subjects were to return to the office within 2 weeks of the Screening Visit to begin the 4-week Baseline Phase. The Baseline Phase was to begin with Visit 1 (Day –28) and end at Visit 2 (Day 1). At Visit 2, subjects who satisfied the randomization criteria were to be randomized in a 1:1 ratio at each center to receive either Depakote ER tablets or matching placebo and enter the 12-week Experimental Phase.

The Experimental Phase was to begin on Day 1 and consist of a 2-week dose titration / adjustment period followed by a 10-week fixed-dose treatment period. The physician was to maintain subject contact through telephone at Visit 3 (Day 8) and Visit 4 (Day 15) and office visits at Visits 5 (day 29), 6 (Day 57) and 7 (Day 85). If a subject experienced intolerance to study drug after Visit 4 (Day 15) and required a permanent dose reduction, the subject was to be discontinued from the study. A schematic of the study procedures is presented in Table 2.1 below.

Table 2.1: **Study Procedures**

Procedures	**Screening Visit**	**Baseline Phase**		**Experimental Phase**				
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Day	- 42	-28	1	8	15	29	57	85
Informed consent	X							
Physical Examination	X							X
Headache history	X							
Headache Assessment Symptomatic Med. use			X	X	X	X	X	X
Dispense Headache Diary		X	X			X	X	X
Prior & Concurrent Medication Assessment	X	X	X	X	X	X	X	X
Dispense Study Drug			X			X	X	X
Study Drug Accountability						X	X	X

It was estimated approximately 240 subjects (male and female subjects 12 years of age or older) would need to be enrolled into the Baseline Phase at up to 25 centers in order to randomize 105 subjects to each treatment group.

Study Subjects

A total of 327 subjects completed the Screening Visit and 262 were enrolled into the Baseline Phase of the study by 24 investigators. The first subject entered the Baseline Phase on August 22, 1998, and the last subject completed the study on April 13, 1999. Two hundred thirty-nine (239) of the 262 enrolled subjects were randomized. A total of 237 subjects entered the Experimental Phase of the study and was treated with study medication. These 237 subjects are referred to as "all randomized subjects." A summary of study subjects is given in Table 2.2 below.

Table 2.2: Study subjects

	Number of Subjects	
	Placebo	Depakote ER
All Randomized Subjects Data set	115	122
Subjects included in the Safety Analysis	115	122
Subjects included in the Efficacy Analysis		
Intent-to-Treat Data set	115	119
Evaluable Data set	110	117

The sponsor's summary of demographic characteristics is presented in Table 2.3 below. No statistically significant differences were detected between treatment groups in age, sex, race, weight or height among all randomized subjects.

Table 2.3: Demographics

Demographic Characteristic	Treatment Group n (%)		p-value
	Placebo (N = 115)	Depakote ER (N = 122)	
Sex:			0.874
Female	90 (78%)	97 (80%)	
Male	25 (22%)	25 (20%)	
Race. [1]			0.553
Caucasian	99 (86%)	109 (89%)	
Black	7 (6%)	10 (8%)	
Asian	1 (1%)	1 (1%)	
Other	8 (7%)	2 (2%)	
Age (years):			0.334
Mean (SD)	41.3(11.97)	39.8(11.24)	
Min - Max	16 - 69	16 - 69	
Height (inches):			0.950
Mean (SD)	65.7(3.41)	65.7(4.08)	
Min - Max	58 - 73	54 - 77	
Weight (lb): [2]			0.956
Mean (SD)	164.3 (40.41)	164.0 (45.09)	
Min - Max	100 - 297	108 - 334	
1: Non-Caucasian races were combined for calculation of p-value 2: At Visit 2			

3. SPONSOR'S EFFICACY AND STATISTICAL ANALYSES

3.1 Protocol defined Primary efficacy variable

The 4-week Baseline and Experimental Phase migraine headache rates were to be calculated as the total number of migraines during the particular phase multiplied by the

ratio of 28 days to the actual number of days in that phase. The primary efficacy variable was the Experimental Phase reduction from baseline in 4-week migraine headache rate.

The principal secondary variables considered is the Experimental Phase (at least 50) percent reduction from baseline in 4-week migraine headache rates.

Two data sets were to be evaluated to compare the treatment groups. The primary data set was to be an intent-to-treat data set that included all data from randomized subjects who received study drug and provided at least one headache evaluation during the Experimental Phase. The second data set, the evaluable data set, was to consist of data from all protocol compliant subjects in the intent-to-treat data set.

The van Elteren test, a non-parametric method that extends the use of the Wilcoxon two-sample rank sum test to the multi-center case, was to be the primary method of analysis for the primary efficacy variable and for the principal secondary variable.

Table 3.1: Four-week Migraine Headache Rates Overall Summary and Treatment Comparisons Intent-To-Treat Data

	PLACEBO						
EVALUATION	N	Mean (SD)	Min	25%	Median	75%	Max
Baseline Phase (BP)	115	4.2 (1.94)		2.9	3.7	5.4	
Experimental Phase (EP)	115	3.6 (2.29)		2.0	3.0	5.0	
EP change from BP	115	-0.6 (2.01)	–	–1.9	–1.0	0.3	
	DEPAKOTE ER						
EVALUATION	N	Mean (SD)	Min	25%	Median	75%	Max
Baseline Phase (BP)	119	4.4 (1.62)		3.0	4.0	5.3	
Experimental Phase (EP)	119	3.1 (2.03)		1.7	2.8	4.1	
EP change from BP	119	-1.2 (2.03)	-	-2.5	-1.3	–0.1	

Table 3.2: Treatment Comparisons- p-values

Evaluation/ Analysis method	Unweighted	Weighted
Baseline Phase (BP)		
Nonparametric	0.205	0.147
Parametric (square-root trans.)	0.256	0.217
Parametric (untransformed)	0.371	0.386
EP change from BP		
Nonparametric	0.008 (favoring Depakote ER)	0.006 (favoring Depakote ER)
Parametric (square-root trans.)	0.045 (favoring Depakote ER)	0.021 (favoring Depakote ER)
Parametric (untransformed)	0.016 (favoring Depakote ER)	0.010 (favoring Depakote ER)

The sponsor's results of the analysis of the primary variable across time are shown in Table 3.3 below.

Table 3.3: Four-Week Migraine Headache Rates Across Time

Evaluation Period Mean	Treatment Groups	
	Placebo (N = 115)	Depakote ER (N = 119)
Days 1 – 28		
Baseline Phase	4.2	4.4
Experimental Phase	3.7	3.5
Experimental Phase Change	-0.5	-0.8*
Days 29 – 56		
Baseline Phase	4.2	4.4
Experimental Phase	3.5	3.1
Experimental Phase Change	-0.7	-1.2*
Days 57 – 84		
Baseline Phase	4.2	4.4
Experimental Phase	3.6	3.1
Experimental Phase Change	-0.6	-1.2*

*: (p-value ≤ 0.05)

3.2 Principal Secondary Variables

The principal secondary efficacy variables were 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 the Experimental Phase reduction from baseline in the number of migraine headache days per 4 weeks. A summary of the results for these variables is shown in Table 3.4 below.

Table 3.4: Summary of Principal Secondary Variables (ITT Dataset)

	Treatment Group	
	Placebo (N = 115)	Depakote ER (N = 119)
Percent Reduction from Baseline in 4-Week Migraine Headache Rate		
Experimental Phase Median	22.4%	32.3%
Proportion of Subjects With at Least a 50% Reduction in Migraine Headache Rate		
Number (%) of Subjects	28 (24%)	36 (30%)
Number of Migraine Headache Days per 4 weeks		
Baseline Phase Mean	5.8	6.3
Experimental Phase Mean	5.1	4.7
Experimental Phase Mean Change	-0.7	-1.7
* Statistically significant difference versus placebo treatment group per primary analysis method		

3.3 Other Secondary Variables

In the analysis of other secondary variables, Depakote ER-treated subjects experienced greater Experimental Phase mean reductions from baseline in the 4-week migraine headache rates with nausea, aura, photophobia, and phonophobia compared with placebo-

treated subjects; however, none of these differences were statistically significant. The sponsor's results are shown in Table 3.5 below.

Table 3.5: 4-Week Migraine Headache Rates With Particular Associated Symptoms

Associated Symptom Evaluation Period Mean	Treatment Group	
	Placebo #	Depakote ER #
Nausea	(N = 107)	(N = 106)
Baseline Phase	2.5	2.6
Experimental Phase	2.0	1.6
Experimental Phase Change	-0.5	-1.0
Vomiting	(N = 46)	(N = 43)
Baseline Phase	0.7	0.9
Experimental Phase	0.4	0.6
Experimental Phase Change	-0.3	-0.3
Aura	(N = 33)	(N = 29)
Baseline Phase	1.9	2.4
Experimental Phase	1.5	1.8
Experimental Phase Change	-0.4	-0.6
Photophobia	(N = 110)	(N = 111)
Baseline Phase	3.5	3.7
Experimental Phase	2.7	2.5
Experimental Phase Change	-0.8	-1.2
Phonophobia	(N = 104)	(N = 108)
Baseline Phase	2.9	3.1
Experimental Phase	2.4	2.2
Experimental Phase Change	-0.5	-0.9

4. SPONSOR'S OVERALL CONCLUSIONS

Overall, 122 subjects received at least one dose of Depakote ER in the migraine study. The majority of subjects in the migraine study received 1000 mg per day during the fixed-dose period of the study.

This double-blind placebo-controlled clinical study demonstrated that Depakote ER is efficacious in the prophylactic treatment of migraine headaches. Analysis of the primary efficacy variable demonstrated statistically significant treatment differences, favoring Depakote ER.

The mean reduction in 4-week migraine rates during the Experimental Phase for Depakote ER-treated subjects of 1.2 (from a baseline mean of 4.4) was statistically significantly greater than the mean reduction in placebo-treated subjects of 0.6 (from a baseline mean of 4.2; p=0.006). Furthermore, statistically significantly greater differences were seen with Depakote ER in all three 4-week intervals of the 12-week treatment phase. A statistically significant difference was also observed between treatment groups, favoring Depakote ER, in the analysis of Experimental Phase reduction from baseline in number of migraine headache days per 4 weeks.

5. REVIEWER'S COMMENTS

The ITT population consisted of 79% female patients and 21% males. The subjects were mostly (87%) Caucasian. The average age of patients was 40 years. The 4-week migraine headache rate was the protocol defined primary efficacy endpoint. Gender-wise subgroup analysis of the primary endpoint is presented below in Section 5.2. As percentages of Blacks, Asians, and others were very small, race-wise subgroup analysis is not undertaken.

5.1: Baseline comparison

Descriptive statistics for the Baseline Phase Duration (BPDAYS) are shown in Table 5.1 below.

Table 5.1: Baseline Duration

	N	Mean	SD	Minimum	Maximum
Placebo	115	30.27	4.098		
Depakote ER	122	30.01	4.426		

Descriptive statistics for the Baseline Phase Headache Rate (BPRATE) are presented in Table 5.2 below.

Table 5.2: Baseline Headache Rate

	Placebo	Depakote ER
N	115	122
Minimum		
Q1	2.89	3
Median	3.73	4
Q3	5.42	5.25
Maximum		
Mean	4.195	4.382
SD	1.936	1.638

The Wilcoxon rank-sum test on Baseline Phase Rate indicates that the test drug is not significantly different from placebo (p-value = 0.1586).

5.2 Protocol defined primary endpoint: ITT data

Descriptive statistics for the Experimental Phase Duration (EPDAYS) are shown in Table 5.3 below.

Table 5.3: Experimental Phase Duration

	N	Mean	SD	Minimum	Maximum
Placebo	115	78.95	20.69		
Depakote ER	119	77.1	21.63		

The primary efficacy variable was the Experimental Phase reduction from baseline (Baseline Phase) in 4-week migraine headache rate derived from headache assessments taken at each office visit. That is, Headache Rate Reduction = EPRATE – BPRATE. Descriptive statistics of this reduction are as follows.

Table 5.4: Headache Rate Reduction

	N	Mean	SD	Minimum	Maximum
Placebo	115	0.642	2.015		
Depakote ER	119	1.223	2.027		

Protocol defined Primary analysis

For stratified analyses, SAS FREQ/CMH PROCedure with options of modified ridit scores produces the van Elteren's extension of the Wilcoxon rank sum test. For these data, the p-value for the "Row Mean Scores Differ" is 0.006. That is, there is a statistically significant difference between Depakote and placebo with respect to the headache rate reduction.

The pooled t-test also rejects the null hypothesis of equality of means in favor of the alternative hypothesis that the mean reduction for Depakote ER subjects is larger that of placebo (p-value = 0.0145).

Subgroup analyses

Genderwise descriptive statistics for the change in headache reduction rate for placebo and Depakote ER are shown in Table 5.5 below.

Table 5.5: Subgroup analysis for gender
Reduction in Headache rate

	Female			**Male**		
	N	Mean	Std. Dev.	N	Mean	Std. Dev.
Placebo	90	0.53	2.1	25	1.06	1.65
Depakote ER	94	1.32	1.96	25	0.82	2.26

For the subgroup of female patients, one way analysis of the change in headache rate indicated that Depakote ER is significantly different from placebo (p-value = 0.0081). For the subgroup of male patients, one way analysis of the change in headache rate indicated

that Depakote ER is not significantly different from placebo (p-value = 0.6782). As majority of patients (87%) are Caucasians, subgroup analysis for race is not done.

5.3 Principal secondary efficacy variable

As reported by the sponsor, estimates of the proportions of subjects who experienced at least fifty (50) percent reduction in headache rate under placebo and Depakote are 0.24 and 0.30, respectively. The chi-square test indicates that these proportions are not statistically significantly different (p-value = 0.126).

6. OVERALL CONCLUSIONS

The ITT data for the protocol defined primary efficacy endpoint provide sufficient evidence in support of the sponsor's claim that the reduction in Experimental Phase headache rate from baseline under Depakote ER is significantly greater than that under placebo. The ITT data for the principal secondary efficacy endpoint do not support these conclusions.

However, the headache rate for 21.3% of subjects under Depakote ER increased during the experimental phase. The headache rate for 27.8% of subjects under placebo increased during the experimental phase.

/S/

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21 pages redacted from this section of the approval package consisted of draft labeling