CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-168

Medical Review(s)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21-168**
Sponsor:	**Abbott**
Drug:	**Depakote ER**
Proposed Indication:	**migraine**
Material Submitted:	**Request for Pediatric Studies Waiver**
Correspondence Date:	**9/30/99**
Date Received / Agency:	**9/30/99**
Date Review Completed	**8/1/00**
Reviewer:	**Armando Oliva, MD**

1. Introduction

The NDA for Depakote ER in the prophylaxis of migraine was submitted on 9/30/99. As part of that submission, the sponsor has requested a partial waiver of the pediatric study requirements for the prophylaxis of migraine headaches.

The request is based upon the premise that the drug product does not represent a meaningful therapeutic benefit because:

a. the formulation is a large compressed tablet (approximately 1 gram) which should be swallowed whole, not chewed or crushed. Therefore it is not designed for the younger pediatric population; and

b. approximately 6.6 percent of the total migraine population are between the ages of 9 and 16. Within this group, only a smaller subset may be able to swallow a Depakote ER tablet, because of its size. Therefore it is not likely that the number of patients necessary for a study will be available to evaluate the safety and efficacy of Depakote ER, for the prophylaxis of migraine headache.

2. Comments

There is no question that the use of valproate in the pediatric population for migraine prophylaxis would represent a therapeutic benefit. The question the sponsor raises is whether this particular formulation should be studied in that population. Due to the large tablet size, the sponsor states that only a small subset would be able to swallow it.

I believe that Depakote ER in migraine prophylaxis would represent a significant therapeutic benefit in the adolescent population. The formulation would be an attractive treatment option because of increased compliance associated with once daily dosing regimens. Furthermore, other sponsors are routinely conducting acute migraine efficacy studies in adolescents and recruitment has not been a problem. Therefore, I would recommend granting a waiver for pediatric studies in patients under the age of 11 but I would encourage testing of the formulation in adolescents (12-17 year olds).

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. /S/

ao 8/1/00
cc:
HFD-120
NDA 21-168

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Depakote ER**
Generic Name:	**Divalproex Sodium**
Sponsor:	**Abbott**
Indication:	**Migraine Prophylaxis**
NDA Number:	**21-168**
Original Receipt Date:	**10/4/99**
Clinical Reviewers:	**Armando Oliva, MD**
Review Author:	**Armando Oliva, MD**
Review Completed:	**6/7/00**

Table of Contents

1. Background

Depakote ER is an extended release formulation of divalproex sodium. The proposed indication is for migraine prophylaxis. The sponsor has developed this formulation with the hope that less frequent dosing will result in improved compliance. The currently marketed product, Depakote, is already approved for this indication (Depakote itself is a delayed release (DR) product). The product labeling for Depakote states that the recommended starting dose for migraine prevention is 250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day.

This NDA provides data from a single double blind, placebo-controlled clinical study (M98-845). It also contains the results of a single pharmacokinetic study which compared the ER formulation with the marketed tablets (M98-924). The sponsor confirmed the adequacy of a single study to support this indication in a teleconference with the Division on 6/1/99.

No safety update is planned since the studies are complete and there are no ongoing studies.

The sponsor has already submitted another NDA for this formulation. This is NDA 20-782 and it contained 7 phase 1 studies designed to characterize and qualify the ER formulation for commercial use. The formulation was compared to the marketed product in three populations: non-induced volunteers, epilepsy patients who were concurrently receiving enzyme-inducing anticonvulsants, and under rigorous meal conditions. The ER formulation was shown to have a relative bioavailability to the marketed formulation of about 80-95%, depending on the nature and timing of meals.

On 6/17/98, the Division issued a non-approvable letter which cited a concern for non-bioequivalence under fasting conditions. In a subsequent meeting, the Division indicated that an evaluation of the effects of food extremes would need to be conducted to obtain approval for the use of Depakote ER for epilepsy in order to demonstrate that administering the product with food would correct for the lack of bioequivalence in the fasting state. Study M98-924 was designed to assess the effects of a low calorie/low fat meal. This study is presented to support statements in the clinical pharmacology section for Depakote ER labeling. The results of this study was also submitted to the epilepsy NDA (20-782) on 4/26/99. The results did not show equivalence of the ER formulation relative to the reference formulation with respect to AUC nor an acceptable ratio for C_{min}.

2. Proposed Labeling

The sponsor proposes separate labeling for the ER formulation.

Description

Each Depakote ER tablet contains 500mg of divalproex sodium.

Pharmacology
The mechanism by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain GABA levels.

Pharmacokinetics
Bioavailability, relative to an i.v. injection, is about 80-95%. After multiple dosing, Depakote ER given once daily produces equivalent or lower fluctuation than regular Depakote DR tablets given twice daily. The bioavailability relative to the delayed release tablet ranged from 89-97% (fasting) and 81% (food). These results suggest that higher doses of Depakote ER may be needed to produce equivalence to Depakote DR tablets.

Indication
Prophylaxis of migraine headache.

Contraindication, Warnings, and Precautions
Same as current Depakote labeling.

Adverse Events
Most common AE's in migraine patients were nausea, dyspepsia, diarrhea, vomiting, abdominal pain, and somnolence.

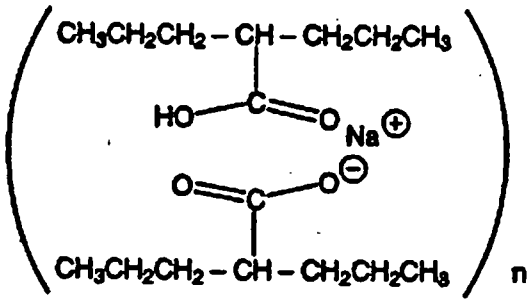
Dosing
500mg once daily for one week, then 1000mg once daily. To convert patients from Depakote DR to Depakote ER, it should be noted that the relative bioavailability is generally in the 80-95% range.

Patient Information
The patient product information is similar to the current Depakote PPI; with the exception that the ER formulation has been inserted in all references to Depakote.

3. Chemistry, Manufacturing and Controls

Generic Name:	**Divalproex sodium**
Trade Name:	**Depakote ER**
Chemical Name:	**Sodium hydrogen divalproate**
Alternative Name:	**Valproic acid semisodium salt**
Molecular Formula:	**$[(CH_3CH_2CH_2)_2\ CHCOO]_2\ HNa$**
Molecular Weight:	**310.41**

Figure 1: Chemical Structure – Divalproex Sodium



4. Animal Pharmacology & Toxicology

The NDA references the preclinical information contained in the original Depakote NDA (18-723). No new animal data are provided.

5. Human Pharmacokinetics

The sponsor has conducted a total of eight clinical pharmacology studies to characterize the ER formulation. The clinical review volumes do not contain information regarding the human pharmacokinetics of the formulation. For this, I refer the reader to the biopharm review. The following information is obtained from the draft labeling.

5.1 Absorption

[

]

5.2 Distribution

[

]

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

[

]

6.1.3 Study Procedures

After satisfying screening procedures, patients who were receiving or who had recently received migraine prophylaxis medications were to complete a washout period equivalent to at least 5 half-lives of these medications. Eligible patients who had not previously received migraine prophylactic medications or who had already "washed-out" could have proceeded directly to the baseline phase of the study. Visit 1 marked the beginning of this phase. At this visit, a brief neurological examination and prior and concurrent medication assessments were performed and headache diaries were issued.

Patients were instructed to record, in the headache diary, each headache experienced (migraine or not) and investigators were instructed to record every headache event that occurred since the previous visit (protocol page 16, Vol. 18, page 088). Headaches separated by any headache-free period were to be reported as separate events. Investigators were instructed to record on the case report forms:

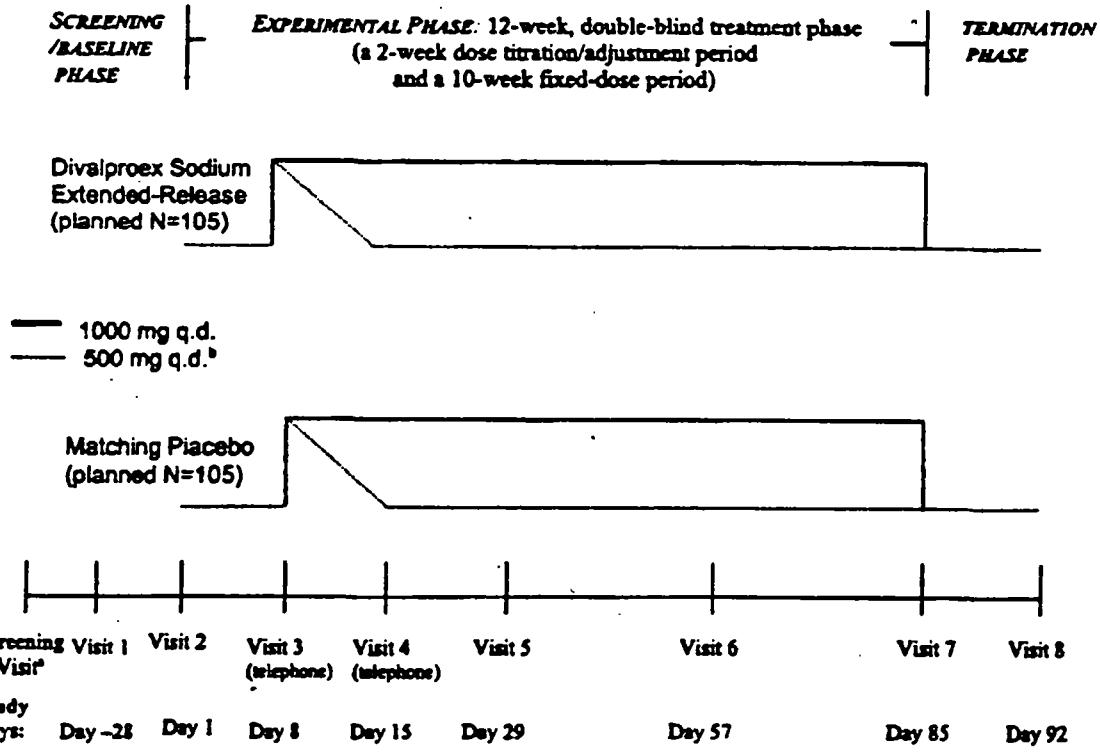
- Approximate start and stop date/time of the attack (if the subject falls asleep, then the end time is the time the patient wakes up free from symptoms)
- Type of headache attack per IHS diagnostic criteria as determined by the investigator based upon review of the diary (migraine, tension, cluster, other)
- Functional ability rating associated with each attack (1=normal activity, 2=disturbs normal activity, but no interruption or bed rest, 3=interrupts normal activity and/or bed rest is required, 4=emergency room treatment or hospitalization
- Symptomatic medication use

Those patients who were compliant in maintaining a headache diary during the 4-week baseline phase, and who experienced at least 2 migraine headaches during that period (separated by at least 24 hours) were eligible for randomization into the experimental phase. Visit 2 occurred 4 weeks after visit one and marked the end of the baseline phase and the start of the experimental phase. Eligible patients were randomized 1:1 to receive either Depakote ER or placebo and began the 12-week double blind treatment phase. This phase included a 2-week dose titration period plus a 10-week fixed dose treatment period. During the first week of the dose titration period, each subject received one tablet of Depakote ER 500mg or matching placebo per day. After one week, patients were to receive the 1000 mg/d dose regimen, taken as two tablets of Depakote ER 500mg or matching placebo once a day with the evening meal. If a patient experienced unacceptable intolerance during the second dosing week, the investigator could permanently reduce the dose to 500 mg/d for the remainder of the experimental phase; otherwise, subjects were to receive the 1000 mg/d regimen for the remainder of the experimental phase.

All patients who received study drug were to enter the 1-week termination phase after completing the 12-week experimental phase or upon premature discontinuation from it. All patients were to take one tablet of study drug (500mg or placebo) daily during the termination phase.

A schematic of the study design is shown in Figure 2 (Study report Figure 9.1a, page 11, Vol. 17, page 031). Additional study visits occurred monthly during the experimental phase, and at the end of the termination phase (visits 5, 6, 7, and 8), during which headache diaries were collected, safety assessments were made (visits 5, 7, 8), and enough additional study medication until the next visit was dispensed (visits 5, 6, and 7). Two telephone visits (visits 3 and 4) occurred at the end week 1 and 2 of the experimental phase for dose adjustment purposes.

Figure 2: Study Schematic



a The Screening Visit was to occur within 2 weeks of starting the Baseline Phase: a washout period equivalent to at least five half lives of any prophylactic antimigraine medication was also required prior to the start of the Baseline Phase.
b Between Days 9 and 15, if a subject could not tolerate the randomized total daily dose of 1000 mg/day, the subject was permitted to continue treatment with divalproex sodium extended-release 500 mg/day or matching placebo for the remainder of the Experimental Phase.

6.1.4 Efficacy Measures

Headache diaries were used to collect information regarding start and end times, type, symptomatic medication usage, functional ability, and associated symptoms of each headache attack. Functional ability and associated symptoms for non-migrainous

headaches were not collected on CRF's. Symptomatic medication usage for non-migrainous headaches was collected throughout the study, but not on a per-headache basis.

The primary efficacy measure was the reduction from baseline in the 4-week migraine headache rate obtained during the 3-month experimental phase.

The principal secondary efficacy measure was the percent reduction from baseline in the 4-week migraine headache rate obtained during the 3-month experimental phase Other measures included the proportion of patients who achieved at least a 50% reduction in headache frequency, the proportion of patients who were headache free or with at least 75% reduction in migraine headache rate during the experimental phase, as well as experimental phase changes from baseline in the following variables: average functional disability rating for migraines that occurred, 4-week rates of headaches with particular associated symptoms, the proportions of migraine headaches treated with a particular class of medication, and the average amount (*i.e.*, number of doses) of particular common symptomatic medications used to treat each migraine.

6.1.5 Safety Measures

Adverse events and concomitant medication use were monitored throughout the study. A brief neurological examination was performed at all office visits. Blood tests were performed at screening and visits 2, 5, 7 and termination. Urinalysis was performed at screening and visits 2 and 7. Pregnancy tests were performed in women of childbearing potential at screening and visits 2, 5 and termination. ECG was obtained only at screening, but could be repeated during the study at the discretion of the investigator, if necessary.

6.1.6 Statistical Analysis Plans

The planned sample size of 105 patients per treatment groups (230 total) was based on the results obtained in previous Depakote migraine prophylaxis studies. Assuming that 75% remain on 1000 mg/day and 25% drop to 500mg/d, then the planned sample size provides 91% power to detect a statistically significant treatment difference at the two-tailed α=0.05 level. This assumes a signal to noise ratio between drug and placebo of 0.46 (which is the expected treatment difference between the two groups divided by the expected standard deviation).

The primary and principal secondary efficacy endpoints were to be analyzed using the van Elteren test, a non-parametric method which extends the use of the Wilcoxon two-sample rank sum test to the multicenter case. As an alternative method, the two-way ANOVA including factors for center, treatment, and center by treatment interaction was to be used.

The proportion of subjects who were migraine headache-free or achieved at least a 50% or 75% reduction in 4-week rates were to be analyzed using Cochran-Mantel-Haenszel test with center as the stratification factor.

The primary and principal secondary variables were also to be analyzed for each 28-day period in the experimental phase.

Other secondary endpoints were to be analyzed with appropriate methods. Efficacy variables were also summarized by age (<40, ≥40), gender, race, and dose reported at Visit 4 (end of 2-week titration in experimental phase).

All safety data were tabulated and summarized using descriptive statistics. Adverse events incidences were analyzed using Fisher's exact test. Laboratory data were analyzed using ANOVA.

The sponsor used the following algorithm to calculate the migraine headache frequency. Migraines separated by less than 24 hours were combined and considered as a single migraine for all analyses.[2] The 4-week headache rate was calculated by using the absolute number of migraines during that period multiplied by the ratio 28 days divided by the number of days in the period. For example, if a patient had 12 headaches during the experimental phase which lasted 80 days, then the 4-week migraine rate would be 12 x 28/80 or 4.2. The first day of the baseline phase was the date of visit 1, and the last day was the day before the first day study drug was taken. The sponsor states that they amended the algorithm three days prior to breaking the blind. This was not documented in a protocol amendment, so I cannot verify the timing of this change. The algorithm was amended such that migraines separated by less than 24 hours *in the same study period* were considered as a single attack.

To more accurately assess migraine rates for subjects whose headache diary information was considered by the investigator to be unreliable during specified intervals of the study and to be consistent with the calculation methods used in the previous Depakote study, the sponsor used the following modification. If a patient reported no headache during an investigator-specified unreliable interval, then the migraine rate was assumed to be the rate during the remaining portion of the particular study phase.

After the blind was broken, the sponsor noted that the between group difference in the baseline number of migraine days per 4 weeks approached statistical significance ($p=0.087$ in the primary non-parametric analysis and $0.48 \leq p \leq 0.089$ in the secondary parametric analysis). Therefore, the sponsor added supplementary non-parametric and parametric analyses to control for this possible confounding baseline factor.

6.2 Study Population

6.2.1 Patient Accounting

A total of 327 patients completed the screening visit, and 262 were enrolled in the baseline phase. Two-hundred thirty-nine (239) were randomized; however, two randomized subjects (placebo, and Depakote ER) were dispensed study medication but never took any because one couldn't return to the study site (the placebo patient) and the

[2] This is completely arbitrary but is consistent with acute migraine studies which count a 2nd headache within 24 hours as a recurrence of the initial attack and not a second attack.

other had too many headache days at visit 2 (Depakote ER). In both cases, all study medication dispensed was recovered. This results in 237 as the number of patients randomized and treated. Table 1 (study report page iii, Vol 17, page 010) summarizes the various study populations. A total of 237 were treated, of whom 122 received Depakote ER.

Table 1: Patient Accounting

Number of Patients	PBO	Depakote ER	Total
Planned	105	105	210
Screened			327
Enrolled			262
Randomized and Treated	115	122	237
Safety Population	115	122	237
ITT Population	115	119	234
Evaluable Population	110	117	227

Among all subjects, the most frequently reported primary reason for discontinuation was adverse event (9% placebo, 8% Depakote ER). This is shown in Table 2 (study report table 10.1a, page 50, Vol. 17, page 070).

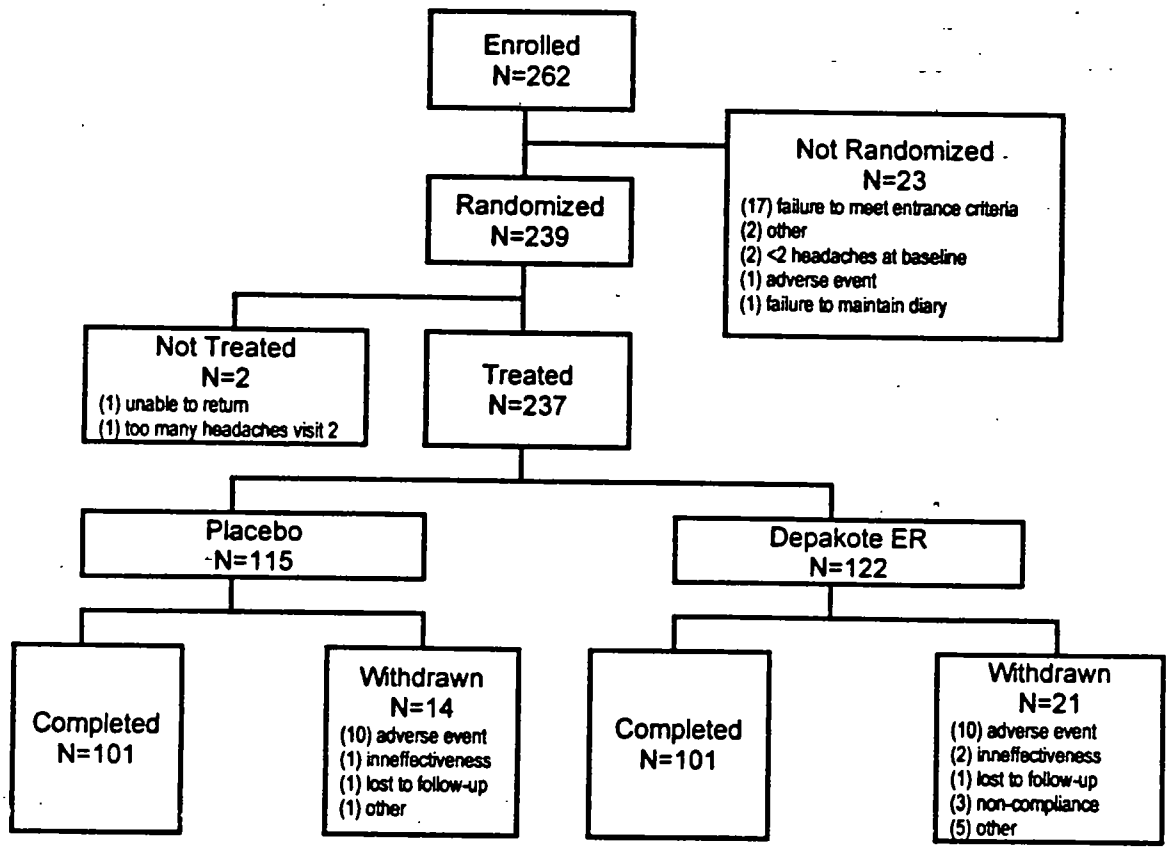
Table 2: Premature Discontinuations

Primary Reason	PBO (n=115)	Depakote ER (n=122)	p-value
Adverse Event	10 (9%)	10 (8%)	>0.999
Ineffectiveness	1 (1%)	2 (2%)	>0.999
Lost to follow-up	1 (1%)	1 (1%)	>0.999
Noncompliance	1 (1%)	3 (2%)	0.622
Other[1]	1 (1%)	5 (4%)	0.214
Total	14 (12%)	21 (17%)	0.360

[1] Other included could not make appointments (2), failure to meet entrance criteria, subject withdrew consent, unavailability due to full time job, and required daily medication for tooth pain.

A schematic of all patient dispositions is shown in Figure 3 (study report figure 10.1a page 51, Vol. 17, page 071).

Figure 3: Disposition of Enrolled Subjects



6.2.2 Demographics and Baseline Characteristics

The mean age of the randomized patients was 40.5 (range 16-69). As is typical of migraine studies, females comprised 88% of the study population, and 88% were Caucasian. A summary of baseline demographic data is shown in Table 3 (study report table 11.2a page 56, Vol. 17, page 076). There were no significant differences between the two groups.

Table 3: Demographics

Demographic Characteristic	PBO (N=115)	Depakote ER (N=122)	p-value
Sex			0.874
Female	90 (78%)	97 (80%)	
Male	25 (22%)	25 (20%)	
Race			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	

Demographic Characteristic	PBO (N=115)	Depakote ER (N=122)	p-value
Height			0.950
Mean (SD)	65.7 (3.41)	65.7 (4.08)	
Min-Max	58-73	54-77	
Weight (lb)			0.956
Mean (SD)	164.3 (40.41)	164.0 (45.09)	
Min-Max	100-297	108-334	

Among all randomized subjects, the average number of years with migraine was 20.2 (range 1-58.8 years). There were no significant differences noted between treatment groups for the following variables: the number of years with migraine, the particular types of headaches ever experienced, the maximum severity of migraine, the particular associated symptoms of migraine, the number of migraines within the previous three months, the number of migraine prophylactic regimens. These variables are summarized in Table 4 (study report table 11.2b page 58, Vol. 17, page 078).

Table 4: Disease Characteristics

Disease Characteristic	PBO (N=115)	Depakote ER (N=122)	p-value
Years with Migraine			0.442
Mean (SD)	20.8 (12.29)	19.6 (12.24)	
Min-Max	1.0-58.8	1.5-51.7	
Headaches Experienced			
Migraine without aura	111 (97%)	118 (97%)	>0.999
Migraine with aura	45 (39%)	41 (34%)	0.418
Acephalgic Migraine	0 (0%)	2 (2%)	0.498
Tension	53 (46%)	51 (42%)	0.516
Other	17 (15%)	10 (8%)	0.152
Maximum Severity			0.698
Moderate	12 (10%)	10 (8%)	
Severe	84 (73%)	88 (72%)	
Excruciating	19 (17%)	24 (20%)	
Associated Symptoms			
Nausea	112 (97%)	118 (97%)	>0.999
Vomiting	70 (61%)	73 (60%)	0.895
Aura	45 (39%)	41 (34%)	0.418
Photophobia	112 (97%)	121 (99%)	0.358
Phonophobia	111 (97%)	119 (98%)	0.715
Other	36 (31%)	26 (21%)	0.104
No. of Migraines in preceding 3 months			0.294
Mean (SD)	13.1 (6.8)	13.7 (6.8)	
Min-Max	6-36	6-42	
No. Of Prophylactic Medications Used			0.926
Mean (SD)	0.7 (1.05)	0.6 (0.81)	
Min-Max	0-6	0-3	
No. of Failed Adequate Trials of Prophylactic Medications			0.315
0	85 (74%)	95 (78%)	
1	5 (4%)	10 (8%)	
2	18 (16%)	12 (10%)	
>2	6 (5%)	3 (2%)	

Among all randomized patients, there were no statistically significant differences between treatment groups during the baseline phase in the 4-week migraine headache rate (placebo 4.2, Depakote ER 4.4, p=0.17), number of migraine headache days per 4 weeks, 4-week rates in the number of migraines with particular associated symptoms, average functional ability rating, proportion of migraine headaches treated with any symptomatic medication or with particular classes of symptomatic medications (non-steroidal anti-inflammatory medication, non-non-steroidal anti-inflammatory medication, opiate, ergot, or triptans), or average number of doses of all or particular common symptomatic medications used to treat each migraine headache.

Placebo patients took Midrin more often at baseline than Depakote ER patients (p=0.029), and the average number of Midrin doses was also higher (p=0.025).

6.2.3 Compliance

Investigators assessed compliance at each visit during the experimental and termination phases. This was a general assessment as pill counts were not recorded on the CRF and no formal calculations of compliance were done. Nonetheless, the proportion who generally took medication as prescribed was 74% for placebo patients and 75% for Depakote ER patients.

6.3 Efficacy

6.3.1 Four-week Migraine Headache Rate

The primary efficacy analysis compared the 4-week migraine headache rate reduction from baseline during the experimental phase between drug and placebo. The ITT population consisted of 234 patients, of which 119 took Depakote ER and 115 took placebo. The van Elteren non-parametric test using a weighted treatment comparison was the prespecified primary analysis method. The results are shown in Table 5 (study report table 11.4a page 63, Vol. 17, page 083).

Table 5: Four-Week Migraine Headache Rates, Changes from Baseline

	PBO (n=115)	Depakote ER (n=122)
Baseline Phase	4.2	4.4
Experimental Phase	3.6	3.1
Change from Baseline	-0.6	-1.2*

* p≤0.05

Depakote ER was associated with statistically significant reduction from baseline in the 4-week migraine rate. The weighted and unweighted treatment comparisons of the parametric analyses of the square root transformed and untransformed data also all favored Depakote ER and were statistically significant (p≤0.045).

6.3.2 Secondary Analyses

The principal secondary analysis compared the percent change from baseline in the 4-week migraine rate. This and other secondary analyses are shown in Table 6 (study report table 11.4b page 65, Vol. 17 page 085).

Table 6: Secondary Efficacy Analyses

	PBO (n=115)	Depakote ER (n=122)
% Reduction from Baseline in 4-week migraine rate		
Experimental Phase median	22.4%	32.3%*
Proportion with ≥50% Reduction in migraine rate		
Number (%) of patients	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
Change from Baseline	-0.7	-1.7*

* p≤0.05

The primary efficacy and secondary variables listed above were also analyzed for each 4-week interval of the 12-week experimental phase (days 1-28, 29-56, and 57-84). In these analyses, an LOCF approach for patients who prematurely discontinued before entering a 28 day period, such that the value of the preceding period was used to estimate the patient's value for the period(s) containing no data.

Nominally significant reductions, favoring Depakote ER, were detected for the primary variable, the 4-week migraine rate, in each 28 day period per the weighted treatment comparison of the non-parametric analysis (the planned primary analysis method, Table 7, study report table 11.4c page 66, Vol. 17, page 086). None of the principal secondary variables had nominally significant reductions in all three 4-week periods; however, all of the secondary variables listed in Table 6 showed nominally significant drug-associated reductions in 2 of the three periods, although not necessarily the same two periods for each variable.

Table 7: Four-week Migraine Rate Across Time

	PBO (n=115)	Depakote ER (n=122)
Days 1-28		
Baseline Phase	4.2	4.4
Experimental Phase	3.7	3.5
Change from Baseline	-0.5	-0.8*
Days 29-56		
Baseline Phase	4.2	4.4
Experimental Phase	3.5	3.1
Change from Baseline	-0.7	-1.2*
Days 57-84		
Baseline Phase	4.2	4.4
Experimental Phase	3.6	3.1
Change from Baseline	-0.6	-1.2*

* p≤0.05

Depakote ER was associated with a nominally significant percent reduction in baseline migraine rate and in a reduction in baseline headache days per 4 weeks, compared to placebo. The proportion who had at least 50% reduction in migraine headache rate was

numerically higher for Depakote ER (30% vs. 24%) but this failed to reach nominal significance.

There were a total of seven (6%) placebo patients and eight (7%) Depakote ER patients who had 4-week migraine rate reductions from baseline of at least 75%. This was not nominally significant. Three placebo patients became headache free (3%) and no Depakote ER patient became headache free. This was nominally significant in favor of placebo (p=0.05). However, 2 of the three received treatment for 7 days or less, and the third only had one migraine in the baseline phase and should not have been randomized.

Table 8 (study report table 11.4e page 69, Vol. 17, page 089) shows 4-week rates for migraines with particular associated symptoms. No analysis was nominally significant.

Table 8: Four-week Migraine Rates with Particular Associated Symptoms

	PBO	Depakote ER
Nausea	***N=107***	***N=106***
Baseline Phase	2.5	2.6
Experimental Phase	2.0	1.6
Change from Baseline	-0.5	-1.0
Vomiting	***N=46***	***N=43***
Baseline Phase	0.7	0.9
Experimental Phase	1.5	1.8
Change from Baseline	-0.3	-0.3
Aura	***N=33***	***N=29***
Baseline Phase	1.9	2.4
Experimental Phase	1.5	1.8
Change from Baseline	-0.4	-0.6
Photophobia	***N=110***	***N=111***
Baseline Phase	3.5	3.7
Experimental Phase	2.7	2.5
Change from Baseline	-0.8	-1.2
Phonophobia	***N=104***	***N=108***
Baseline Phase	2.9	3.1
Experimental Phase	2.4	2.2
Change from Baseline	-0.5	-0.9

The sponsor also analyzed the proportion of headaches treated with symptomatic medications, average number of doses of the commonly used symptomatic medications. In general, these were numerically in favor of drug but failed to reach nominal significance (the one exception was average number of aspirin doses used was nominally lower for Depakote ER patients-using a non-parametric analysis).

6.3.3 Subgroup Analyses

The sponsor performed analyses of the experimental phase reduction in the 4-week migraine rate from baseline in various demographic subgroups of the ITT population: age (<40, ≥40), race (Caucasian, non-Caucasian), and gender. Treatment group

differences did not differ significantly across the categories of any of the demographic subgroup variables as evidenced by the lack of any statistically significant subgroup by treatment interactions.

6.3.4 Drug Dose Used

Most patients (94% of the ITT population) remained on the 1,000 mg/d dose. A few patients (4 placebo, 14 Depakote ER) reduced their dose to 500 mg/d. Their numbers were too small to compare between group differences across different dose groups and this analysis was not performed.

6.3.5 Sponsor's Efficacy Conclusions

From the analyses presented the sponsor concludes (study report page 76, Vol. 17, page 096):

- Depakote ER was demonstrated to be effective vs. placebo in the prophylactic monotherapy of patients with migraine headaches, based on the reduction in the 4-week migraine rate from baseline (0.6 for placebo vs. 1.2 for Depakote ER, $p \leq 0.05$).
- Statistically significant differences favoring Depakote ER were detected in the reductions in 4-week migraine rate during each 4-week interval of the 12-week experimental phase.
- The percent reduction in the 4-week migraine rate (the principal secondary variable), and the reduction from baseline in number of migraine days per 4-weeks were also statistically significant, favoring Depakote ER.
- The treatment difference in the proportion of patients achieving at least a 50% reduction in 4-week migraine rate did not reach statistical significance.

6.3.6 Reviewer's Efficacy Analyses

The efficacy data for this study was supplied in a single SAS transport file dataset called hq.xpt. The dataset contained headache diary information for every randomized patient in the study. There were a total of 4,592 records, and each record contained information for one headache, such that there were multiple records per patient. Each headache event was numbered sequentially, and key variables were provided such as the study date (negative numbers for baseline, positive numbers for double blind and termination phase). Each event was also flagged as to which phase of the experiment the event occurred (*e.g.*, baseline, double blind, termination). Also provided was the start/stop time/date for each event, and other descriptive variables (associated symptoms, etc.). The dataset included the investigator's diagnosis for the event (migraine headache with aura, migraine headache without aura, tension headache, other). In cases where the event was diagnosed as "other," a separate descriptive field contained additional diagnostic information (*e.g.*, eye strain, sinus headache, etc.). The efficacy dataset contained records for 4,592 headaches experienced by the 239 patients that were randomized to double blind treatment (placebo = 116, Depakote ER = 123).

A separate dataset, sd.xpt, contained dosing information. It contained start and stop dates for each dose taken in the study, both in the double blind phase and in the termination phase. It contained dosing information for the 237 patients that were randomized and treated (outlined in Figure 3, page 12).

6.3.6.1 Drug Exposures

Using the drug exposures dataset (sd.xpt), I performed the following analyses to evaluate the extent of drug exposures. Each row in the dataset contained dosing information since the previous recorded visit. I subtracted the interval end date from the start date and added "1" to determine the number of days of treatment for that interval. Then, I added the results from each row, grouping by study phase (double-blind vs. termination) to get the number of days each patient was treated for each interval. I multiplied the dose taken during that interval by the number of days in the interval to get a cumulative dose. I added all the data (dates, cumulative doses) for each interval within the double blind treatment period. I then calculated a mean daily dose for each patient during the double blind period by dividing the total cumulative dose by the number of days in the treatment period. The planned double blind treatment period was 12 weeks (85 days). The actual distribution of double blind treatment durations is shown in Table 9. It shows that 82% of patients completed at least 80 days of double blind treatment (80% for Depakote ER and 84% for placebo patients).

Table 9 (RA): Summary of Exposures During Double Blind Phase

	PBO	Depakote ER	Total
Randomized & Treated	115	122	237
Treated ≥15 days	110 (96%)	116 (95%)	226 (95%)
Treated ≥30 days	107 (93%)	110 (90%)	217 (92%)
Treated ≥60 days	103 (90%)	103 (84%)	206 (87%)
Treated ≥80 days	97 (84%)	98 (80%)	195 (82%)
Total Days	9123	9236	
Total Dose (mg)	8457500	8277500	
Mean Days	79	76	
S.D. (days)	±21	±24	
Mean Dose (mg/d)	927	896	

The mean number of days treated in the double blind phase was 79 for the placebo group and 76 for the Depakote ER group. The mean dose was 927 mg/d for the placebo group and 896 mg/d for the Depakote ER group.

6.3.6.2 Migraine Headache Rates

At each patient visit, investigators reviewed the headache diary and classified each headache using IHS criteria, as one of the following: migraine without aura, migraine with aura, tension headache, or other.

Only migraine headaches with or without aura were used to calculate the monthly migraine headache rate (normalized to 28 days) during the three month double blind treatment period.

The efficacy dataset hq.xpt contained headache data for 4,592 headaches that the 239 randomized patients experienced and recorded. Two patients, (10825 and 12212, both 25 y/o females) failed to take any study medication (these are the two "randomized but not

treated" patients identified in Figure 3, page 12). I removed these two patients from the analysis, resulting in 237 patients (with 4,575 headaches) in the ITT population.

The distribution of headaches, by treatment group, type, and study phase, is shown in Table 10. The headaches in the "off" phase occurred in patients who discontinued early and occurred after they were off study medication. I removed these from the analysis. The headaches in the "pre" phase occurred prior to the start of the 4-week baseline period. I also removed these from the analysis. Lastly, I removed the headaches occurring during the termination phase, as these don't contribute to the migraine headache rate experienced during the double blind treatment phase. This resulted in 4,323 headaches experienced during the baseline and double blind phases for the 237 patients.

Table 10 (RA) – Distribution of Headaches

Phase	Headache Type	PBO	Depakote ER	Total
BASELINE	MIGRAINE HEADACHE WITH AURA	68	80	148
	MIGRAINE HEADACHE WITHOUT AURA	528	610	1138
	OTHER	6	3	9
	TENSION HEADACHE	69	40	109
DB	MIGRAINE HEADACHE WITH AURA	163	157	320
	MIGRAINE HEADACHE WITHOUT AURA	1220	1083	2303
	OTHER	19	10	29
	TENSION HEADACHE	165	102	267
TERMINATN	MIGRAINE HEADACHE WITH AURA	19	6	25
	MIGRAINE HEADACHE WITHOUT AURA	99	75	174
	TENSION HEADACHE	12	13	25
OFF	MIGRAINE HEADACHE WITH AURA	0	4	4
	MIGRAINE HEADACHE WITHOUT AURA	7	7	14
	TENSION HEADACHE	1	0	1
PRE	MIGRAINE HEADACHE WITH AURA	1	1	2
	MIGRAINE HEADACHE WITHOUT AURA	2	5	7
TOTAL		**2379**	**2196**	**4575**

Using the data contained in file pt.xpt (overall subject and study information), I obtained the dates of each visit for each patient. I used visit 1 as the start of the baseline phase, visit 2 as the start of the double blind phase, visit 7 as the start of the termination phase and visit 8 as the end of the termination phase. I calculated the duration of the baseline phase for each patient by subtracting visit 2 – visit 1 and calculated the duration of the experimental phase by subtracting visit 7 – visit 2 (if the patient discontinued early, visit 7 recorded the date of the discontinuation). I imported these number (BPDays = number of baseline phase days; EPDays = number of experimental phase days) to the original efficacy dataset.

In the original efficacy dataset, I then removed all the non-migraine headaches, since they were not counted in the analysis. This resulted in 3,909 migraines (3441 migraines without aura and 468 migraine with aura). Out of interest, the 38 headaches classified as "other" were: sinus headache (31), eye strain (6), and headache with cold (1).

I then counted the number of migraines each patient experienced in each phase (baseline and double blind) and calculated the rate. The formula I used for the baseline (BP) and experimental phase (EP) migraine headache rate was the same used by the sponsor:

$$BP\ Migraine\ headache\ rate = \#\ of\ headaches\ in\ BP \times (28 \div BP\ Days)$$

$$EP\ Migraine\ headache\ rate = \#\ of\ headaches\ in\ EP\ phase \times (28 \div EP\ Days)$$

From the visit diary dataset (vd.xpt), I identified 14 patients that had unreliable headache diary information, as determined by the investigator in the case report form. They were evenly divided among placebo (7) and Depakote ER (7) patients. Two periods of unreliability occurred prior to double blind treatment, and lasted only one day each. The other twelve occurred during the double blind phase and ranged from 1-33 days (mean 13 days for PBO and 12 days for Depakote ER, p=0.87, t-test). These were relatively small number of days (155) compared to the total number of double blind observation days in the experiment (Table 9) so I chose not to adjust the migraine rates as a result. (The sponsor adjusted the rates by assuming that the migraine headache rate during the unreliable days was equal to the migraine headache rate observed during the remainder of the respective phase).

The mean headache rates are shown in Table 11. I used a simple t-test for my analysis, (the distribution of "change from baseline" was normal so this seemed like a reasonable test to use, although it is different from the sponsor's prespecified analysis). The result showed a significant difference in the change from baseline in favor of Depakote ER compared to placebo.

The sponsor decided to count migraines separated by less than 24 hours *in the same study period* as a single attack. I chose to count each migraine attack separately if they were reported as separate headaches by the patient, even though some attacks were separated by less than 24 hours. The reason why I chose this method was completely arbitrary. In a way, it is a measure of the "robustness" of the primary efficacy results. That is, if this change in counting migraines made a significant change in the results, then the treatment effect could be questioned. This reason explains why my numbers are higher (and different) from the sponsor's (as it turned out, 933 headaches, out of 4,575 total, occurred less than 24 hours after the end of the previous headache in the same phase).

Table 11 (RA): Mean Headache Rates (Counting All Migraines Separately)

	PBO (n=115)	Depakote ER (n=122)
Baseline Phase	4.85	5.36
Experimental Phase	4.52	3.94
Change from Baseline	-0.33	-1.42*

*p=0.014 (t-test)

(sponsor's analysis Table 5, page 14[3])

	PBO (n=115)	Depakote ER (n=122)
Baseline Phase	4.2	4.4
Experimental Phase	3.6	3.1
Change from Baseline	-0.6	-1.2*

* p≤0.05

When all migraines are counted separately, my analysis shows a slightly greater treatment effect in favor of drug, compared to the sponsor's analysis.

I also compared the proportion of patients whose EP headache rate was at least 50% or lower than the BP rate. This is shown in Table 12. Although in favor of drug (32% vs. 23%), the results did not reach nominal significance. This is consistent with the sponsor's findings (30% vs. 24%, NS, Table 6, page 15)

Table 12 (RA): Proportion Experiencing ≥50% Reduction in Migraine Headache Rate (Counting All Migraines Separately)

	PBO (n=115)	Depakote ER (n=122)
Non-responder	89 (77%)	83 (68%)
Responder (≥50% reduction in migraine headache rate)	26 (23%)	39 (32%)

p=0.11 (chi-square)

I compared the mean duration of the migraine headaches between the two groups. There was a numerical baseline imbalance that approached nominal significance such that the mean duration of all headaches during the baseline phase in the placebo group was 9.8 hours vs. 11.1 hours for the Depakote ER group (p=0.08, t-test). The mean duration of migraines during the double blind phase was 9.5 hours for Depakote ER and 9 hours for placebo (p=0.36, t-test). These results are difficult to interpret for various reasons, including the numerical baseline imbalance, and the fact that duration of migraines is confounded by symptomatic medication use.

I also compared the mean duration of headaches for each patient, both at baseline and during treatment. The mean duration for each patient at baseline was 11.1 hours for placebo and 12.3 hours for drug (p=0.40, t-test). During double blind treatment, it was 10.9 hours for placebo and 11.8 hours for drug (p=0.58, t-test). The mean change from baseline in headache duration for each patients was –0.3 hours for placebo and –0.4 for drug (p=0.94, t-test).

6.3.6.3 Efficacy in Adolescents

The protocol allowed enrollment of adolescents as young as age 12. In fact, the youngest patient enrolled was 16 years of age. I analyzed the efficacy of treatment in the 16-17 age groups. Unfortunately, there were only 4 patients under the age of 18. These are listed

[3] This analysis differs from mine in that the sponsor counted two (or more) headaches that occurred within 24 hours during the same study phase as one attack.

below. There was only one adolescent patient who was treated with drug. Clearly the numbers are too small to draw any conclusions regarding efficacy in this population.

Table 13: Efficacy In Adolescents

ID	Age	Sex	TRT	BP	EP	Change	% (EP/BP)
12414	16	MALE	0	3.50	3.67	0.17	1.05
11813	16	MALE	1000	4.38	0.66	-3.72	0.15
11514	17	MALE	0	3.61	1.24	-2.38	0.34
10713	16	FEMALE	0	7.00	0.64	-6.36	0.09

BP = Baseline Phase Monthly Migraine Rate; EP = experimental Phase Monthly Migraine Rate

6.3.6.4 Classification of Migraine Headaches

In the study, patients recorded every headache in a patient headache diary. The investigator used this information to classify the headaches as one of the following (as shown in Table 10, page 19): migraine headache with aura, migraine headache without aura, tension headache, or other. As shown in Table 14, a similar proportion of headaches were classified as "migraine" in both treatment groups. According to the protocol and reiterated by the sponsor in a communication dated 1/5/00, the investigators used IHS criteria "without modification" to classify the headaches by type. Since IHS criteria are written to identify a patient with a particular headache disorder and not to identify individual headaches, some modification is necessary to apply these criteria to individual headaches. Unfortunately, since patient diary data was not submitted (and according the sponsor is not available in electronic format), I was initially unable to verify whether the classification was done accurately and consistently between the two treatment groups. One can imagine the possible scenario where there was a bias in classifying Depakote-treated headaches as non-migraine, thereby artificially lowering the monthly migraine rate for drug.

Table 14 (RA): Proportion of Headaches Classified as Migraine

Phase	PBO	Depakote ER
Baseline	596/671 (88.8%)	690/733 (94.1%) p<0.001
Experimental Phase	1383/1567 (88.3%)	1240/1352 (91.7%) p=0.002

p-values are from Fisher's exact test

In both the baseline and experimental phases, a higher proportion of headaches in the Depakote ER group were classified as "migraine" compared to the placebo group. This does not suggest "under-classifying" of migraine in the Depakote ER group. The slight drop in percentage of classified migraine headaches in the Depakote ER group from baseline to experimental phase (94.1% to 91.7%) might be expected if there is an effect on migraine frequency, but not in the frequency of the other headache types with treatment (see below).

In order to address a possible "migraine classification bias" between treatment groups, as described above, I contacted the sponsor on 2/14/00 and requested that they submit raw headache diary information. I asked for additional headache variables that were collected in the patient diary, but were not captured in the case report form. The purpose was to classify headaches as either migraine or non-migraine according to an internally-developed "modified" IHS criteria for individual headaches. This classification algorithm is described fully in Appendix A - page 38 and is the same algorithm which I have used in other reviews.

The sponsor informed us that the headache diaries were kept at the local sites and the information was not transcribed into electronic format and the data requested were not easily available. We agreed that they would audit 20% of the diaries and obtain the necessary data for review. With the help of Dr. Koti, our biostatistician, we provided the random number "seed" in order to select random diaries for the audit. The sponsor audited 64 patient diaries (roughly 27% of the 227 patients in the ITT population). They submitted the requested data on 4/28/00 for review.

The 64 patients audited for this analysis recorded a total of 1176 headaches. Of these, 1047 were recorded as a headache which occurred during either the baseline phase or the treatment phase. Of these, 92% (n=966) were classified as migraine on the case report form and would have been included in the original ITT analysis. Of these 966, 64% (n=673) can be classified as migraine using the migraine algorithm described in Appendix A - and these were roughly evenly distributed between placebo (340/518, 66%) and drug groups (333/529, 63%). As a result, there did not appear to be a "mis-classification bias" in favor of the drug group. One question that remains unanswered is why is the percentage of "definite migraines" using this algorithm differ so greatly from (and much lower than) the percentage of headaches classified as migraine on the case report form. One can imagine several scenarios why this may be the case – the most likely of which is the possibility is not sensitive to detect all migraines (but it should be quite specific, and an imbalance between groups would suggest a mis-classification bias).

Using my own analysis, I applied the migraine classification algorithm to all 1091 headaches submitted and counted as "migraine" on the case report form (these migraines occurred at any time during the study, and not necessarily during baseline and double blind phase). The percentage of migraines in placebo-treated patients fulfilling the classification of "definite migraine" using the algorithm was 65% (356/544) vs. 64% (348/547) for Depakote ER. This difference was not nominally significant (p=0.53 – chi-square).

Of the 1047 "migraines" that occurred during either baseline or double-blind phase (*i.e.*, that were used in the primary efficacy analysis, 65% (336/518) of the headaches in placebo-treated patients were "definite migraines" using the algorithm vs. 64% (338/529) of migraines in the Depakote ER group. This difference was also not nominally significant (p=0.74 – chi-square). I conclude that there was no classification bias of migraines that favored drug.

The sponsor analyzed the demographics and disease characteristics of the 64 patients that were audited and concluded they were similar between the two groups, and similar to the ITT population.

Baseline migraine rates in this subset of 64 patients were 4.0 and 4.3 for the placebo and Depakote ER groups, respectively (vs. 4.2 and 4.4 in the ITT analysis). Reduction from baseline rates were 0.7 and 1.4 for placebo and Depakote ER, respectively (vs. 0.6 and 1.2 in the ITT analysis).

When including only those headaches which fit the migraine classification algorithm, baseline "definite migraine" rates were 2.8 and 3.4 for placebo and Depakote ER groups, respectively. Reduction in "definite migraine" rates from baseline were 0.4 and 1.2 for placebo and Depakote ER, respectively.

All of these numbers favor drug and are consistent with the results of the primary ITT analysis.

6.3.6.5 Overall Headache Rate

One solution to the theoretical issue of "under-classification" of migraine headaches in the experimental phase Depakote ER treatment group (which, as described above probably did not occur) is to analyze overall headache rates between groups. This approach "assumes" that all headaches are migraine. It is also a test of the robustness of the finding, since any treatment effect is certainly diluted by inclusion of headaches, many if not all of whom are not migraine. This analysis is shown in Table 15. The result shows that the change in overall headache rates was numerically higher in the Depakote ER group, and this almost reached nominal significant (p=0.0547). This analysis suggests that, if under-classification of migraine headaches in the experimental phase Depakote ER group did occur, it probably didn't result in a significant treatment effect due to this type of bias.

Table 15 (RA): Overall Headache Rates

	PBO (n=115)	Depakote ER (n=122)
Baseline Phase	5.49	5.68
Experimental Phase	5.06	4.32
Change from Baseline	-0.43	-1.36*

*p=0.0547 (chi-square)

6.3.6.6 Tension Headache Rate

The distribution of tension headaches is shown in Table 10, page 19. Out of interest, I analyzed the effect of Depakote ER on the monthly tension headache rate. This was not an intended analysis in the protocol. Table 17 shows the tension headache rates in the study. None of the comparisons were nominally significant. The results are difficult to interpret because the prevalence of tension headaches were so small, but there is no evidence from these data that Depakote ER has an effect on tension headaches.

Table 16 (RA): Tension Headache Rates

	PBO (n=115)	Depakote ER (n=122)
Baseline Phase	0.58	0.30
Experimental Phase	0.48	0.36
Change from Baseline	-0.10	0.06

6.3.6.7 Duration of Baseline Phase

The protocol specified duration of the baseline phase was 28 days. Our biostatistician noticed that there was a wide range of days during which patients participated in the baseline phase. The vd.xpt dataset contained the dates of each visit for each patient. I took the start of the baseline phase as the date for visit 1 and the start of the experimental phase as the date for visit 2. A simple subtraction of dates (visit2 date – visit1 date) yielded the duration of the baseline phase for each patient. The distribution of baseline days are shown in Table 17.

Table 17: Distribution of the Number of Days in the Baseline and Experimental Phase

	PBO (mean ± SD)	Depakote ER (mean ± SD)	p-value (t-test)
Baseline	30.3 ± 0.4 range 24-49	30.0 ± 0.4 range 25-62	0.63
Experimental Phase	79.4 ± 2.1	75.8 ± 2.0	0.21

Although the baseline phase generally was longer that 28 days for most patients, there was no difference between drug and placebo. The mean duration of the experimental phase was numerically lower in the Depakote ER group, but this did not reach nominal significance.

6.3.7 Reviewer's Efficacy Conclusions

From the data submitted, I conclude that

- Depakote ER is effective for the prophylaxis of migraine headaches, based on the comparison with placebo in the change in 4-week migraine headache rate from baseline.
- The percentage of responders (*i.e.*, those achieving ≥50% reduction in baseline migraine rate) was numerically higher for Depakote ER but this did not achieve nominal significance.
- The efficacy of Depakote ER in adolescents is not established, because so few patients under the age of 18 were studied.

6.4 Safety

All 237 randomized patients (115 placebo, 122 Depakote ER) who were treated with study drug were evaluated for safety.

6.4.1 Extent of Exposure

All 237 patients in the safety population received at least one dose of study drug during the experimental phase of the study. Two-hundred twenty-four (110 placebo, 114 Depakote ER) entered the fixed dose period of the study (beginning of visit 4).

The average dose of study drug during the experimental phase was 907mg/d in the placebo group and 871mg/d in the Depakote ER group. One hundred six (106) of the 110 placebo patients (96%) entering the fixed dose period achieved 1,000mg/d compared to 100 of the 114 Depakote ER patients (88%). One hundred (100) of the 110 patients who entered the fixed dose period remained on 1000 mg/d in the placebo group (91%), compared with 98 of the 114 patients in the Depakote ER group (86%). The extent of exposures are summarized in Table 18 (study report table 12.1a page 78, Vol. 17, page 098).

Table 18: Doses of Study Drug During the Experimental Phase

	PBO	Depakote ER
Avg Experimental Phase Dosage	***N=115***	***N=122***
(mg/d)	907.2	870.6
(mg/kg/d)	12.9	12.3
Dose at the start of the fixed dose phase	***N=110***	***N=114***
500mg	4 (4%)	4.4
1000mg	106 (96%)	100 (88%)
Dose at the end of the Experimental Phase		
500mg	10 (9%)	16 (14%)
1000mg	100 (91%)	98 (86%)

During the experimental phase, placebo patients were treated for an average of 79.4 days (range 5-111) and Depakote ER patients were treated for an average of 75.8 days (range 1-102).

6.4.2 Symptomatic Medications

Symptomatic medication use was common and similar between the two groups (placebo 97%, Depakote ER 95%). The most common symptomatic medication used during the experimental phase was Imitrex (placebo 38%, Depakote ER 39%). Tylenol was the most commonly used medication other than for symptomatic migraine treatment (placebo 22%, Depakote ER 17%).

6.4.3 Deaths

There were no deaths reported.

6.4.4 Serious Adverse Events

Six patients (placebo 4, Depakote ER 2) reported a total of 11 serious adverse event. These are listed in Table 19 (adapted from study report table 14.3.2_1.2, Vol. 17, page 333).

Table 19: Serious Adverse Events

PTID	Age/Sex	SAE	Reason Serious
Placebo			
6551 10913	48/F	Breast carcinoma	HO
795 11111	51/F	GI hemorrhage Apnea	HO
8096 11603	47/F	Nausea	HO
7373 12211	31/F	Abdominal pain Diarrhea Vaginal hemorrhage	HO HO RI
Depakote ER			
7346 10708	29/F	Tachycardia Ventricular arrhythmia Nausea	HO HO HO
14177 11002	31/F	Endometrial disorder	HO

HO = hospitalization
RI = required intervention

Of the 11 SAE's, two were judged probably related to study drug (placebo – GI hemorrhage, Depakote ER – nausea).

6.4.5 Adverse Dropouts

A total of 20 patients discontinued the experimental phase prematurely due to an adverse event. These were evenly distributed between the two treatment groups (placebo 10/115 – 9%, Depakote ER 10/122 – 8%). Somnolence (Depakote ER 3) and nausea (placebo 1, Depakote ER 2) were the most commonly reported AE's leading to discontinuation. The adverse dropouts (ADO's) are listed in Table 20 (adapted from study report table 14.3.2_1.3, Vol. 17, page 334). There were no identifiable Depakote-associated AE's leading to dropout that would suggest a treatment-related effect of the drug, with the possible exception of somnolence.

Table 20: Adverse Dropouts

PTID	Age/Sex	ADO	Relation to Study Drug
Placebo			
6551 10913	48/F	Breast carcinoma	No relation
795 11103	51/F	Dyspepsia	Probable
795 11106	64/F	Dyspepsia	Probable
795 11111	51/F	GI hemorrhage	Probable
8264 11204	56/F	Flu Syndrome	No relation
8264 11206	54/F	Lymphadenopathy	Possible
4708 11401	56/F	Nausea	Possible
5409 11804	43/F	Rash	Probable
7373 12206	33/F	Chest pain	Probably not

PTID	Age/Sex	ADO*	Relation to Study Drug
14172 12306	29/F	Urticaria	Probably not
Depakote ER			
14166 10104	53/F	Somnolence	Probable
14167 10310	48/F	Nausea	Probable
7346 10707	29/F	Tachycardia	No relation
6551 10911	38/F	Cholecystitis	No relation
795 11113	51/F	Somnolence	Probable
8264 11202	68/F	Agitation	Possible
8264 11205	55/F	Nausea	Probable
8264 11208	43/F	Elevated Ammonia Level	Possible
2725 11303	47/M	Asthenia	Probable
5209 11802	37/F	Somnolence	Probable

* "NPN" was not defined

6.4.6 Adverse Events

Eighty-one of the 115 (70%) placebo patients and 83 of the 122 (68%) Depakote ER patients reported at least one treatment-emergent adverse event. No statistically significant differences were detected between treatment groups in either the overall incidence or in the incidence of any specific treatment-emergent AE.

The most commonly occurring AE's in the Depakote ER group (≥5% of patients) are listed in Table 21 (study report table 12.2b page 83, Vol. 17, page 103). The most commonly reported AE (incidence of ≥10% of patients in either treatment group) were infection (placebo 14%, Depakote ER 15%), nausea (placebo 9%, Depakote ER 7%), and asthenia (placebo 10%, Depakote ER 15%). The most common body system affected was "body as a whole" (placebo 39%, Depakote ER 38%).

Adverse events involving the gastrointestinal system (nausea, vomiting, abdominal pain, dyspepsia, diarrhea) and somnolence had numerically higher incidences in the Depakote ER group compared to placebo.

Table 21: Most Commonly Reported Adverse Events*

COSTART Term	Depakote ER (n=122)	PBO (n=115)
Any Event	83 (68%)	81 (70%)
Infection	18 (15%)	16 (14%)
Nausea	18 (15%)	10 (9%)
Asthenia	9 (7%)	12 (10%)
Flu Syndrome	10 (8%)	10 (9%)
Abdominal Pain	8 (7%)	6 (5%)
Dyspepsia	8 (7%)	5 (4%)

Diarrhea	9 (7%)	4 (3%)
Sinusitis	4 (3%)	9 (8%)
Somnolence	8 (7%)	2 (2%)
Vomiting	8 (7%)	2 (2%)

* ≥5% in the Depakote ER group

6.4.7 Laboratory Data

Hematology and chemistry assessments were planned at the screening visit, visit 2 (end of the baseline phase), and at visits 5 (one-month), 7 (three-month), and 8 (end of study). Urinalysis was planned at screening, visit 2, and visit 7 only. A serum pregnancy test in women of child-bearing potential was planned at screening, and visits 2, 5, and 8.

6.4.7.1 Analysis of Means

The sponsor compared experimental phase mean changes from baseline for each laboratory parameter. Statistically significant changes between Depakote ER and placebo were noted in certain cases. These are shown in Table 22 (study report table 12.4a page 88, Vol. 17, page 108).

Table 22: Statistically Significant Mean Changes from Baseline Hematology Values

Parameter	PBO (n=105)	Depakote ER (n=111)	p-value
Platelet (x10^9/L)			
Baseline	258.8	261.2	
Mean Δ to Minimum	-17.1	-40.3	<0.001
Mean Δ to Maximum	17.1	-6.3	<0.001
Mean Δ to Final	-2.8	-23.5	<0.001
Neutrophils (%)			
Baseline	59.6	60.9	
Mean Δ to Minimum	-3.8	-7.0	0.004
Mean Δ to Maximum	4.5	2.1	0.025
Mean Δ to Final	0.4	-2.8	0.004
Lymphocytes (%)			
Baseline	31.3	30.0	
Mean Δ to Maximum	3.5	5.9	0.029
Mean Δ to Final	-0.4	2.2	0.019
Monocytes (%)			
Baseline	6.2	6.2	
Mean Δ to Maximum	0.6	1.5	<0.001
PTT (sec)			
Baseline	29.7	31.0	
Mean Δ to Maximum	4.7	2.5	0.038

There was a nominally significant drop in platelet counts in the Depakote ER group compared to placebo. This was persistent in the final laboratory assessments and consisted of a mean drop of 24 x 10^9/L. Considering that the baseline platelet count was 261, this does not represent a clinically significant drop. The other changes noted above do not appear to be clinically significant.

Statistically significant differences in chemistry values between the two treatment groups were also observed. These are shown in Table 23 (study report table 12.4b page 90, Vol. 17, page 110). None of the changes appear to be clinically significant.

Table 23: Statistically Significant Mean Changes from Baseline Chemistry Values

Parameter	PBO (n=106)	Depakote ER (n=111)	p-value
BUN (mg/dl)			
Baseline	13.0	12.4	
Mean Δ to Minimum	-1.5	-0.7	0.026
Mean Δ to Maximum	1.6	2.5	0.033
Mean Δ to Final	-0.2	0.9	0.011
Creatinine (mg/dl)			
Baseline	0.7	0.7	
Mean Δ to Minimum	0.0	-0.1	0.014
Mean Δ to Maximum	0.1	0.0	0.027
Uric Acid (mg/dl)			
Baseline	4.6	4.3	
Mean Δ to Minimum	-0.3	-0.1	0.001
Mean Δ to Maximum	0.4	0.7	0.001
Mean Δ to Final	-0.1	0.3	<0.001
Calcium (mg/dl)			
Baseline	9.2	9.2	
Mean Δ to Minimum	-0.2	-0.4	0.001
Mean Δ to Maximum	0.2	0.0	<0.001
Mean Δ to Final	0.0	-0.2	0.001
Phosphate (mg/dl)			
Baseline	3.5	3.5	
Mean Δ to Minimum	-0.2	-0.4	0.025
Total Protein (g/dl)			
Baseline	7.1	7.1	
Mean Δ to Minimum	-0.2	-0.3	0.003
Mean Δ to Maximum	0.2	0.1	0.031
Alk Phos (IU/L)			
Baseline	71.9	67.7	
Mean Δ to Minimum	-3.4	-10.9	<0.001
Mean Δ to Maximum	5.2	-3.9	<0.001
Mean Δ to Final	1.4	-7.6	<0.001
SGOT/ALT (IU/L)			
Baseline	21.5	19.4	
Mean Δ to Final	0.6	2.9	0.031
Cholesterol (mg/dl)			
Baseline	198.2	191.6	
Mean Δ to Maximum	10.8	4.9	0.034

No statistically significant differences were note between treatment groups in the experimental change from baseline urinalysis values.

6.4.7.2 Analysis of Outliers

A summary of patients who met pre-defined criteria for very low or very high hematology values are shown in Table 24 (study report table 12.4c page 92, Vol. 17, page 112).

Table 24: Summary of Hematology Outliers (with normal baseline values)

Parameter	Criteria	PBO (n=105)	Depakote ER (n=118)
Hb (g/dL)	≤11.5 (males) ≤9.5 (females)	0	3 (3%)
	≥18.5 (males) ≥16.5 (females)	0	0
Hct (%)	≤37 (males) ≤32 (females)	2 (2%)	2 (2%)
	≥55 (males) ≥50 (females)	0	0
RBC ($x10^{12}$/L)	≤3.8 (males) ≤3.5 (females)	1 (1%)	0
	≥7 (males) ≥6 (females)	0	0
WBC ($x10^9$/L)	≤2.8	0	1 (1%)
	≥16	0	0
Neutrophils (%)	≤15	0	2 (2%)
Lymphocytes (%)	≥70	0	2 (2%)
Eosinophils (%)	≥10	2 (2%)	1 (1%)

A summary of patients who met pre-defined criteria for very low or very high chemistry values are shown in Table 25 (study report table 12.4e page 94, Vol. 17, page 114).

Table 25: Summary of Chemistry Outliers (with normal baseline values)

Parameter	Criteria	PBO	Depakote ER
Glucose (mg/dL)	≤45	0/100	1/92 (1%)
	≥250	0/100	0/92
SGPT/ALT (U/L)	≥129 (males) ≥102 (females) (or 3xULN for either)	0/107	1/95 (1%)
T. Bili (mg/dL)	≥2	1/108 (1%)	0/102
Phosphate (mg/dL)	≤1.5	0/110	0/104
	≥5.5	0/110	1/104 (1%)

There were no predefined high/low criteria for serum amylase. Seven (7) Depakote ER patients and 5 placebo patients with normal baseline amylase values (≤88 U/L) subsequently had serum amylase values above the normal range. Three of 7 Depakote ER patients had amylase values that were at least twice baseline, but all three were normal on retest.

There were 6 placebo patients and 9 Depakote ER patients who met pre-defined criteria for high urinalysis values post-baseline. These were generally increased RBC or WBC consistent with urinary tract infection or non-clean catch samples in women. One placebo and one Depakote ER patient had proteinuria, and one other Depakote ER patient had 3+ glucose.

6.4.8 Vital Signs

Vital signs including systolic/diastolic blood pressure, pulse, and body weight were done at screening and visit 7 (end of 3-month experimental treatment phase). Body weight was also recorded at visit 2 (the start of the experimental treatment phase). There were no statistically significant differences between treatment groups in experimental treatment phase changes from baseline to final visit in any vital sign or weight variable. No vital signs outlier information was provided in the study report.

6.4.9 ECG

Post-baseline ECG's were not recorded in this study.

6.4.10 Sponsor's Safety Conclusions

The incidence of any adverse events were 70% for placebo patients and 68% for Depakote ER patients. No statistically significant differences were detected between groups in either the overall incidence or in the incidence of specific COSTART-coded treatment emergent adverse events.

Serious adverse events were experienced by 3% of placebo patients and 2% of Depakote ER patients. Only two patients (placebo 1, Depakote ER 1) had SAE's which the investigators considered probably related to drug (gastrointestinal hemorrhage, and nausea, respectively).

Nine percent (9%) of placebo patients and 8% of Depakote ER patients discontinued due to an adverse event. Somnolence and nausea were the most common AE's associated with dropouts.

Although several patients met predefined FDA/sponsor criteria for hematology, blood chemistry, or urinalysis values, only one (elevated non-protein nitrogen) of these discontinued because of these abnormalities, and the majority had normal final laboratory values.

Results of other safety analyses, including vital signs, were unremarkable.

6.4.11 Reviewer's Safety Analyses

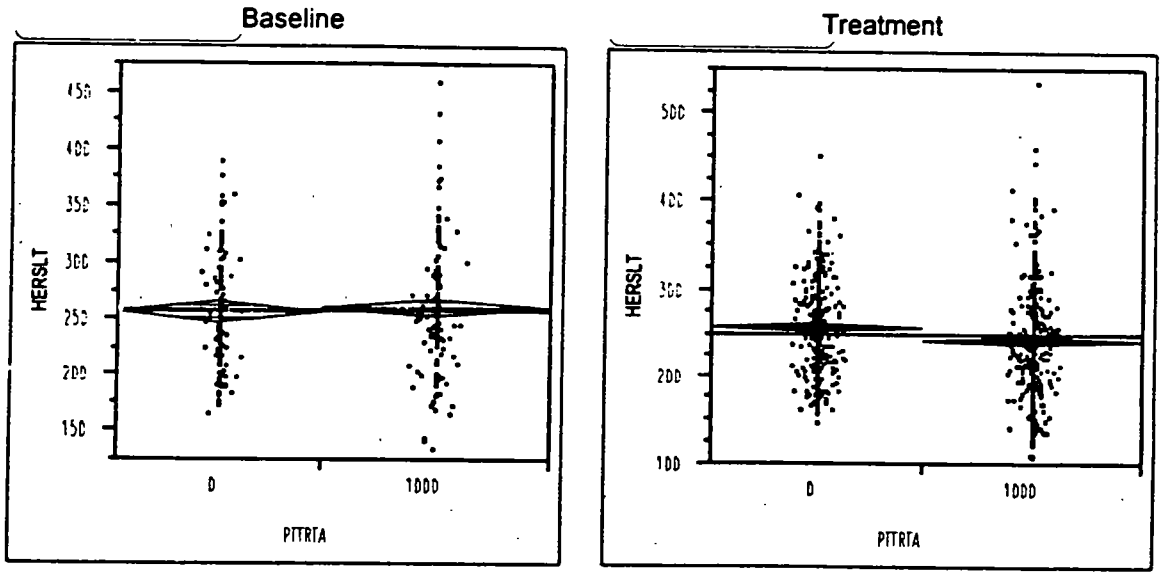
Since divalproex sodium is a marketed product and the sponsor's safety analyses failed to raise any substantial safety concerns, I did not feel the need to conduct a separate safety analysis of the data presented, with the exception of the platelet counts. The sponsor's analysis revealed a nominally significant drug-associated drop in mean platelet counts (Table 22: Statistically Significant Mean Changes from Baseline Hematology Values, page 29). I chose to investigate this further.

The hematology data were provided in a dataset called he.xpt. The dataset contained 1197 records, and each record represented a single platelet measurement at some point during the study. Ninety-three (93) records had no treatment assignment, presumably because they were not randomized. An additional 5 records had missing platelet values. I deleted these from the dataset as well. This resulted in 1100 records for 239 patients (116 on placebo, and 123 on drug).

The timing of the measurement was coded by the variable HERXDY, which was basically the study day. Negative numbers signified pre-treatment or baseline values. Each patients had anywhere from 1-7 platelet measurements made during the study, with the most common number of platelet measurements obtained was 5.

The mean platelet count at baseline for the placebo patients was 257K, and for the Depakote ER patients was 261K, and this was not significantly different (p=0.56, t-test). Among the post-treatment values, the mean platelet count for placebo patients was 257K (unchanged) and for Depakote ER patients was 242K. This was significantly lower (p<0.001, t-test). This confirms the sponsor's finding of a nominally significant drop in mean platelet counts in the Depakote ER group. The drop is modest (<20K) and of questionable clinical significance.

Figure 4: (RA) Distribution of Platelet Counts



To explore this finding further, I examined the outliers. In the treatment phase, the range of platelet counts were 149-454 for placebo and 110-537 for Depakote ER (Table 26).

Table 26: (RA) – Platelet Counts

	N	Platelet Count (x 10^3/cc) Mean	S.D.	Minimum	Maximum
Baseline					
PBO	123	257	50		
1000	137	261	58		

	N	Platelet Count (x 10^3/cc) Mean	S.D.	Minimum	Maximum
Treatment					
PBO	415	257	53		
1000	425	242	59		

Although Depakote ER-treated patients tended to have lower platelet counts, the lowest platelet count measured was 110K.

I point out that current Depakote labeling already contains a warning regarding the possibility of thrombocytopenia. This warning is also present in the proposed draft labeling for Depakote ER. The description thrombocytopenia reported in this section includes some platelet counts which were less than 75K. It also states that this phenomenon may be dose related. Since this study contained a single fixed dose, a relationship to dose cannot be confirmed.

It appears that the proposed warning section more than adequately describes the platelet findings encountered in this study.

This drop in platelet count appears to occur fairly early during treatment. At week one, it was not apparent (mean placebo platelet count = 257K, vs. 262K for Depakote ER), but was apparent at week 5, which is the next time that a substantial number of platelet counts were available for comparison (260K for placebo vs. 234K for Depakote ER, p=0.002), and was still present at week 13 (260K for placebo and 231K for Depakote ER). The finding was still present at the termination visit (259K for placebo, and 232K for Depakote ER, p<0.001). The labeling states that the thrombocytopenia resolves with discontinuation but this could not be confirmed in this study from the data provided.

6.4.12 Reviewer's Safety Conclusions

The results of the safety analysis provided by the sponsor provide no new safety concerns regarding the use of this formulation.

7. Labeling Review

My labeling review focuses on the clinical sections of the labeling, beginning with the clinical trials section onwards. I used the approved labeling for Depakote delayed release tablets as a template for my review. I attach the full text of labeling, along with the recommended changes, in Appendix B - page 43.

7.1 Clinical Pharmacology – Clinical Trials

This section describes the results of the single efficacy study. It is generally acceptable with the following minor exceptions:

- The sub-heading "Clinical Trials" should be placed preceding the description of the migraine prophylactic study. Since there is only one indication (migraine prophylaxis), the subheading "migraine" is not necessary.
- The section states that [redacted]. I believe this is incorrect. It is the positive results demonstrated in this study, in conjunction with the positive results obtained in

two previous trials using a different formulation, that establishes the efficacy of this formulation (*i.e.*, the results of a single study is not enough, but is acceptable in this case because of the previous experience with Depakote). I have modified the labeling to reflect this distinction.

- Although patients aged 16-69 were treated, only four were below the age of 18. I've added a statement to reflect this to imply that efficacy in adolescents is not established. I have not included an explicit statement in this regard. I don't think one is necessary in this section, but I include such a statement in the Precautions pediatric section (see below).

7.2 Indication

The indication section is quite similar to that found in Depakote labeling. I've added the words "in adults" to emphasize that efficacy is established in adults only and the medication is indicated in the adult population only.

7.3 Warning

The warning section is identical to the warning section in the approved Depakote labeling.

7.4 Precautions

This precautions section is identical to the precautions section in the approved Depakote labeling. I recommend the following changes:

- In the Pediatric section. I recommend the addition of a paragraph right at the beginning stating that the effectiveness of DEPAKOTE ER in pediatric patients has not been established. Because of the know risks of divalproex sodium in this population (when used for other indications), the use in pediatric patients is not recommended.
- Remove all references to dosing in this section, since use in this population is not recommended.
- Move the analogous statement in the geriatric section (*i.e.*, lack of efficacy and safety) to the beginning of the section to be more consistent with the new pediatric section.

7.5 Adverse Reactions

The adverse reactions section describes the adverse dropouts from both the Depakote ER trial and also the Depakote delayed release trials. It lists the common AE's occurring at an incidence of ≥5% in Depakote ER treated patients and greater than placebo (this is similar to what is described in the delayed release labeling). It also mentions AE's occurring with delayed release in migraine, epilepsy, mania, and other populations (taken from approved Depakote delayed release labeling).

7.6 Overdosage

The overdosage section is identical to that contained in currently approved Depakote delayed release labeling.

7.7 Dosage and Administration

The dosage and administration starts out with the sub-heading "Migraine." This sub-heading is not necessary since there are no other indications for this formulation. The sub-heading can be added at a later date if new indications for the formulation emerge.

The section describes [redacted]

[redacted] This was never evaluated and may be an unnecessary [redacted]. Therefore, I believe this information should be deleted.

The section on general dosing advice is taken directly from the delayed release labeling. It recommends a lower starting dose for the elderly. However, 500mg is the only available dosage form. Therefore, I have added a statement that a lower starting dose can only be achieved by the use of the delayed release formulation. The same applies to the sentence suggesting a lower starting dose in patients who experience gastrointestinal irritation.

7.8 Patient Information Leaflet

This portion of labeling is almost identical to the leaflet contained in the approved delayed release labeling, with the exception that Depakote ER has been substituted for all occurrences of Depakote. One statement states that Depakote ER is prescribed for uses other than migraine prevention. Since it is not approved for other uses, and since off-label use is likely, I changed it to read "since Depakote ER may also be prescribed for uses other than ...."

8. Statistical Review

Dr. Kallappa Koti provided the statistical review of the single efficacy study. He concludes that the ITT data for the 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. He also concludes that the analysis of the principal secondary measure was negative and does not support the primary efficacy conclusion.

He also points out that 21.3% of subjects on Depakote ER experienced an increase in their migraine rate during the experimental phase. My calculation is comparable at 20% (24/122). However, I also note that the percentage of placebo patients experiencing a worsening during treatment was numerically much higher at 37% (43/115, p=0.0025, chi-square).

9. Conclusions

I conclude that Depakote ER is both safe and effective for the prophylaxis of migraine headaches.

10. Recommendations

Form a clinical standpoint, I recommend approval of the NDA, with appropriate changes in the labeling as described in 7, page 34 (Labeling Review), and in Appendix B - page 43 below.

I point out that there is a labeling supplement currently under review in house which will strengthen all Depakote product labeling. The results of that review will necessarily impact on the final labeling of this product, and is not reflected in the changes recommended in Appendix B.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. /S/ 8/1/00

ao 6/7/00
cc:
HFD-120
NDA 21-168
electronic copy-Katz

Appendix A - Migraine Classification Algorithm

The following algorithm is a modification of IHS criteria for the diagnosis of migraine with or without aura (1.1 and 1.2) that enable the classification of individual headaches as migraine. I shared the algorithm with the sponsor.

Classification of Individual Headaches in Migraine Studies

Controlled clinical trials in migraine typically enroll subjects with established diagnoses of migraine, with or without aura, according to International Headache Society (IHS) diagnostic criteria.[4] In acute migraine studies, subjects usually take study medication at the earliest onset of a moderate or severe migraine. Efficacy is assessed by comparing the proportion of subjects who respond to treatment at 2 hours between drug and control groups. These studies generally assume that, having enrolled migraine sufferers, headaches treated with study medication are, in fact, migraines. This may not always be the case. It is useful to verify that the actual headaches treated in these studies are migraine. This is especially important in acute migraines studies that examine the use of known analgesics. It is theoretically possible that an analgesic appears to be effective against migraine in a well designed study simply because a large number of tension headaches were treated instead.

In migraine prophylaxis studies, subjects take study medication for a period of time during the active treatment phase. Efficacy is assessed by comparing the migraine headache frequency during treatment between drug and control groups. Subjects typicaily record all headaches experienced during treatment in a headache diary. Only those headaches deemed to be migraines are included in the primary efficacy analysis. It is crucial to be able to distinguish between migraine and non-migraine headaches, and that the headaches be classified accurately and consistently across all treatment groups in order to avoid bias.

This document proposes an algorithm to classify individual headaches in migraine studies. The algorithm is based on the application of established IHS diagnostic criteria for migraine disorders. In order to classify individual headaches as migraine, the IHS criteria require some modification because some criteria either do not apply or are impractical to apply to individual headaches.

In order to understand the development of the algorithm, it is important to review the established IHS diagnostic criteria for migraine disorders. It is important to remember that the algorithm should only be used to classify headaches reported by subjects who have already met IHS criteria at study entry.

IHS criteria 1.1 for a "Migraine without Aura" diagnosis require the following:
A. At least 5 attacks fulfilling B-D

[4] Cephalalgia 1988:8 (suppl 7); 19-28.

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). In children below age 15, attacks may last 2-48 hours. If the patient falls asleep and wakes up without migraine, duration of attack is until time of awakening.

C. Headache has two of the following characteristics:
   1. unilateral location
   2. pulsatile quality
   3. moderate or severe intensity (inhibits or prohibits physical activity)
   4. aggravation by walking stairs or similar routine physical activity

D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

E. At least one of the following:
   1. history, physical, and neurological examinations do not suggest one of the disorders listed in groups 5-11 (not shown here)
   2. history and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

Criterion 1.1A does not apply to individual headaches.

Criterion 1.1B presents a problem and should not be applied to individual headaches. In an acute migraine trials, the duration of the migraine may be less than 4 hours if the episode is successfully treated with study medication. Therefore, it would be inappropriate to decide that a headache is not a migraine simply because of its short duration in such a setting. In migraine prophylaxis studies, subjects are allowed to take abortive or analgesic medications for their migraines. There again, a migraine may last less than 4 hours due to successful acute treatment. Therefore, the duration of the headache in these studies cannot be used to identify individual migraines.

Criterion 1.1C and 1.D can easily be applied to individual headaches, provided appropriate characteristics for each headache are recorded in the patient headache diary.

Criterion 1.1E is impractical to apply to individual headaches because it would require medical re-evaluation during or after each incident. Subjects have already met this criterion (or the corresponding criterion for migraine with aura) at study entry.

IHS criteria 1.2 for a "Migraine with Aura" diagnosis requires the following:

A. At least 2 attacks fulfilling B

B. At least 3 of the following 4 characteristics:
   1. one or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction
   2. at least one aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession
   3. no aura symptoms lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.

4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).

C. At least one of the following:

1. history, physical, and neurological examinations do not suggest one of the disorders listed in groups 5-11 (not shown here)
2. history and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
3. such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

Criterion 1.2A does not apply to individual headaches.

Criterion 1.2B is impractical to apply to individual headaches because it is unreasonable to collect such detailed information about the aura for each headache during a clinical trial. It seems safe to assume that subjects that experience an aura with their headaches in clinical trials have already met criterion 1.2B at study entry. Therefore, it does not appear necessary to apply 1.2B to individual headaches other than to identify whether or not an aura was present during the headache.

Criterion 1.2C is also impractical to apply to individual headaches for the same reason given for 1.1E above.

In order to apply the algorithm, it is necessary that appropriate headache characteristic data be collected in the patient diary. Table 27 lists the minimum data elements required for classification.

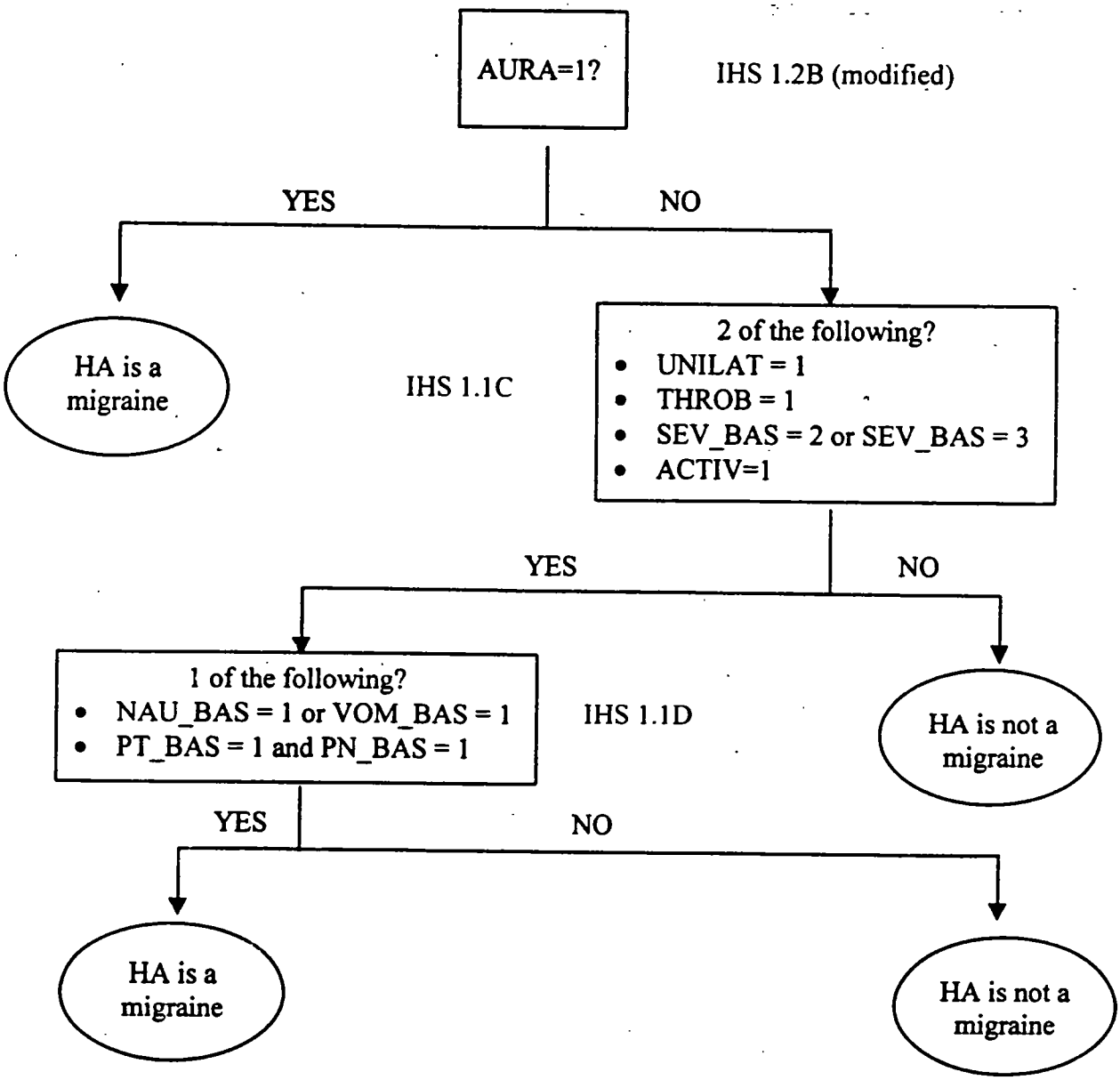
Table 27: Headache Characteristics

Variable Name	Variable Label	Format	Decode	Comment
DUR	Headache Duration	Number	Minutes or Hours	Duration of headache (may be collected data, or derived from start/stop date/time
AURA	Is aura present?	Number	0=no 1=yes	
SEV_BAS	Baseline Pain Severity	Number	0=none 1=mild 2=moderate 3=severe	Baseline pain severity prior to initial dose
NAU_BAS	Baseline Nausea	Number	0=absent 1=present	
VOM_BAS	Baseline Vomiting	Number	0=absent 1=present	
PT_BAS	Baseline Photophobia	Number	0=absent 1=present	
PN_BAS	Baseline Phonophobia	Number	0=none 1=present	
UNILAT	Is the baseline pain unilateral?	Number	0=no 1=yes	
THROB	Is pain throbbing or pulsating?	Number	0=no 1=yes	
ACTIV	Is the pain worsened by physical activity?	Number	0=no 1=yes	aggravation by walking stairs or similar activity

Taking these considerations in mind, the algorithm, based on "modified IHS criteria" is shown in Figure 5. If the headache has an aura, then it's a migraine. If there is no aura, then the headache must meet criteria 1.1C and 1.1D in order to be classified as a migraine.

Again, it is emphasized that the algorithm should only be used to classify headaches reported by subjects who have already fully met at least one of the IHS criteria at study entry.

Figure 5: Classification of Individual Headaches in Migraine Studies



Appendix B - Depakote ER Labeling

This section contains the sponsor's draft labeling, along with my recommended changes.

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