CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-168/S-004

PHARMACOLOGY REVIEW

April 24, 1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

NDA: 20-782

REC'D: 6/16/97

SPONSOR: Abbott Laboratories

DRUG: Divalproex Sodium [redacted] (Depakote [redacted] Tablets

CATEGORY: Antiepileptic

EVALUATION and RECOMMENDATION:

No preclinical pharmacology/toxicology studies were submitted to this NDA for a new formulation of Depakote, and there are no unusual excipients in the new formulation. The pharmacology/toxicology data submitted by Abbott to previous NDAs for sodium valproate (NDA 18-081, Depakene) support approval of the [redacted] dosage form and no additional studies are needed.

cc: NDA 20-782
HFD-120
HFD-120/GFitzgerald/EFisher/JWare
RLL 5/11/98
gg7

Ed Fisher, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Divalproex Sodium
PRODUCT (Brand Name):	DEPAKOTE
DOSAGE FORM:	ER Tablets
DOSAGE STRENGTHS:	250 mg and 500 mg
NDA:	20-782, 21-168 (SLR-004)
NDA TYPE:	Response to NA letter
SUBMISSION DATE:	6/26/02, 8/7/02, 11/13/02
SPONSOR:	Abbott Laboratories Inc.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISON:	DPE I, HFD 860
OND DIVISION:	HFD 120

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EXECUTIVE SUMMARY

This application intends to support the conversion of Depakote DR to Depakote ER if the Depakote ER doses are 8-20% higher than that of Depakote DR tablets. A dose conversion table is provided in the label for conversion from Depakote DR to Depakote ER tablets based on the results from the two studies submitted in this application.

RECOMMENDATION

NDA 20-782 is acceptable from the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics provided the DSI inspection results are acceptable. For the conversion from Depakote DR to Depakote ER, the adequacy of data beyond a DR dose of 3000 mg cannot be established from a pharmacokinetic point of view as only 4 subjects were enrolled at DR doses greater than 3000 mg. This judgement is deferred to the reviewing Medical Officer.

Labeling changes recommended on pages 14-16 of the review should be conveyed to the sponsor.
Labeling comment on page 17 should be conveyed to the Medical Officer.

Veneeta Tandon 11/26/02

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. 11/26/02

APPEARS THIS WAY
ON ORIGINAL

In response to the non-approval letter for NDA 20-782, the sponsor has conducted two multiple dose comparative bioavailability studies with the ER and DR formulations, one study (M00-232) in healthy subjects and the second study (M01-274) in patients with epilepsy taking concomitant AEDs. The study designs for these studies were discussed at length in meetings with the agency prior to conduct of the studies.

In both studies Depakote ER formulation taken QD was found equivalent to Depakote DR formulation taken BID or TID in terms of AUC, Cmax and Cmin at ER doses 8-20% higher than that of the DR formulation. In both studies the ER regimen was administered under fasting conditions, the morning DR regimen was also given under fasted condition, however, the latter doses were given under modified fasting conditions.

The following Table shows the results based on agency's bioequivalence criteria. Two one-sided test was performed on log transformed AUC. For Cmax and Cmin one-sided test was performed on log transformed Cmax and untransformed Cmin. The reviewer calculated log transformed 90% CI on all parameters and is reported in this Table as well. The doses evaluated are given in the Table below.

Healthy Subjects:

Regimens T vs R	Parameter	Central Value* Test (T)	Central Value* Reference (R)	Point Estimate**	Upper/Lower 95% confidence bound	90% CI
1000 mg ER vs. 875 mg DR (N=35)	AUC24	1923	1887	1.019	-	0.966-1.075
1500 mg ER vs. 1250 mg DR (N=33)	AUC24	2393	2170	1.103	-	1.068-1.139
1000 mg ER vs. 875 mg DR (N=35)	Cmax	94.01	110.2	0.853	0.892	0.814-0.892
1500 mg ER vs. 1250 mg DR (N=33)	Cmax	114.6	125.3	0.914	0.939	0.889-0.939
1000 mg ER vs. 875 mg DR (N=35)	Cmin	65.32	59.11	1.105+ range (0.53-1.96)	1.014	0.997-1.198
1500 mg ER vs. 1250 mg DR (N=33)	Cmin	82.37	66.11	1.246+ range (0.71-1.86)	1.164	1.157-1.330
* Antilogarithm of the least square means for logarithms						
** Antilogarithms of the difference of the least square mean for logarithms						
+ Ratio (T/R) of the least square means						

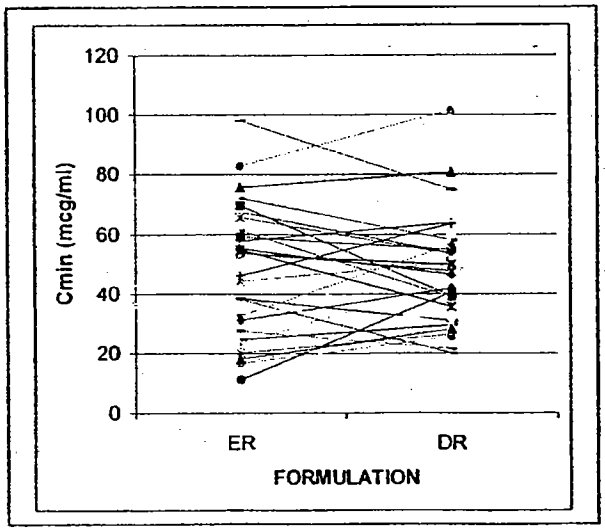
The results show that:

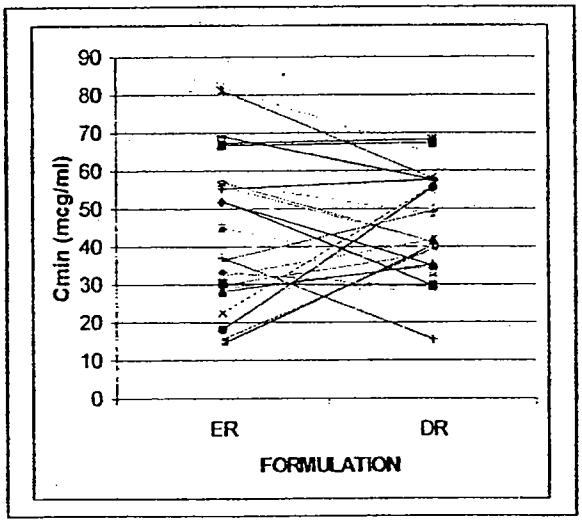
- For AUC24: Both 1000 mg ER/875 mg DR regimen and 1500 mg ER/1250 mg DR regimen are equivalent in terms of AUC as the 90% CI are within the acceptable bioequivalence limits.

Regimens T vs R	Parameter	Central Value* Test (T)	Central Value* Reference (R)	Point Estimate**	Upper/ Lower 95% confidence bound	90% CI	p-value
ER QD vs. DR Q8H (N=64)	AUC24	1551	1539	1.008 range (0.87-1.05)		0.964-1.055	0.7575
ER QD vs. DR Q8H (N=64)	Cmax	83.27	92.59	0.899 range (0.82-1.09)	0.938	0.864-0.938	0.0001
ER QD vs. DR Q8H (N=64)	Cmin	45.85 range (20.1-98.2)	44.82 range (15.5-101.4)	1.022 range (0.28-2.40)	0.950+	0.888-1.06	0.6149
* Antilogarithm of the least square means for logarithms							
** Antilogarithms of the difference of the least square mean for logarithms							
+ Ratio (T/R) of the least square means							

The results show that:

- For AUC: The ER QD regimen is equivalent to the DR TID regimen at the evaluated doses in terms of AUC, as the 90% CI on log transformed data was within the acceptable limits
- For Cmax: The ER QD regimen is equivalent to the DR TID regimen at the evaluated doses in terms of Cmax, as the protocol specified criteria of one-sided 95% upper confidence bound for the ratio of the Cmax central values were lower than 1.25 and the 90% CI calculated by the reviewer was also within the acceptable limits.
- For Cmin: The ER QD regimen is equivalent to the DR TID regimen at the evaluated doses in terms of Cmin one-sided 95% lower confidence bound for the ratio of the Cmin central values on untransformed Cmin were greater than 0.8. The 90% CI on log transformed Cmin values calculated by the reviewer were also within the acceptable limits. The stick plot for individual subject Cmin values for the ER and DR regimen is given below.





As we can see from the above table there are very few subjects (N=4) enrolled at doses higher than 3000 mg. From PK standpoint a total of 4 subjects at DR doses greater than 3000 mg may not be adequate to assess the equivalence of the DR and ER regimen for doses >3000-5000 mg.

The sponsor's survey from the Physicians Drug and Diagnosis Audit (PDDA), estimated that 80% of the adult epilepsy patients with another AED received daily doses of 2000 mg/day or less. An efficacy and safety trial (Study M88-194) conducted by the sponsor to support approval in complex partial seizures indicated that 62% of the subjects had an average daily dose in the maintenance period of 2500 mg or less, although doses up to 6000 mg/day (=91.2 mg/kg/day) were used. There were 90% subjects who averaged less that 4000 mg/day, seven subjects averaged more than 4000 mg/day (=60 mg/kg/day). The maximum epilepsy dose in the current labeling is 60 mg/kg/day.

Based on these historical data there are 20-40% of the subjects taking Depakote doses greater than 2000 mg/day. Study M01-274 in patients with epilepsy has enrolled fewer subjects at doses greater than 2000 mg/day. The dose of 3000 mg/day does seem to have adequate number of subjects, but the other doses have subjects ranging from 1-4. The adequacy of the number of subjects at the higher doses of Depakote needs to be evaluated by the reviewing Medical Officer.

Is the Sponsor's rationale for studying total concentrations of valproic acid acceptable, given the nonlinear protein binding?

The sponsor has developed an equation describing the relationship between total and free concentrations of valproic acid.

Free valproic acid plasma concentrations were calculated from the total concentration for each sample using the following equation (based on data from Study M98-938; NDA 20-593, S-006), where the % free valproate increases from about 10% at total concentrations of 50 μg/ml to 19% at total concentrations of 150 μg/ml.

$$C_{Free} = 0.0009.C_{Total}^2 + 0.0527.C_{Total}$$

Using this equation it was found out that the predicted free concentrations were not different from those derived from the analysis of total valproate levels.

For comparison of DR and ER regimens, if AUC are similar, then the two regimens should produce similar average total concentration (Cavg=AUC/24). Therefore, if the average total concentrations are similar, then average free concentrations and exposure to free drug should be similar and equivalent, irrespective of nonlinear protein binding.

ER/DR: Linear trend		0.5764
ER/DR: 3500 vs 875 mg		0.1010

*for ER AUC vs DR AUC

- The primary test for dose group and regimen interaction was not statistically significant (p=0.0645)
- A secondary test comparing the ER/DR relative bioavailability between the lowest (875 mg) and highest (3000 mg) DR dose groups was also not statistically significant (p=0.1010).
- A test for linear trend with Depakote DR dose on the ER/DR relative bioavailability was also not statistically significant (p=0.5764)
- The least square mean point estimates of ER/DR relative bioavailability of dose normalized AUC ratios for the different Depakote DR dose groups were 0.99, 0.80, 0.84, 0.96 and 0.85 for above 5 dose groups respectively.
- Looking at individual Cmins no trend was observed between dose group and low Cmins for the ER regimen.

What was the effect of concomitant antiepilepsy drugs (AED) in patients when converting from Depakote DR to Depakote ER regimen?

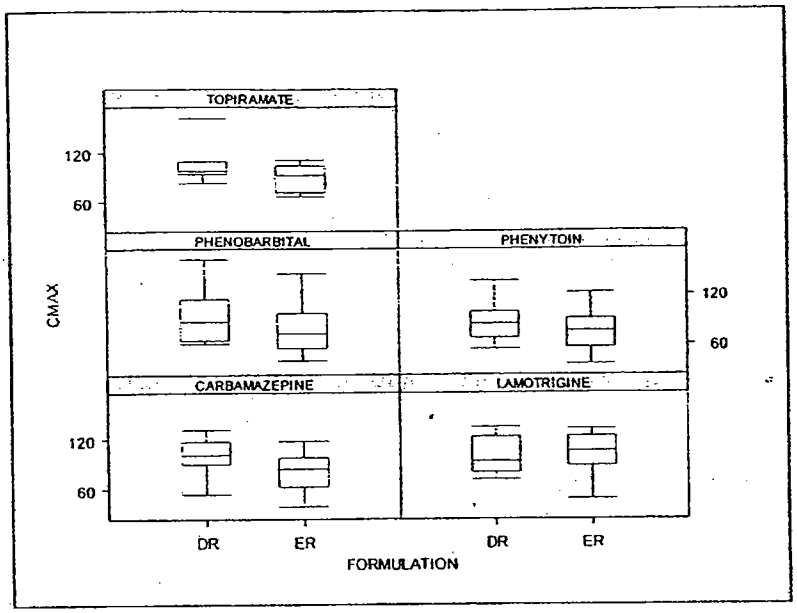
Concomitant AEDs are known to induce hepatic microsomal enzymes and may thus reduce systemic bioavailability of valproate. No specific trends could be determined in the PK parameters (AUC, Cmax and Cmin) based on coadministered AEDs. The AEDs evaluated were Carbamazepine (N=15), Topiramate (N=5), Phenobarbital (N=4), phenytoin (N=28), Lamotrigine (N=11) and Primidone (N=1). Oxcarbazepine was not evaluated.

The concomitant AED dose, frequency and the point estimate for the ER/DR relative bioavailability is shown in the following Table.

	Point Estimate	p-value	Dose (mg/day)		AED Concentration (µg/ml)			
AED			Min	Max	Min	Max	Frequency	Percent
Carbamazepine	0.79	0.0001	200	1500			15	23.4
Lamotrigine	0.93	0.2432	50	400			11	17.2
Phenobarbital	0.87	0.1493	120	250			4	6.3
Phenytoin	0.89	0.0047	150	600			28	43.8
Primidone			1000	1000			1	1.6
Topiramate	0.96	0.6782	100	400			5	7.8

*There was one subject of primidone, the subject was classified as a phenobarbital-user since primidone is metabolized to phenobarbitone after absorption.

Any particular trend is not likely to be observed, as the same enzyme inducing effect of the AED would be anticipated in both ER and DR regimen. Looking at the individual Cmin it was found that out of the 20 subjects that had lower Cmin values, 10 were on phenytoin, 5 on carbamazepine, 2 on lamotrigine, 2 on phenobarbital, and 1 on



Are the analytical methodologies for the assessment of valproic acid adequate?

Was the DSI inspection of Study M01-274 satisfactory?

The DSI inspection results are expected by the end of November. The acceptability of the study results will depend on the DSI inspection results

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

Comment to the Medical Officer:

1. *In the conversion Table 5, the BE study did not provide adequate number of subjects beyond an ER dose of 3500 mg. Only 4 subjects were enrolled at doses higher than 3500 mg. The conversion outlined in the Table beyond this dose should be made on a Clinical basis.*
   In addition to these high doses there are various interim doses (increments of 250 mg ER dose) that have not been evaluated directly, however, increments of 500 mg in the range from 1000-3500 mg has been evaluated with reasonable number of subjects in each dose group. Hence, the sponsor's proposal of adding dose increments of 250 mg up to 3500 mg ER dose in the Dose Conversion Table should be acceptable.
2. *Even though equivalence was shown between ER and DR (at AUC, Cmax and Cmin), the sponsor proposed the following statement* "Plasma valproate C_{min} concentrations for DEPAKOTE ER on average are equivalent to DEPAKOTE DELAYED-RELEASE TABLETS, but may vary across patients after conversion. . If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL) (see **Pharmacokinetics**-Absorption/Bioavailability)" *When equivalence is demonstrated such a statement is unusual.*

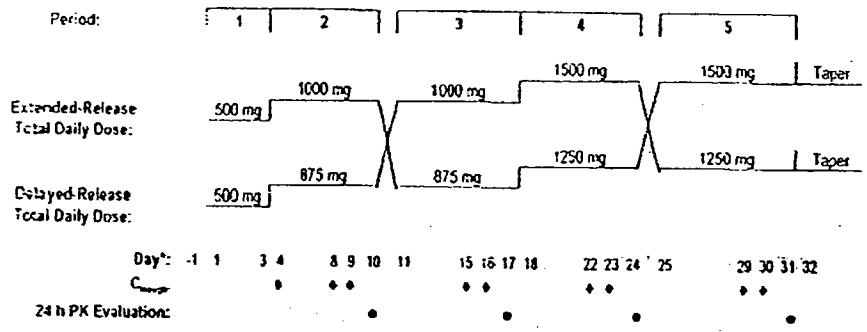
Study M00-232: *Comparison of the bioavailability of Depakote ER formulation (1000 and 1500 mg total daily dose) relative to Depakote DR formulation (875 and 1250 mg total daily dose) in healthy volunteers*

Objectives:

The primary objective of this study was a pharmacokinetic comparison of Depakote ER QD regimen to that of Depakote DR BID regimen, with larger daily doses for the ER regimen. The ratios for comparison were 8:7 and 6:5.

The study design is as follows:

Study Design	Multiple dose, titration, fasting, open label, randomized, single center, 5-period crossover design
Study Population	N=35 healthy subjects, Gender:23M &12F [Sequence 1:15M &3F, Sequence 2: 8M&9F] Age:19-55 yrs (mean 36 yrs), Weight: 59.3-105.3 kg (mean 76.4 kg), Race: 30 Caucasians, 4 Black, 1 Asian Mean age, weight and race were similar for the two dose sequences
Treatment Group	A1: Depakote ER 1000 mg QD, A2: Depakote ER 1500 mg QD, B1: Depakote DR 875 mg given as divided doses BID(500+375 mg), B1: Depakote DR 1250 mg given as divided doses BID (625+625 mg), 5-Period, 2 sequence : Equal numbers in two sequence groups as below



	Depakote ER: Lot 67-791-AA-21 for 500 mg Depakote DR: Lot 65-533-AA-21 for 125 mg, 65-526-AA-21 for 250 mg, 67-709-AA-21 for 500 mg
Dosage and Administration	1000 mg ER given as: two 500 mg tablets at AM 1500 mg ER given as : three 500 mg tablets at AM 875 mg DR given as: one 500 mg tablets at AM and 250+125 mg tablets at PM 1250 mg DR given as: 500+125 mg tablet at AM and PM Diet: -Morning doses administered under fasting conditions

Acceptance Criteria

- The range of acceptability for the ratio of the regimen central values should be 0.80-1.25 for AUC (90% CI)
- The ratio of the Depakote ER central value to that of Depakote DR central value for Cmin should be ≥0.80 (95% CI)
- The ratio of the Depakote ER central value to that of Depakote DR central value for Cmax should be ≤1.25 (95% CI)
- All these were tested at a significance level of 0.05

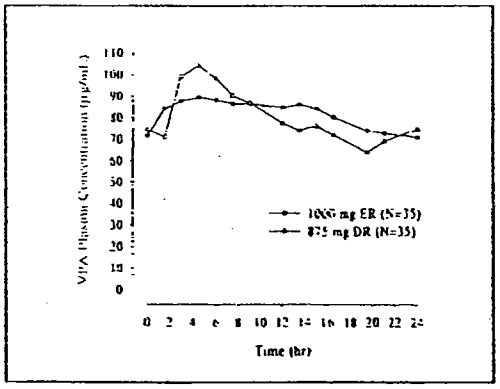
Pharmacokinetic Results:

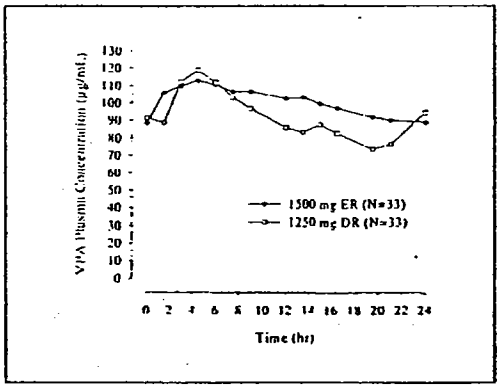
The mean pharmacokinetic parameters ± SD (%CV) are given in the following Table:

	Depakote Regimen			
PK Parameters	1000 mg ER Test (N=35)	875 mg DR Reference (N=35)	1500 mg ER Test (N=33)	1250 mg DR Reference (N=33)
AUC24 (µg.h/ml)	1970 ± 402 (20)	1920 ±355 (18)	2422 ± 397* (16)	2204 ±345 (16)
Cmax (µg/ml)	96.0 ± 18.5* (19)	112 ±18.0 (16)	116 ± 17* (15)	127 ± 19.3 (15)
Cmin (µg/ml)	65.4 ± 17.5 (27)	59.1 ± 12.9 (22)	82.2 ± 19.1* (23)	66.4 ± 14 (21)
Tmax(h)	7.7 ± 5.3 (69)	4.0 ± 1.5 (36)	6.2 ± 4.1(66)	4.5 ± 2.7 (62)
DFL	0.386 ± 0.146* (38)	0.6790 ± 0.158 (24)	0.344 ± 0.150* (44)	0.667 ± 0.171 (26)

*Statistically significantly different than reference DR regimen ($p<0.05$)

The mean pharmacokinetic profiles for the 1000 mg ER/875 mg DR regimen and the 1500 mg ER /1250 mg DR regimen are shown in the following figures:





It is interesting to note that the mean Depakote DR BID regimen profile does not show two peaks.

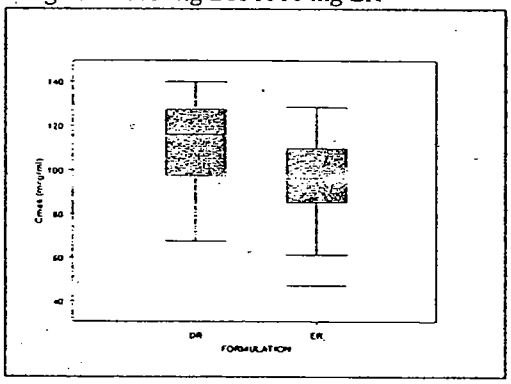
This lack of or delay of the second peak after the second dose is quite likely due to the effect of evening meals based on the sponsor's discussions. The morning dose was given after a 10 hour fast, where as the evening dose was given under modified fasting conditions with dosing 3.5 hours after a light snack and dinner 1 hour after the evening dose. The DR dosage form is an enteric coated tablet that is designed to resist dissolution in the acidic gastric environment. Therefore dissolution and absorption of valproic acid

One-sided test for Cmax:

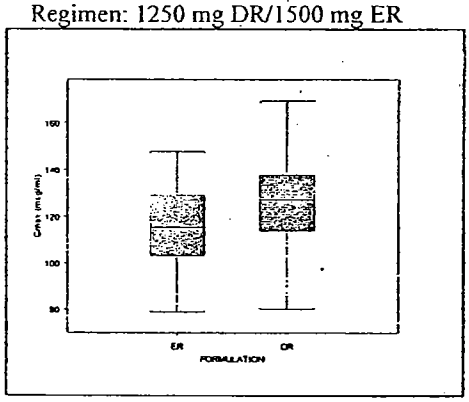
Regimens T vs R	Parameter	Central Value* Test (T)	Central Value* Reference (R)	Point Estimate**	Upper 95% confidence bound	90% CI
1000 mg ER vs. 875 mg DR	Cmax	94.01	110.2	0.853	0.892	0.814-0.892
1500 mg ER vs. 1250 mg DR	Cmax	114.6	125.3	0.914	0.939	0.889-0.939
* Antilogarithm of the least square means for logarithms						
** Antilogarithms of the difference of the least square mean for logarithms						

- The ER regimen is acceptable for Cmax based on the protocol specified criteria, as the analysis for the log-transformed Cmax showed that the 95% upper confidence bound for the ratio of the regimen Cmax central values were lower than 1.25
- The 90% CI calculated by the reviewer were also within the acceptable limits.
- The box plots showing the distribution of Cmax for the two sequences are shown below:

Regimen: 875 mg DR/1000 mg ER



Regimen: 1250 mg DR/1500 mg ER

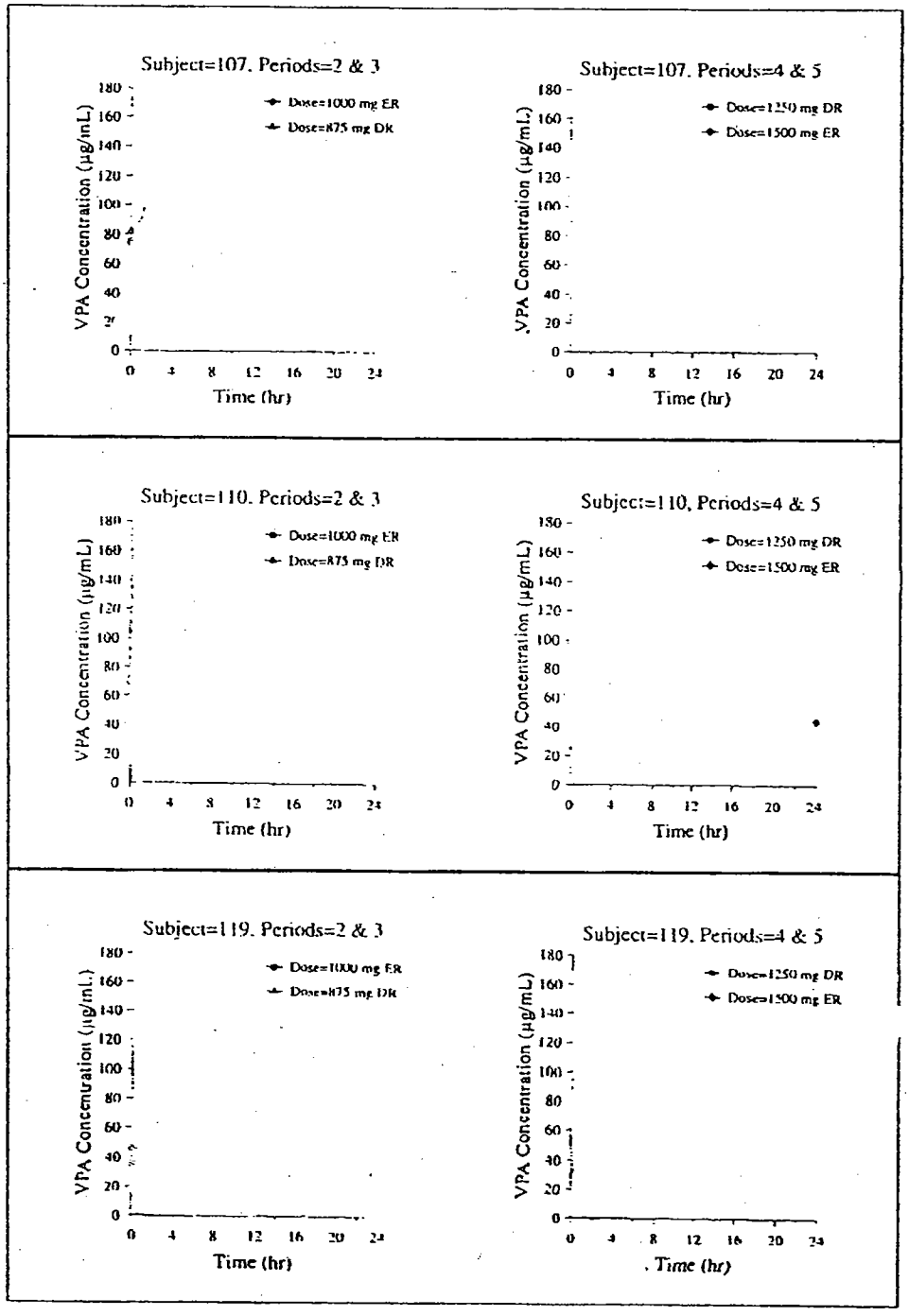


- In both regimens the ER has lower Cmax, as compared to the DR.

One-sided test for Cmin:

Regimens T vs R	Parameter	Central Value* Test (T)	Central Value* Reference (R)	Point Estimate*	Lower 95% confidence bound	90% CI
1000 mg ER vs. 875 mg DR	Cmin	65.32	59.11	1.105 (0.53-1.96)	1.014	0.997-1.198
1500 mg ER vs. 1250 mg DR	Cmin	82.37	66.11	1.246 (0.71-1.86)	1.164	1.157-1.330
* Ratio (T/R) of the least square means						

- The ER regimen is acceptable for Cmin based on the protocol specified criteria, as the analysis for the Cmin showed that the 95% upper confidence bound for the ratio of the regimen Cmin central values were greater than 0.80
- The 90% CI on log transformed Cmin as calculated by the reviewer were within the acceptable limits for the 1000 mg ER/875 mg DR regimen, but was outside the upper


Subject=107, Periods=2 & 3
Dose=1000 mg ER
Dose=875 mg DR
VPA Concentration (µg/mL)
Time (hr)
Subject=107, Periods=4 & 5
Dose=1250 mg DR
Dose=1500 mg ER
VPA Concentration (µg/mL)
Time (hr)
Subject=110, Periods=2 & 3
Dose=1000 mg ER
Dose=875 mg DR
VPA Concentration (µg/mL)
Time (hr)
Subject=110, Periods=4 & 5
Dose=1250 mg DR
Dose=1500 mg ER
VPA Concentration (µg/mL)
Time (hr)
Subject=119, Periods=2 & 3
Dose=1000 mg ER
Dose=875 mg DR
VPA Concentration (µg/mL)
Time (hr)
Subject=119, Periods=4 & 5
Dose=1250 mg DR
Dose=1500 mg ER
VPA Concentration (µg/mL)
Time (hr)

Relative Bioavailability:

- The estimates of relative bioavailability of 1000 mg ER compared to 875 mg DR regimen was (—
- The estimates of relative bioavailability of 1500 mg ER compared to 1250 mg DR regimen was —

Overall Conclusions:

- In healthy volunteers for 1000 mg ER/875 mg DR and 1500 mg ER/1250 mg DR comparisons, equivalence was established between ER and DR for AUC, Cmax and Cmin. Depakote ER DFL was lower than Depakote DR DFL.

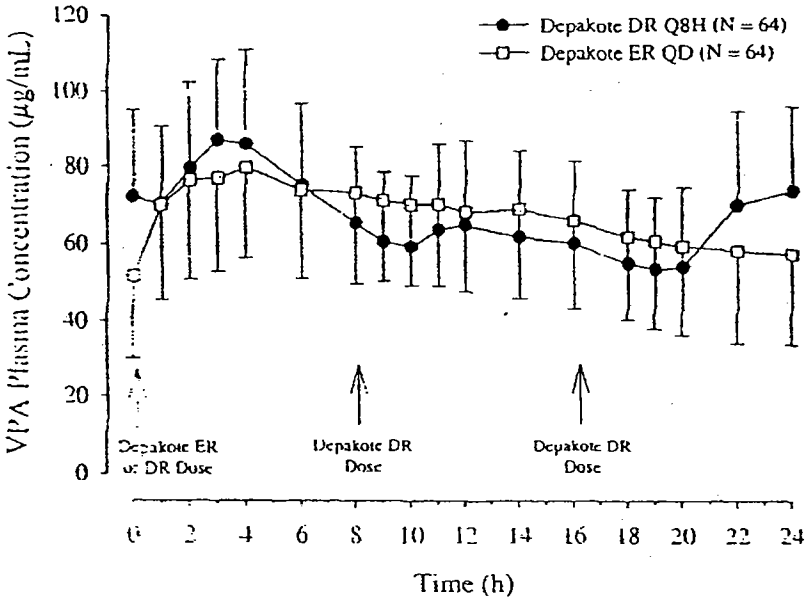
	Depakote ER: Lot 66-661-AA-21 for 500 mg Depakote DR: Lot 73-405-AA-22 for 125 mg, 73-370-AA-21 for 250 mg, 72-366-AA-21 for 500 mg
Dosage and Administration	Depakote ER total daily dose was 8-20% higher than the Depakote DR dose. Each dose was taken orally with 240 ml water, doses administered is given in the results section. DR doses ranged from 875 mg-4250 mg, however, fewer subjects were recruited at doses greater than 3500 mg. Subjects received drug (ER and DR) from Day 1-7 and 8-14 in a crossover manner All subjects received all regimens Concomitant AEDs administered to all subjects. <u>Diet:</u> -Morning doses administered after a 10 hr fast and 4 hrs fasting post dose -Midday and Evening doses in between meals as shown below Meal Schedule relative to Day 7 and 14: Regimen AM Dose Lunch Midday Dose Snack Dinner PM Dose Depakote ER 0730 1130 None 1700 2100 None Depakote DR 0730 1130 1530 1700 2100 2330 Meal Content was identical on Extensive PK sampling Days, no grape fruit juice allowed.
Sampling: Blood	<u>Trough Concentrations on Days -1, 3, 5, 6, 10, 12, and 13:</u> 10 minutes prior to dosing (0 hr) on Study <u>PK Profile for VPA on Days 7 and 14:</u> 10 minutes prior to dosing (0 hr) and 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 14, 16, 18, 19, 20, 22 and 24 hours post morning dose <u>AED Concentrations on Day –1</u>: one sample will be taken for AED concentration assay only for verifying compliance
Urine	None
Feces	None
Analysis	<u>For Valproic acid (VPA):</u> [redacted] [redacted] as internal standard <u>Lower Limits of Quantitation</u> Plasma Urine Valproic acid: [redacted] none (linear range: [redacted] Accuracy and Precision [redacted]

<u>Criteria for Evaluation</u>:

Pharmacokinetic Analysis:

Parameters evaluated were AUC24, Cmax, Cmin and degree of fluctuation (DFL) [DFL=(Cmax-Cmin)/Cavg; where Cavg=AUC_{24}/24]

The mean (SD) valproic acid plasma concentration time profile (N=64) is shown in the following figure:



The mean (SD) pharmacokinetic parameters for VPA at each dose level is given in the following Table:

Depakote Total Daily Dose	N	Pharmacokinetic Parameters AUC_{24} (µg-h/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)	T_{max} (h)	DFL
DR Formulation	64	1600.6	96.1	44.9	6.5	0.790
		(431.2)	(24.8)	(15.8)	(6.6)	(0.232)
ER Formulation	64	1630.5	86.8	45.9	7.1	0.641
		(507.5)	(24.4)	(20.1)	(5.9)	(0.270)
875 mg DR	10	1080.2	66.4	28.8	5.8	0.841
		(174.5)	(13.0)	(6.17)	(6.7)	(0.213)
1000 mg ER	10	1248.8	64.0	37.7	10.4	0.524
		(369.8)	(18.6)	(13.6)	(8.5)	(0.172)
1250 mg DR	11	1383.4	80.7	38.4	5.2	0.768
		(311.4)	(15.1)	(11.9)	(6.2)	(0.231)
1500 mg ER	11	1371.6	77.7	39.2	6.6	0.733
		(422.1)	(23.5)	(17.1)	(4.4)	(0.400)

was lower than the DR regimen. However, these dose groups had fewer subjects (1-4 in total).

- Mean DFL was lower for ER regimen at all doses.
- The test statistic for period effects was only significant for Cmax (p=0.0455) and not for the other parameters for the ER and DR comparisons.
- Total Variability (%CV) in the PK parameters is given below:

Parameter	Depakote DR Q8H (n=64)	Depakote ER QD (n=64)
AUC	27	31
Cmax	26	28
Cmin	35	44

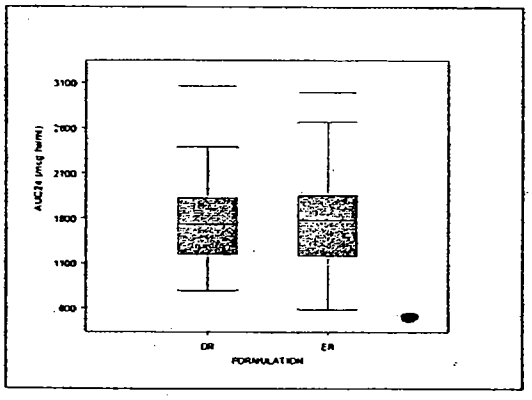
Statistical Results:

Two one-sided test for AUC24:

Regimens T vs R	Parameter	Central Value* Test (T)	Central Value* Reference (R)	Point Estimate**	90% CI	p-value
ER QD vs. DR Q8H	AUC24	1551	1539	1.008 range (0.87-1.05)	0.964-1.055	0.7575
* Antilogarithm of the least square means for logarithms						
** Antilogarithms of the difference of the least square mean for logarithms						

- Two one sided test based on log transformed AUC24 showed that the Depakote ER QD was equivalent to Depakote DR Q8H with respect to AUC24, since the 90% CI were within the 0.80-1.25 range.
- The box plots showing the distribution of AUC24 for the two formulations is shown below:

Regimen: DR Q8H/ ER QD



- The DR and ER regimen have an overlapping range of AUC24 values.

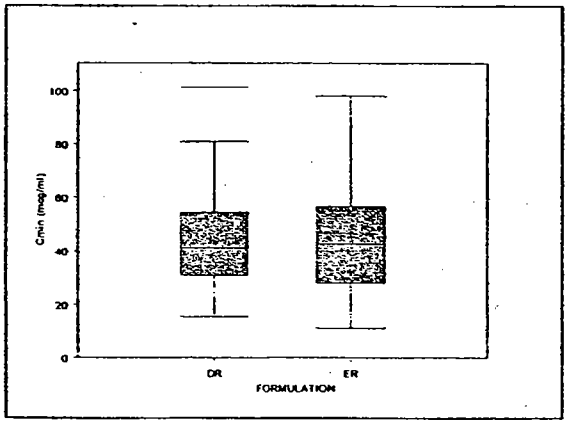
- The parameter Cmin was not log transformed by the sponsor as the data showed that the logrithm of Cmin had a less symmetric probability distribution than the untransformed data.
- The ER regimen is acceptable for Cmin, as the analysis for the Cmin showed that the 95% lower confidence bound for the ratio of the regimen Cmin central value was 0.95, which is greater than 0.80, as specified in the protocol.
- The mean Cmin for the ER was not statistically significantly different from the mean Cmin of the DR product.
- The 90% CI on log transformed Cmin as calculated by the reviewer were within the acceptable limits (0.88-1.06) for Cmin
- On Discussions with Dr. Don Schuirmann, Division of Biometrics, it was found that the sponsor's method for calculating 90% CI on untransformed data is not acceptable and methodology of LOCKE based on Fieller's theorem should be used. The program was provided by Dr. Schuirmann and was run by the reviewer. The 90% CI based on this method was 0.95-1.09 and was within the acceptable limits for BE testing. Thus equivalency in terms of Cmin was established based on all three statistical criteria, as shown in the following Table.

Statistical Tests for Cmin:

Statistical Criteria	Confidence bound or Confidence Interval
One-Sided Test (Untransformed Data) Lower 95% Confidence bound	0.95
Two-sided Test (Log-transformed Data) 90% Confidence Interval	0.88-1.06
LOCKE'S Method (Untransformed Data) 90% Confidence Interval	0.95-1.09

- The box plots showing the distribution of Cmin for the two regimen is shown in the following figure and the Stick plots show the individual differences in Cmin:

Regimen: DR Q8H/ ER QD



2125	3	4.7
2250	4	6.3
2500	4	6.3
3000	8	12.5
3500	1	1.6
4000	2	3.1
4250	1	1.6

To investigate whether the bioavailability of the Depakote ER formulation relative to that of the Depakote DR Q8H changed with the Depakote DR dose, two approaches were taken by the sponsor:

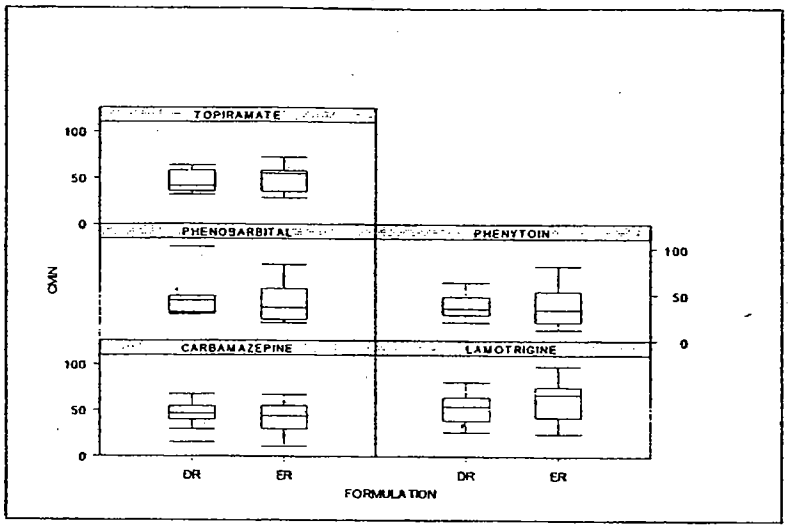
1. A regression analysis was conducted on the ratio of dose normalized ER AUC24 to DR AUC24 values. The regression model included effects for sequence and total daily DR dose. The results showed that the bioavailability of Depakote ER relative to Depakote DR was independent of the total daily Depakote DR dose (p= 0.3041)
2. An analysis was conducted on the natural logarithm of dose normalized AUC24 using an ANOVA after collapsing the total daily DR dose groups in the study into several larger dose groups. The dose groups were:
   - vi) Low: 875 mg DR; N=10
   - vii) Low intermediate: 1250-1375 mg DR; N=15
   - viii) Intermediate: 1750 mg DR; N=15
   - ix) High intermediate: 2000-2500 mg DR; N=12
   - x) High: 3000-4250 mg DR, N=12

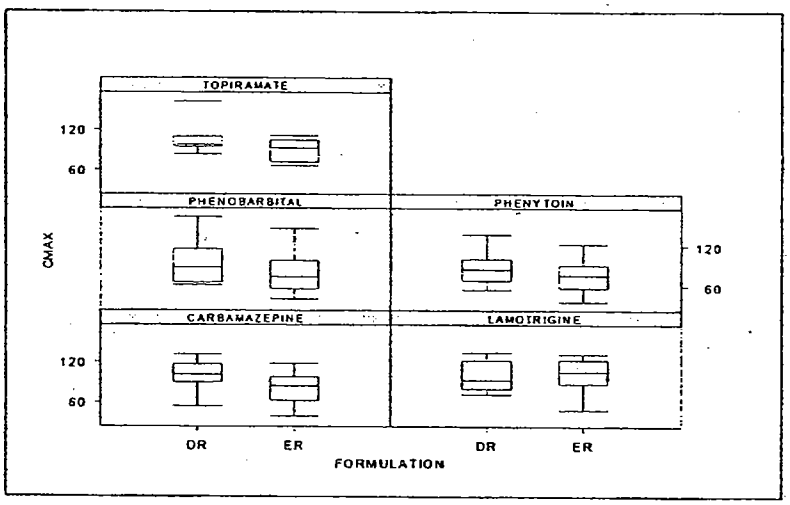
The ANOVA model had fixed effects for sequence, dose group, the interaction between sequence and dose group, regimen, period, the interaction between dose group and regimen, a random effect for subject nested within the sequence and dose group combination.

The ER/DR relative bioavailability as given by the point estimate and the p-value is given in the following Table

Parameter	Point Estimate ER/DR Relative Bioavailability	p-value
ER/DR: 875 mg dose group; N=10	0.99	0.8193
ER/DR: 1250 mg dose group; N=15	0.80	0.0001
ER/DR: 1750 mg dose group; N=15	0.84	0.0016
ER/DR: 2250 mg dose group; N=12	0.96	0.5368
ER/DR: 3500 mg dose group; N=12	0.85	0.0094
ER/DR: Linear trend		0.5764
ER/DR: 3500 vs 875 mg		0.1010

- The primary test for dose group and regimen interaction was not statistically significant (p=0.0645)
- A secondary test comparing the ER/DR relative bioavailability between the lowest (875 mg) and highest (3000 mg) DR dose groups was also not statistically significant (p=0.1010).





No specific trends could be determined in the PK parameters based on coadministered enzyme inducing AEDs. Looking at the individual Cmin it was found that out of the 20 subjects that had lower Cmin values, 10 were on phenytoin, 5 on carbamazepine, 2 on lamotrigine, 2 on phenobarbital, and 1 on topiramate. Any particular trend is not likely to be observed, as the same enzyme inducing effect of the AED would be anticipated in both ER and DR regimen.

Overall Conclusions:

- DR doses of 875-4250 mg have been compared in patients with corresponding 8-20% higher ER doses, however only 4 patients were enrolled at DR doses greater than 3000 mg.
- ER doses 8-20% higher than the DR dose were equivalent in terms of AUC, Cmax and Cmin in the dose range studied according to the statistical criteria, with the

NDA 20-782
Drug Name: Depakote[R] — (divalproex sodium ——— 500 mg tablets)
Sponsor: Abbott laboratories
Indication: Epilepsy
Type of submission: Original NDA
Date of submission: June. 16, 1997

Reviewer: Rae Yuan, Ph.D

This submission is to seek an approval on ——— formulation of Depakote (— 500 mg valproic acid equivalent) that is developed to be given either as monotherapy or adjunctive therapy to patients with various types of seizures. Currently, Depakote is marketed in 3 dosage strengths as delayed-release (DR, enteric-coated) tablets containing 125, 250, or 500 mg valproic acid equivalent per tablet. In most patients with epilepsy, Depakote is administered as BID, TID or QID regimens. The ——— formulation will allow a once-daily administration with less fluctuation in plasma concentration than the currently available tablets. Biopharmaceutic studies that are pertinent to the labeling change are included in this review.

Study1: Evaluation of the Absorption Characteristics of Two Oral Dosage Forms of Divalproex Sodium Under Multiple-Dose Conditions (M 95-376)

Background: This is a bioequivalence study that compares the bioavailability of the test formulation to the reference formulation after multiple dosing. The 500 mg DR tablet, administered q12h, was used as the reference. The test formulation is the 500 mg — tablet (——— formulation), administered as 1000 mg (2 x 500 mg) q24h. In addition, the study was also designed to evaluate the food effect on new —. formulation. Pharmacokinetic (PK) parameters from the healthy subjects (n=14) receiving — Depakote with and without food were compared with the PK from the same population who received the reference formulation without food.

Study Objective and Design: See the Attachment, Study 1.

Results:

Both formulations were administered for 6 days to reach steady state. Among the PK parameters estimated on D6, a reduced mean Cmax (85 vs. 99 ug/ml for— vs. DR respectively) and delayed mean Tmax (16 vs. 4 hr for — vs. DR respectively) of the — tablets indicated its ——— characteristics. Using steady-state AUC_{24hr} (equal sampling in the two dosing interval for DR formulation), the sponsor demonstrated that test tablets had the same extent of bioavailability as the reference tablets (90% C.I.:0.82-0.97). However, Cmin of the ——— tablets fails to meet equivalence criteria with Cmin of the delayed release tablets (90% C.I: 0.71-1.03 calculated by the reviewer; 95% C. I.: 0.67-1.07 provided by the sponsor), when both of the formulations were administered under fasting condition. Two subjects (#5 and #10, see the attachment) were found to have particularly low Cmin value from — tablets, as compared to DR tablets. Excluding the subject (#10) who has the lowest ratio of $Cmin\text{-}_{CR}/Cmin\text{-}_{DR}$, the mean value of Cmin —. was found to be within 90% confidence interval boundary with Cmin DR, though at borderline (90% C.I.: 0.81-1.02). However, FDA's policy does not allow dropping any subject for equivalence evaluation. The influence of food intake was such that the confidence intervals for AUC from the ——— ormulation with food are tighter than that from the reference formulation without food (though ——— formulation either with or without food were within the 90% confidence interval criteria, compared to the reference tablets). No statistical difference was found on the new ——— tablets from either with or without food regimen, with respect to AUC. But Cmin was significantly lower under fasting condition than fed condition. The two individuals who were identified as having low Cmin-cr/Cmin-dr ratio under fasting condition exhibited Cmin in the normal range under fed condition. The degree of fluctuation was smaller for the ——— tablets, as compared to the reference tablets

(0.52 vs. 0.62, respectively). Further, — tablets administered with food helped to reduce the degree of fluctuation, compared to under fasting condition.

Comment:

The study shows that valproic acid — given q24 passes 90% confidence interval to valproic acid DR given bid with respect to AUC, but not with respect to Cmin and Cmax under fasting condition. The two subjects who contributed to this failure to meet equivalence criteria had lower concentration from — tablet than that from DR tablet throughout 24 hr sampling interval, which resulted in lower Cmin, Cmax and AUC in —, than in DR. Moreover, Cmin and AUC of — product from these subjects under the fed condition were within the average range as other subjects. Therefore, the lower Cmin under fasting condition from these subjects is not likely due to an experimental error, rather a formulation performance. The difference found in — pharmacokinetic parameters under fasting condition and fed condition may be caused by the food effect on the transit time, pH change or motility change in the GI system.

During the review, the importance of Cmax and Cmin for efficacy and toxicity of this drug was discussed with the medical officer. It was concluded that the lowered Cmax of this ———— product, compared to that of delayed release product may not lead to severe clinical consequences. Although the trough concentration in this study is above the minimum effective concentration (40 ng/ml) proposed in literature (Individualizing Drug therapy—practical Applications of Drug Monitoring, Vol. 2, 1981), it is believed that maintenance of trough concentration at or above the trough levels produced by DR product is essential to be assured of clinical efficacy. Therefore, although the extent of availability from — product is similar to DR product, the — product fails to achieve trough levels produced by DR product.

Study2: Comparison of the bioavailability of three divalproex sodium regimen in patients concomitantly receiving enzyme inducing antiepileptic medications. (M 95-401)

Background: Patients with epilepsy often require more than one medication for adequate control of seizures. The commonly prescribed medications for these patients, such as phenytoin, phenobarbital or carbamazapine, are known to be potent enzyme inducers, which may reduce the systemic exposure to valproic acid. This 3-period crossover study was to compare the effects of these enzyme inducers on the systemic bioavailability of —, vs. DR formulation in 24 patients (details in the Attachment, study 2). It should be noted that some patients in this study received — formulation as bid dosing.

Study Object and Design: See the Attachment

Results: The control-release formulation administered either once or twice daily was equivalent, with respect to AUC_{24hr}, Cmax, and Cmin to the marketed Depakote which was administered qid to the same total daily dose. The enzyme inducers, therefore, had similar effects on the ———— formulation as they did on the already-marketed formulation.

Comments:

(1) The study did not evaluate the effect of AED (anti-epileptic drug) on the control-release formulation PK per se, because there was no control group (which did not take AED) in the study. However, the study did show that under the influence of AED, the control-release formulation and the marketed formulation were equally bioavailable.

(2) The study included only two patients on phenytoin (both receiving 300 mg, bid) and two patients on phenobarbital (one receiving 150 mg tid, one receiving 30 mg QHS), while the rest of the 20 patients were all on carbamazepine (at various dose). Therefore, the AED in this study should probably be refered to as carbamazepine treatment

(3) This study demonstrates that Cmin of — is equivalent to that of DR in epileptic patients, using valproic acid as an adjunct agent. However, valproic acid has also been approved as monotherapy in patients who have not been exposed to epileptid drugs. Thus as indicated in the above study, this — product may not achieve the desired trough concentrations when used as monotherapy.

Study3: Evaluation of the Absorption Characteristics of Three Oral — Dosage Forms of Divalproex Sodium Versus an Intravenous Sodium Valproate Formulation (M95-414)

Background: In the process of developing a hydrogel-based — formulation of depakote that allows once daily administration, the sponsor investigated absolute bioavailability of the — formulation and the absorption properties by exploring the in vivo-in vitro correlation.

Study Object and Design: See the Attachment.

Results: A level A-type correlation of in vivo absorption rate and in vitro dissolution rate was established. The study showed that the absolute bioavailability of the — formulation was 92% and Tmax occurred at 16 hrs after dosing. This corresponded to the complete dissolution, which was reached at 18 hr in vitro. Using Wagner-Nelson method and mixed effect model, the mean percent absorbed was found to be highly (R^2=98%) linearly correlated to the in vitro percent dissolved, with a slope approximately equal to unity.

The dissolution specifications proposed by the sponsor are as follows:

USP Apparatus II (paddle) at —
Medium: —

Specifications: .

Time	Lower limit (% of dissolved)	Upper limit (% of dissolved)
3	n.a.	—
9	—	—
12	—	—
18	—	n.a.

Comment:

The study adequately assessed the absolute bioavailability and in vitro dissolution/in vivo absorption correlation. No "dose dumping" phenomenon is expected from the — tablets.

Other Studies:

In addition to the above reviewed studies, the sponsor also submitted:
study M95-272, a pilot single dose study on 4 — tablets including the to-be-marketed (TBM) formulation;
study M95-288, a multiple dose/nonfasting BE study comparing the TBM formulation with morning or evening dosing regimen to the DR formulation (no difference was found for a.m. or p.m. regimen);

study M95-330, a single dose/nonfasting BE study comparing 2 — formulation including the TBM; and *study M96-479*, a single dose BE study comparing TBM formulation with two additional — formulations. See the attachment for all the biopharmaceutic studies submitted.

COMMENTS to be sent to the sponsor:

1. The proposed controlled-release Depakote 500 mg tablet were shown to be equivalent to the already marketed delayed-released tablets, only with respect to AUC, but not to Cmax or Cmin. Based on the individual data analysis, it appears that the failed equivalence in Cmin is due to the formulation performance. Though the concentration-effect relationship has not be established, the lower Cmin of the — product may result in inadequate efficacy of the product.

2. In the study (M95-401) which evaluated the effect of AED on —formulation bioavailability, the only AED that is adequately investigated is carbamazepine. This information should be reflected accordingly in the labeling.

3. The sponsor proposed the methods and specification for Depakote — However, using IVIVC (in vitro dissolution and in vivo absorption correlation), it is estimated that the difference in the concentrations predicted from the lower boundary and upper boundary of the dissolution specification is more than __ . This range is too wide to be acceptable, according to FDA guidance on *dissolution testing of immediate release solid oral dosage forms*.

RECOMMENDATION:

The AUC of — is equivalent to that of DR. The Cmax of — product is lower than DR formulation, which is acceptable since it was one of the proposed objectives of this — formulation. However, the lowered Cmin of — failed to meet equivalence criteria to Cmin of DR. Therefore, the valproic acid controlled-release product is not considered equivalent to the delayed-release product. Please convey the COMMENTS 1-3 to the sponsor.

Primary Reviewer: Rae Yuan, Ph.D Rae — 4/10/98

Team Leader: Chandra Sahajwalla, Ph.D Chandra 4/10/98

Date of Signature:

CC list: HFD-120, HED-860 (Sahajwalla, Malinowski, Yuan), CDR (Barbara Murphy)

Regimen A: [redacted] formulation 1000 mg q24h administered under fasting conditions (test)

Regimen B: [redacted] formulation 1000 mg q24h administered 30 minutes after breakfast was served (test)

Regimen C: Depakote enteric coated tablet 500 mg q12h administered under fasting conditions (reference)

Eighteen healthy subjects were randomly assigned in equal numbers to three sequences of the regimens:

Regimens		
Period 1	Period 2	Period 3
A	C	B
B	A	C
C	B	A

A schedule of the doses and meal times for the three regimens follows.

Regimen	Formulation	Time of Dose	Breakfast	Lunch	Dinner	Snack
A	Test [redacted]	6:00 a.m.	8:00 a.m.	12 N	8:00 pm	10:30 pm
B	Test [redacted]	6:00 a.m.	5:30 a.m.	12 N	8:00 pm	10:30 pm
C	Reference DR	6:00 a.m. 6:00 p.m.	8:00 a.m.	12 N	8:00 pm	10:30 pm

∴ DR = Delayed Release (enteric-coated).

Subjects: The ages of the 11 male and three female subjects completing the study ranged between 19 and 51 years (mean, 27 years), their heights ranged from 63 to 74 inches (mean, 69 inches), and their weights ranged from 120 to 200 pounds (mean, 161 pounds).

Blood Sampling: Blood samples (7 mL) were taken at 0, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 121, 122, 123, 124.5, 126, 127.5, 129, 130.5, 132, 133, 134, 135, 136.5, 138, 139.5, 141, 142.5 and 144 hours after the first dose of each period.

Analytical Methodology: Plasma samples were analyzed for valproic acid using a [redacted] method with [redacted]

 Study 1 (M95-376) +

Summary

Title: Evaluation of the Absorption Characteristics of Two Oral Dosage Forms of Divalproex Sodium Under Multiple-Dose Conditions

Objective: The objective of the study is a multiple-dose evaluation of the bioavailability and plasma concentration versus time profile of valproate from a new oral tablet formulation of divalproex sodium under fasting and nonfasting conditions versus those of a commercially available divalproex sodium tablet formulation (Depakote®, Abbott Laboratories) under fasting conditions. A secondary objective of this study is to evaluate the bioavailability and plasma concentration versus time profile of valproate from the new formulation of divalproex sodium under fasting versus nonfasting conditions.

Investigator: [redacted]

Formulations: The formulations administered were as follows.

1. Divalproex sodium [redacted] tablets (test), NPRO 6980N, Lot 10-263-AR-04, 500 mg valproic acid equivalents. Potency: 102.9% of label claim.

2. Divalproex sodium delayed release (enteric-coated) tablets (Reference, same as Depakote, Abbott Laboratories) List 6215, Lot 09-460-AA-21. Potency: 99.1% of label claim.

Dosing Dates: The first days of dosing of the respective periods were January 19, February 4 and February 20, 1996, respectively.

Study Design: This was a multiple-dose, open-label, three-period, randomized, complete crossover study. In each period, a six day regimen was administered with a minimum of 16 days separating the first doses of consecutive periods. The three regimens were:

The assay method was the same as that used in previous divalproex sodium studies.

Pharmacokinetic Analyses: Pharmacokinetic parameters were estimated by noncompartmental techniques. The peak observed concentration (C_{max}), time elapsed to peak (T_{max}), and minimum observed concentration (C_{min}) of the last 24 hours (Day 6) of each period were obtained directly from the data. If C_{max} for the reference occurred after the second dose of Day 6, T_{max} was taken to be the time since the second dose rather than the time from the first dose. AUC_{0-24} is the area under the plasma concentration-time curve for the 24 hours following the morning dose on Day 6 as computed by the linear trapezoidal rule. Degree of fluctuation (DFL) is defined as $(C_{max} - C_{min})/C_{avg}$, where $C_{avg} = AUC_{0-24}$ divided by 24 hours.

Results =

Regimen	Mean (Standard Deviation), n=14				
	T_{max} (hr)	C_{max} (ug/mL)	C_{min} (ug/mL)	AUC_{0-24} (ug·hr/mL)	DFL
A	13.6 (6.3)*	80.5 (18.6)*	48.2 (17.0)	1592 (402)*	0.523 (0.231)
B	15.9 (4.5)*	85.0 (12.5)*	55.1 (13.3)	1709 (276)	0.432 (0.127)*
C	3.6 (0.9)	99.4 (15.7)	54.1 (13.1)	1789 (332)	0.623 (0.160)

* Statistically significantly different from Regimen C.
Regimen A: Divalproex Sodium — 2x500 mg once daily, fasting.
Regimen B: Divalproex Sodium — 2x500 mg once daily, nonfasting.
Regimen C: Depakote Tablet: 500 mg twice daily, fasting.

Two One-Sided Test Procedure for Equivalence Assessment, Day 6 AUC

Test	Reference	Relative Bioavailability	
		Point Estimate	90% Confidence Interval
A	C	0.891	0.817 - 0.971
B	C	0.970	0.890 - 1.058
A	B	0.918	0.842 - 1.001

90% C.I. of Cmin (A,C)

.672 = μ − 2.16 SE
1.067 = μ + 2.16 SE
.395 = 2 × 2.16 SE
SE = 0.0914
μ = 0.8695

$t_M = 0.868 - 1.771 \times 0.0914 = 0.707$

$t_M = 0.868 - 1.771 \times 0.0914 = 1.03$

Ratio of Day 6 C_{max} Central Values

Regimens Tests:Reference	Point Estimate	95% Confidence Interval
A:C	0.811	0.742-0.887
B:C	0.861	0.788-0.941
A:B	0.942	0.862-1.030

Ratio of Day 6 C_{min} Central Values

Regimens Tests:Reference	Point Estimate	95% Confidence Interval
A:C	0.847	0.672-1.067
B:C	1.026	0.814-1.293
A:B	0.825	0.655-1.040

90 % (0.707-1.031)

Figure 1. Mean Plasma Valproic Acid Concentrations for Day 6 Following a 1000 mg Dose Once Every 24 Hours (Regimens A and B) or a 500 mg Reference Dose Once Every 12 Hours (Regimen C)

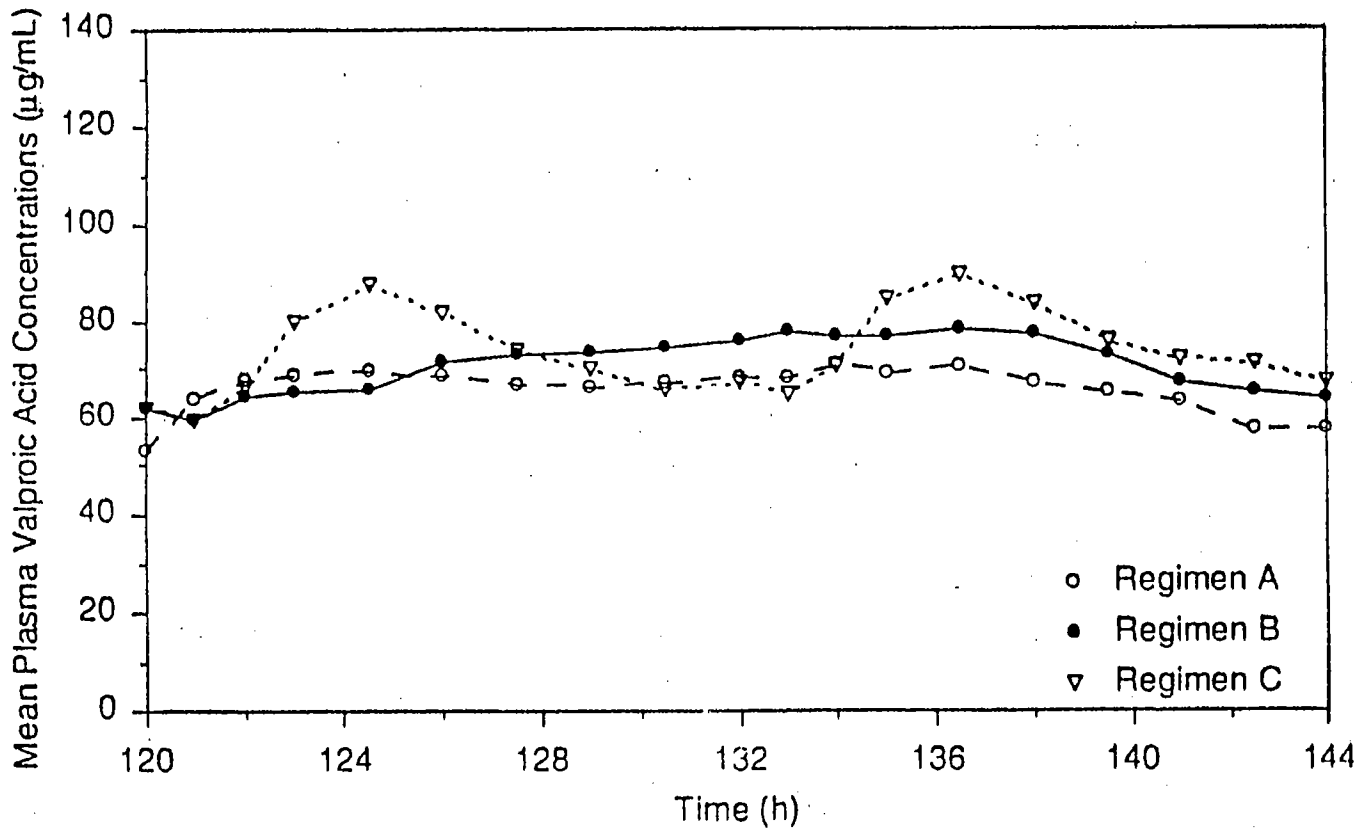


Table 11. Individual Valproic Acid C_{max} Values, Ratios, and Differences on Day 6 for Regimens A, B, and C

Untransformed C_{max} (µg/mL)

	C_{max}			Ratio			Difference		
Subject #	A	B	C	A:C	B:C	A:B	A-C	B-C	A-B
1									
2									
3									
4									
5									
6									
8									
9									
10									
12									
13									
14									
16									
18									
N	14	14	14	14	14	14	14	14	14
Mean	80.5	85.0	99.4				-18.9	-14.4	-4.5
Geom. Mean	78.4	84.1	98.2	0.80	0.86	0.93			
Median	79.7	83.2	99.0	0.81	0.84	0.96	-20.8	-15.3	-4.0
SD	18.6	12.5	15.7				12.2	12.6	15.9
CVs	23.2	14.7	15.8						
Minimum	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Maximum	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Subjects 7,11,15,17 missed at least one period. Their data are not included in any statistical analysis.

Regimen A: test formulation, fasting
Regimen B: test formulation, nonfasting
Regimen C: Depakote, fasting, (REFERENCE)

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Table 13. Individual Valproic Acid C_{min} Values, Ratios, and Differences on Day 6 for Regimens A, B, and C

Untransformed C_{min} (µg/mL)

	C_{min}			Ratio			Difference		
Subject #	A	B	C	A:C	B:C	A:B	A-C	B-C	A-B
1	[redacted]								
2									
3									
4									
5									
6									
8									
9									
10									
12									
13									
14									
16									
18									
N	14	14	14	14	14	14	14	14	14
Mean	48.2	55.1	54.1				-5.9	1.1	-7.0
Geom. Mean	43.9	53.7	52.6	0.83	1.02	0.82			
Median	50.3	52.6	55.2	0.93	0.92	0.98	-3.4	-4.7	-0.7
SD	17.0	13.3	13.1				14.8	9.0	16.2
CV%	35.3	24.2	24.2						
Minimum									
Maximum									

Subjects 7,11,15,17 missed at least one period. Their data are not included in any statistical analysis.

Regimen A: test formulation, fasting
Regimen B: test formulation, nonfasting
Regimen C: Depakote, fasting, (REFERENCE)

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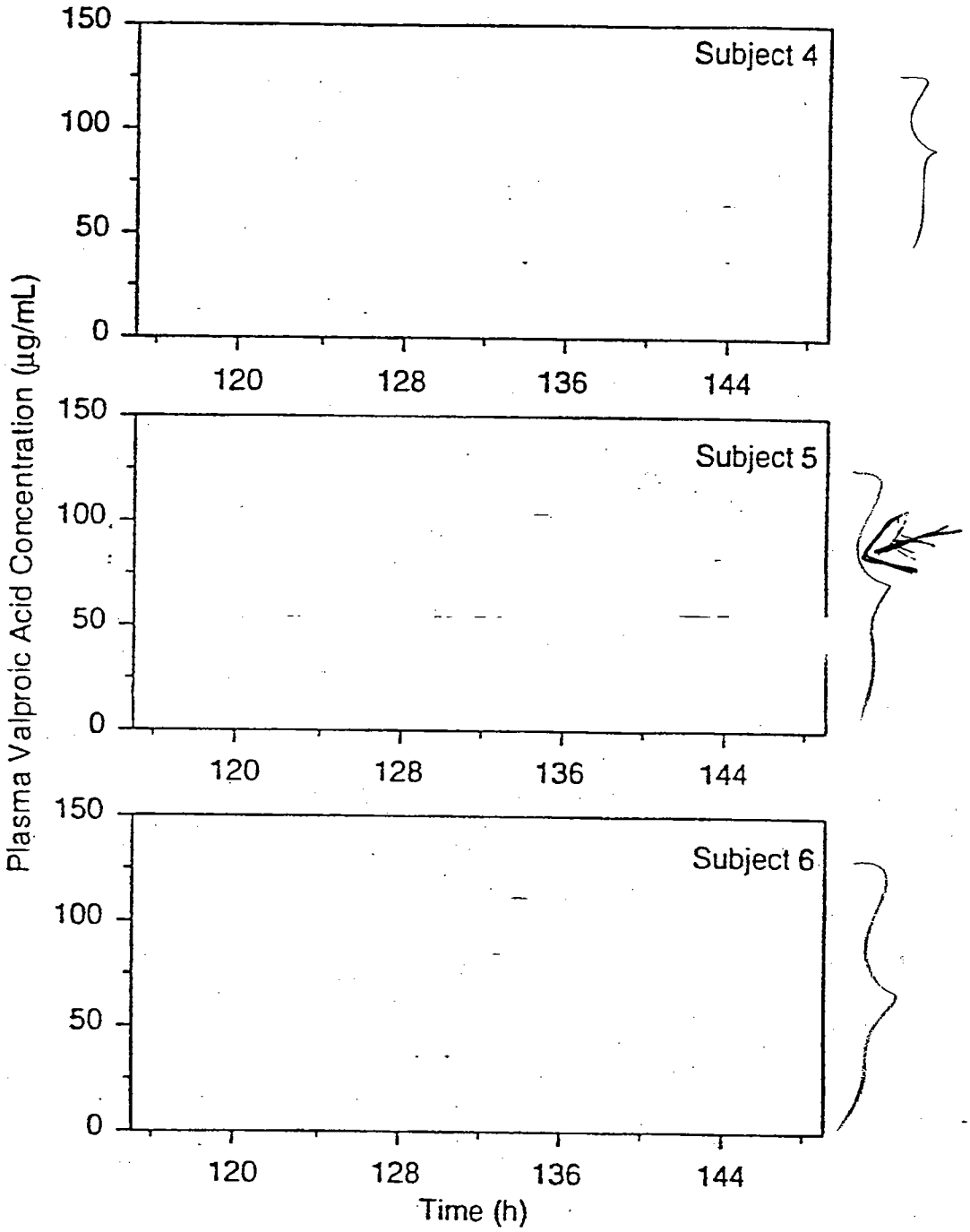
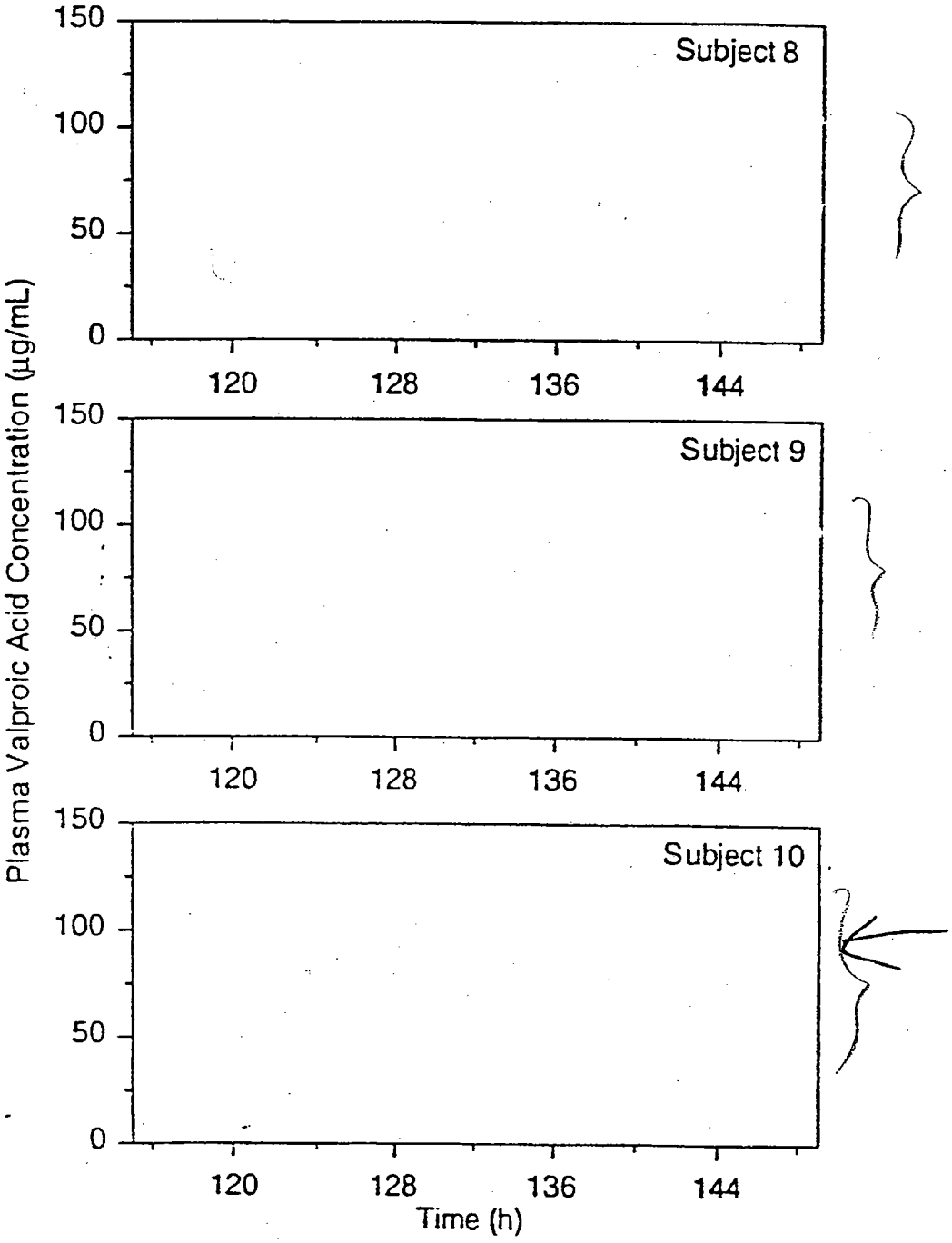
Appendix E

Individual profiles



- o Regimen A, test formulation, fasting
- • Regimen B, test formulation, nonfasting
- ▽ Regimen C, Depakote, reference



o Regimen A, test formulation, fasting
• Regimen B, test formulation, nonfasting
▽ Regimen C, Depakote, reference

Study 2 M95-401 #

Summary

Title: Comparison of the bioavailability of three divalproex sodium regimens in patients concomitantly receiving enzyme inducing antiepileptic medications (Protocol M95-401)

Investigator: The principal investigator was _____ _____. The study drug was administered between February 12, and March 24, 1996.

Study Design: This was an open-label, multiple dose, randomized, three-period, crossover study of three regimens of divalproex sodium in 24 epileptic patients who were otherwise healthy. In addition to divalproex sodium, the patients were also receiving antiepileptic drugs that are known to induce hepatic microsomal enzymes (e.g., carbamazepine, phenytoin or phenobarbital). During the two weeks preceding the study, divalproex sodium total daily doses were adjusted so that they could be divided by 4 using 250- or 500-mg tablets and were given in a BID regimen. On Study Day 1, patients were randomly divided into six groups of equal size and each group received one of the six sequences of the following three regimens:

Regimen A: Divalproex sodium _____ tablet, Formulation B, NPRO 6980N, Lot 10-263-AR-04, supplied in 500 mg dosage strength (potency: 102.9% of label claim), administered on a once daily basis with the dose equal to the patient's current total daily dose of divalproex sodium.

Regimen B: Divalproex sodium _____ tablet, Formulation B, NPRO 6980N, Lot 10-263-AR-04, supplied in 500 mg dosage strength (potency: 102.9% of label claim), administered every 12 hours with each dose equal to half of the patient's current total daily dose of divalproex sodium.

Regimen C: Divalproex sodium tablet (Depakote) in 250 mg (Lot 09-500-AA-21; potency: 99.1% of label claim) and 500 mg (Lot 09-503-AA-21; potency: 103.5% of label claim) dosage strengths, administered every six hours with each dose equal to one-fourth of the patient's current total daily dose of divalproex sodium.

In the first period (Study Days 1-14), one third (8) of the patients were assigned Regimen A, one third (8) of the patients Regimen B, and one third (8) of the patients Regimen C. In the second (Study Days 15-28) and third (Study Days 29-42) periods, the patients were crossed over without an intervening period to receive the assigned regimens such that all patients received all three regimens (Regimens A, B, C) upon completion of the study. The patients received each regimen for 14 consecutive days. All doses were taken orally with 120 mL of water under non-fasting conditions. Throughout the study, administration of the enzyme inducing antiepileptic drugs was kept the same.

Blood Samples and Analytical Methodology: Seven (7) mL blood samples were collected from each patient on Study Days 14, 28, and 42 just prior to morning dosing (0 hour) and at 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 13.5, 15, 16.5, 18, 19.5, 21, 22.5 and 24 hours after the 6:00 a.m. dose. In addition, samples were collected from each patient just prior to the 6:00 a.m. dosing on Study Days 13, 27, and 41.

[redacted]

Data Analysis: Pharmacokinetic parameters for VPA (C_{max}, C_{min}, AUC, and Degree of Fluctuation (DFL)) were determined for the 24 hours of Day 14 of a regimen using standard noncompartmental methods. An analysis of variance (ANOVA) was performed for C_{min}, logarithm of C_{max}, logarithm of AUC and DFL with effects in the model for other antiepeliptic drug (AED), subjects nested within other AED, period and regimen. Preliminary ANOVAs were performed with effects from additional sources in the model, but these were found to be of little or no importance. The additional sources of variation considered were: carry-over from regimen of the preceding period, interaction between other AED and period, and interaction between other AED and regimen. The effects for subjects were random, and all other effects were fixed. Within the framework of the ANOVA, each of the [redacted] tablet regimens was compared to the reference Depakote q6h regimen by a test on the relevant contrast in the regimen effects, with each comparison conducted at significance level of 0.05. In the framework of the ANOVA for the

average AUC values obtained following the administration of the three regimens were similar. The difference between Regimen B and the reference regimen was far from statistically significant for AUC; however, the difference between Regimen A and the reference regimen was marginally significant ($p=0.060$). For C_{min}, the mean for Regimen B was statistically significantly higher than the mean of Regimen A ($p=0.043$) and marginally significantly higher than that of the reference regimen ($p=0.087$). The difference between Regimen A and the reference regimen with respect to C_{min} was far from statistically significant. As expected, the mean DFL tended to be lower with the controlled-release formulation (Regimens A and B) than with the reference regimen. Both Regimen A and Regimen B were statistically significantly different from the reference for DFL ($p=0.024$ and $p<0.001$).

As shown below, the two one-sided tests procedure revealed that Regimens A and B met the equivalence criterion for AUC since the 90% confidence intervals for bioavailability of Regimens A and B relative to that of Regimen C were within the 0.80-1.25 range.

Table 1. Demographic Data and Dose Information from Patients Enrolled in Study M95-401

Patient Number	Race	Sex	Age (yr)	Height (cm)	Weight‡ (kg)	VPA Dose#	Sequence	Other AED		
								Compound	Dose#	Regimen
101	Caucasian	M	27	175.3	76.7	2000	ABC	Carbamazepine	1000	tid
102	Caucasian	F	27	167.6	87.1	2000	BCA	Carbamazepine	1400	tid
103	Caucasian	F	34	160.0	64.4	1000	ACB	Carbamazepine	400	bid
104†	Caucasian	M	36	182.9	62.1	1000	BAC	Carbamazepine	500	tid
105	Caucasian	M	27	181.6	86.2	1000	CBA	Carbamazepine	600	tid
106	Caucasian	F	46	166.4	91.6	3000	CAB	Carbamazepine	400	bid
107	Black	M	26	179.1	75.8	1000	BCA	Carbamazepine	800	bid
108	Caucasian	F	36	172.7	61.7	1000	CBA	Phenytoin	300	bid
109†	Caucasian	F	18	157.5	75.8	1000	CAB	Carbamazepine	900	tid
110	Black	F	19	162.6	74.8	1000	BAC	Carbamazepine	800	bid
111	Caucasian	M	32	165.1	73.5	1000	ACB	Carbamazepine	900	tid
112	Caucasian	F	33	165.1	53.5	2000	ABC	Carbamazepine	1000	tid
113	Caucasian	M	30	172.7	76.7	1000	CBA	Carbamazepine	1200	tid
114	Caucasian	F	31	157.5	65.3	2000	ABC	Carbamazepine	1800	tid
115	Caucasian	M	20	176.5	64.9	1000	CAB	Carbamazepine	600	tid
116	Caucasian	F	21	162.6	67.6	1000	ACB	Phenytoin	300	bid
117	Caucasian	F	32	157.5	55.8	1000	BCA	Carbamazepine	800	tid
118	Caucasian	M	22	182.9	74.8	1000	BAC	Carbamazepine	400	bid
119	Black	F	29	152.4	58.1	1000	BCA	Carbamazepine	1800	bid
120	Black	M	21	176.5	88.5	1000	CAB	Carbamazepine	600	tid
121	Caucasian	M	29	175.3	51.7	1000	ACB	Phenobarbital	150	tid
122	Caucasian	F	22	152.4	44.5	1000	BAC	Phenobarbital	30	QHS
123	Black	M	31	171.5	83.0	2000	ABC	Carbamazepine	1200	tid
124	Caucasian	M	20	181.6	60.3	2000	CBA	Carbamazepine	1200	tid
Mean			28.0	168.9	69.8					
SD			6.5	9.2	13.0					
Min			19.0	152.4	44.5					
Max			46.0	182.9	91.6					

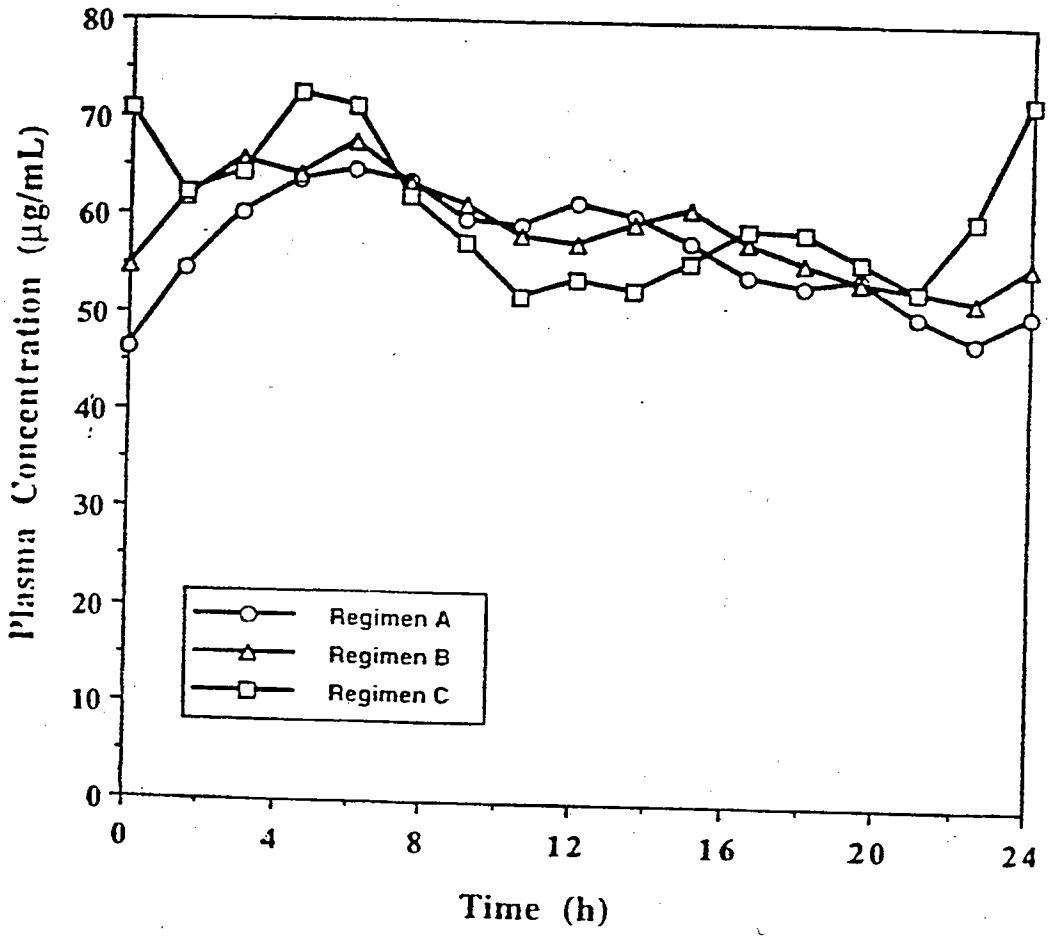
† Patients 104 and 109 withdrew from the study prematurely and were not included in the summary statistics.
# Total daily doses (mg)
‡ Weights at screening

Results:

Regimens Test vs Reference	Relative Bioavailability: Test to Reference Estimate*	90% Confidence Interval
A vs C	0.944	0.898-0.993
B vs C	0.981	0.933-1.031

* Antilogarithm of the difference of the least squares means for logarithms.

Figure 1. Average (N=22) Steady-State Plasma Concentrations of VPA Obtained after Receiving Three Valproate Regimens (Linear Scale)



Regimen A: Divalproex sodium — tablets, QD regimen.
Regimen B: Divalproex sodium ⌣ tablets, BID regimen.
Regimen C: Depakote tablets, Q6H regimen.

VPA Pharmacokinetics

The Day 14 individual pharmacokinetic parameters of VPA are listed in Tables 5, 6 and 7 for Regimens A, B and C, respectively, and the summary statistics are listed below.

	C_{max} µg/mL	C_{min} µg/mL	T_{max} h	AUC_{0-24} µg•h/mL	DFL	CL/F L/h
Regimen A: CR Tablet, QD						
Mean	71.4	39.5	10.3	1366	0.59	1.03
SD	17.5	15.4	5.8	376	0.27	0.40
Min	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Max	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Regimen B: CR Tablet, BID						
Mean	71.[illegible]	45.6	7.0	1418	0.46	0.98
SD	1[illegible]	14.1	5.3	382	0.16	0.35
Min	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Max	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Regimen C: Depakote, QID						
Mean	82.8	41.0	8.8	1440	0.71	0.97
SD	21.8	14.3	8.0	384	0.20	0.37
Min	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Max	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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DEPAKOTE (ABBOTT-50711)
STUDY M95-401
R&D/96/393

APPENDIX D.7

95% Confidence Intervals for Ratio of the Cmin Means

VARIABLE	TEST REGIMEN*	REFERENCE REGIMEN*	N	ESTIMATE OF TEST MEAN	ESTIMATE OF REFERENCE MEAN	ESTIMATE OF RATIO OF MEANS	95% CONFIDENCE INTERVAL
Cmin (mcg/mL)	A	C	22	40.137	40.782	0.984	0.815 - 1.186
Cmin (mcg/mL)	B	C	22	45.452	40.782	1.115	0.992 - 1.269

* Regimen A: Divalproex sodium CR tablets once a day.
Regimen B: Divalproex sodium CR tablets twice a day.
Regimen C: Depakote (REFERENCE).

To obtain 90% C.I. of A to C Cmax (Adjusted)

$0.796 = \mu - 2.069\,SE$
$0.903 = \mu + 2.069\,SE$
$0.107 = 2 \times 2.069\,SE$
$SE = 0.0259$
$\mu = 0.849$
90% C.I. for Cmax
$LLm = 0.849 - 1.714\,SE = 0.805$
$ULm = 0.849 + 1.714\,SE = 0.893$

Regimens	Ratio of C_{max} Central Values		Relative Bioavailability Based on AUC	
Test to Reference	Point Estimate	95% C.I.	Point Estimate	95% C.I.
Unadjusted Values‡				
A to C	0.867	0.814-0.923	0.944	0.889-1.003
B to C	0.870	0.817-0.927	0.981	0.924-1.042
Adjusted Values†				
A to C	0.848	0.796-0.903	0.923	0.870-0.980
B to C	0.851	0.800-0.906	0.959	0.903-1.018

90% C.I. 0.805-0.893

† Drug content adjusted values

90% C.I. AUC (unadjusted)
(0.898 - 0.993)
(0.933 - 1.031)

With and without adjustment for drug content, the criterion for equivalence to the reference regimen with respect to AUC is satisfied by both CR tablet regimens since the

APPENDIX D.9

Table 2

Individual Valproic Acid AUC_24 and Dose Normalized AUC_24 Values For Regimens A, B, C

Untransformed AUC 0-24 (mcg/mL)

Subject	AUC 0-24 A*	AUC 0-24 B*	AUC 0-24 C*	Normalized AUC 0-24 A	Normalized AUC 0-24 B	Normalized AUC 0-24 C
101						
102						
103						
104@						
105						
106						
107						
108						
109@						
110						
111						
112						
113						
114						
115						
116						
117						
118						
119						
120						
121						
122						
123						
124						
N	22	22	22	22	22	22
Mean	1365.8	1417.7	1439.8	1.055	1.094	1.110
Median	1382.4	1392.2	1365.3	0.962	1.029	1.086
SD	376.5	382.2	383.5	0.345	0.341	0.320
CV%	27.6	27.0	26.6	32.7	31.2	28.8
Minimum						
Maximum						

@ Subject missed one period, his data are not included in any statistical analysis.
* Regimen A: Divalproex sodium CR tablets once a day.
Regimen B: Divalproex sodium CR tablets twice a day.
Regimen C: Depakote (REFERENCE).

APPENDIX D.9

Table 2

Individual Valproic Acid Cmax and Dose Normalized Cmax Values For Regimens A, B, C

Untransformed Cmax (mcg/mL)

Subject	Cmax A*	Cmax B*	Cmax C*	Normalized Cmax A	Normalized Cmax B	Normalized Cmax C
101						
102						
103						
104@						
105						
106						
107						
108						
109@						
110						
111						
112						
113						
114						
115						
116						
117						
118						
119						
120						
121						
122						
123						
124						
N	22	22	22	22	22	22
Mean	71.4	71.7	82.8	0.055	0.056	0.064
Median	75.5	71.1	82.7	0.054	0.055	0.064
SD	17.5	17.7	21.8	0.016	0.016	0.018
CV%	24.6	24.7	26.4	28.6	29.3	28.0
Minimum						
Maximum						

@ Subject missed one period, his data are not included in any statistical analysis.
* Regimen A: Divalproex sodium CR tablets once a day.
Regimen B: Divalproex sodium CR tablets twice a day.
Regimen C: Depakote (REFERENCE).

APPENDIX D.9

Table 1

Individual Valproic Acid Cmin and Dose Normalized Cmin Values For Regimens A, B, C

Untransformed Cmin (mcg/mL)

Subject	Cmin A*	Cmin B*	Cmin C*	Normalized Cmin A	Normalized Cmin B	Normalized Cmin C
101						
102						
103						
104@						
105						
106						
107						
108						
109@						
110						
111						
112						
113						
114						
115						
116						
117						
118						
119						
120						
121						
122						
123						
124						
N	22	22	22	22	22	22
Mean	39.5	45.6	41.0	0.031	0.035	0.031
Median	40.5	45.7	38.3	0.029	0.033	0.031
SD	15.4	14.1	14.3	0.015	0.012	0.011
CV%	39.0	31.0	34.9	47.7	34.6	33.5
Minimum						
Maximum						

@ Subject missed one period, his data are not included in any statistical analysis.
* Regimen A: Divalproex sodium CR tablets once a day.
  Regimen B: Divalproex sodium CR tablets twice a day.
  Regimen C: Depakote (REFERENCE).

study 3 M95-414

Summary

Title: Evaluation of the absorption characteristics of three oral [redacted] dosage forms of divalproex sodium versus an intravenous sodium valproate formulation (Protocol M95-414).

Objectives: The objectives of this study were 1) to evaluate the bioavailability and plasma concentration versus time profile of valproate from three new oral controlled-release tablet formulations of divalproex sodium having different dissolution rates versus those of an intravenous sodium valproate formulation and 2) to explore the relationship between *in vitro* dissolution rate versus *in vivo* bioavailability.

Investigator: The study was conducted at [redacted]. The principal investigator was [redacted]. The study drug was administered between 3/12 and 4/2/96.

Study Design: This was a Phase I, single-dose, four-period, nonfasting, open-label, complete-crossover study. Sixteen healthy adult subjects (10 males and 6 females) were randomly assigned in equal numbers to the four sequences of regimens shown below. The sequences were such that one-fourth of the subjects received each regimen in the first study period. The alternate regimens were assigned to the subjects in the subsequent study periods so each subject received all regimens upon study completion, with each regimen assigned to one-fourth of the subjects in each period.

Regimen A: Divalproex sodium tablets (Formulation G, NPRO 7120N; Lot 13-316-AR-01; potency=102.2%), 500 mg valproic acid equivalent per tablet ([redacted] > Formulation B).

Regimen B: Divalproex sodium tablets (Formulation B, NPRO 6980N; Lot 10-263-AR-04; potency=102.9%), 500 mg valproic acid equivalent per tablet (to-be-marketed formulation). TBM

Regimen C: Divalproex sodium tablets (Formulation F, NPRO 7119N; Lot 13-315-AR-01; potency=101.1%), 500 mg valproic acid equivalent per tablet [redacted] < Formulation B).

Regimen D: Injection valproate sodium, NPRO 6731N, Lot 96-045-AR, 500 mg valproic acid equivalents per 5 mL per vial (reference formulation).

Each subject received a single dose of 500 mg valproic acid equivalent once during each of the four study periods. All oral doses were administered with 180 mL of water under nonfasting conditions. Each intravenous dose was to be infused over a 12-hour period; the drug solution was diluted with 5% dextrose in sterile water to a total volume of 500 mL. A one week washout separated the doses of the consecutive study periods.

Blood Samples and Analytical Methodology: Five-mL blood samples were collected into evacuated heparinized collection tubes prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7.5, 9, 10.5, 12, 13, 15, 18, 24, 36, 48, and 72 hours after the dosing in each period. The plasma samples were analyzed for valproate (VPA) concentration using a validated [redacted] method with [redacted]

[redacted]

Results: The mean (±SD) pharmacokinetic parameters of VPA for the four regimens are listed below.

Parameter (units)	Regimen A Mean ± SD	Regimen B Mean ± SD	Regimen C Mean ± SD	Regimen D Mean ± SD
C_{max} (µg/mL)	31.13 ± 9.35	29.74 ± 7.90	39.30 ± 8.80	41.80 ± 8.53
T_{max} (h)	20.6 ± 5.8	15.6 ± 5.0	8.5 ± 3.4	12.7 ± 0.5
β (h^{-1})	0.047 ± 0.009	0.047 ±0.009	0.046 ±0.009	0.046 ±0.008
AUC_∞ (µg·h/mL)	1040 ± 367	1056 ± 347	1148 ± 311	1141 ± 308
CL/F (L/h)	0.56 ± 0.29	0.56 ± 0.33	0.47 ± 0.14	0.47 ± 0.13
V/F (L)	11.91 ± 5.46	11.89 ± 6.19	10.11 ± 1.56	10.24 ± 1.77
FR†	1.19 ± 0.41	1.29 ± 0.46	2.00 ± 0.44	1.96 ± 0.28
Absolute F (%)	0.90 ± 0.18	0.92 ± 0.19	1.01 ± 0.10	-

† Fluctuation Ratio, calculated as quotient of C_{max} and the 24-hour concentration.

Attached are drug release data for Divalproex Sodium [redacted] Tablets, Formulations B, F, and G used in Study M95-414. Individual run data are included for n = 12 tablets tested using the final drug release method. Details of the testing are as follows:

Apparatus: USP Apparatus 2 (paddle), [redacted]

Acid Medium: [redacted]

Drug Release Medium: [redacted]

Assay: [redacted]

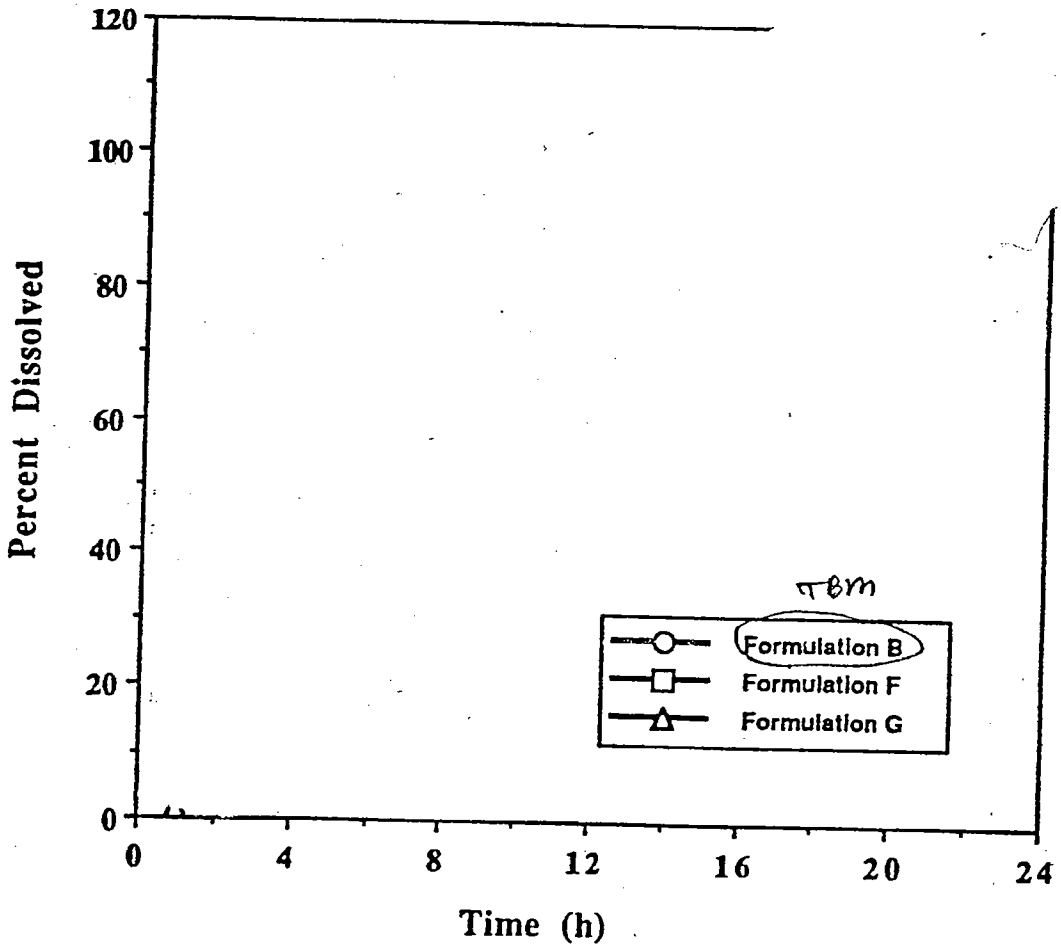
↑ Dissolution

Table I. Individual Run Drug Release Data for Divalproex Sodium — Lot 10-263-AR-04, Formulation B TBM
(Final Drug Release Method)

	% Released						
Run	1	3	5	9	12	18	24hrs
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	3.6	17.9	29.0	48.4	71.3	101.1	103.2
SD	0.8	0.9	1.1	3.7	7.8	2.7	2.1

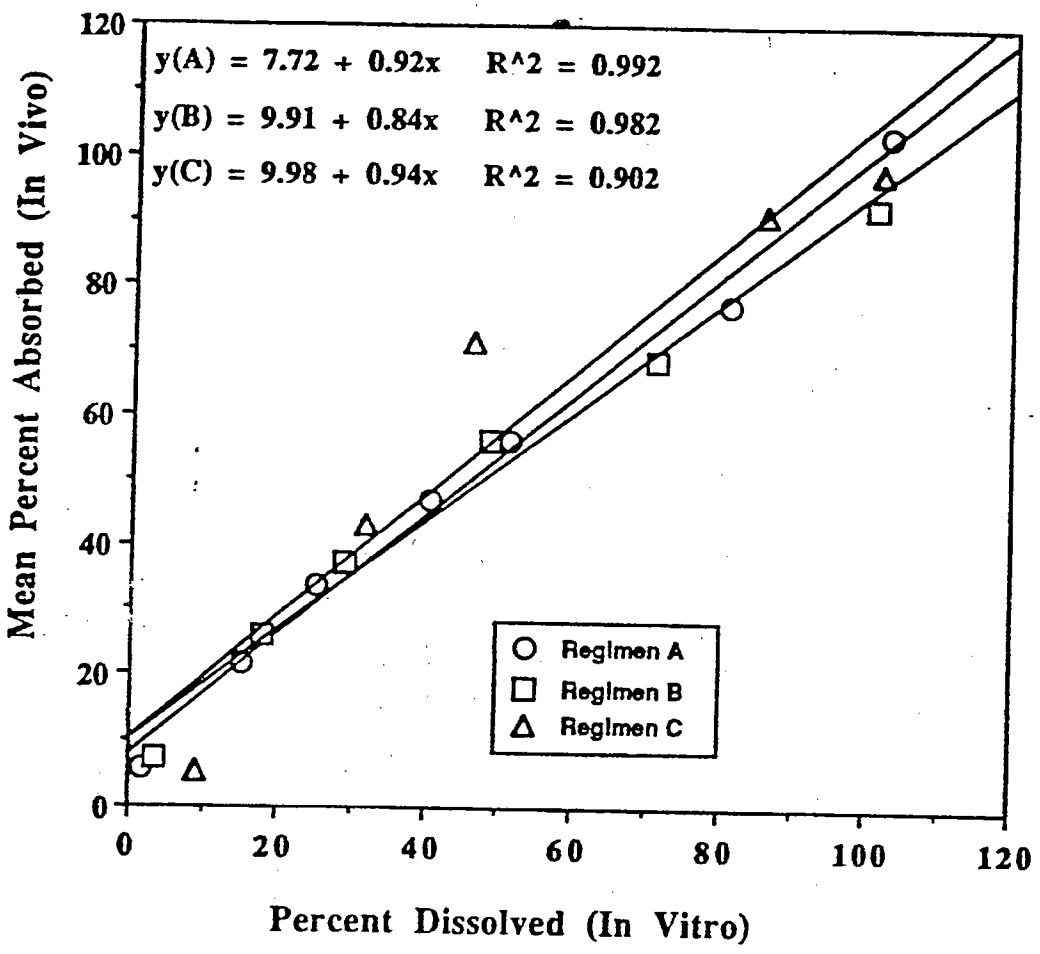
Data Verified [signature] 9/18/96

Figure 1. Dissolution† Profiles Obtained from Divalproex Sodium Formulations B, F and G



† Using Apparatus 2,

Figure 6. ***In Vivo-In Vitro*** **Correlation Obtained From Mean Percent Absorbed Data of Three Different Tablet Formulations† of Depakote**



† For Regimens A, B, and C data up to 24, 18, and 12 hours were used, respectively.

$\%\,abs = 8.79 + 0.90 \times \%\,diss$

Table 2. Biopharmaceutic and Pharmacokinetic Parameters of Valproate from Submitted Studies

Study #	SD/ MD	Daily Dose (mg)	N	Food	Formula*	NPRO/ List	Lot Number	T_{max} (h)	C_{max} (µg/mL)	AUC^{Δ} (µg·h/mL)	C_{min} (µg/mL)	Dfl.
M95-272	SD	500	6	F	—	6752N	01-088-AR-01	10.8 (24.0)	30.3 (16.4)	847 (25.8)	-	-
				F	—	6753N	01-089-AR-01	17.0 (39.7)	23.8 (38.8)	709 (48.2)	-	-
				F	—	6754N	01-090-AR-01	8.8 (55.3)	15.5 (15.7)	533 (41.0)	-	-
				F	—	6755N	01-091-AR-01	10.6 (48.0)	12.9 (11.4)	608 (34.4)	-	-
				F	Depakote	6215	86-695-AY-22	3.7 (14.1)	48.1 (14.3)	879 (24.2)	-	-
			13	NF	—	6752N	01-088-AR-01	7.2 (26.9)	40.9 (12.6)	1005 (26.0)	-	-
				NF	—	6753N	01-089-AR-01	13.2 (40.0)	29.6 (22.6)	967 (38.4)	-	-
				NF	—	6754N	01-090-AR-01	13.2 (43.6)	23.7 (29.0)	879 (30.1)	-	-
				NF	—	6755N	01-091-AR-01	14.1 (48.2)	14.6 (23.7)	698 (37.6)	-	-
				NF	Depakote	6215	86-695-AY-22	9.2 (37.5)	47.4 (15.9)	1041 (32.2)	-	-
M95-288	MD	1000 QD (morning)	8	NF	—	6753N	01-089-AR-01	13.3 (36.3)	87 (17.3)	1771 (22.8)	55.5 (38.7)	0.46 (55.9)
		1000 BID (6am,6pm)		F	Depakote	6215	86-695-AY-22	3.0 (34.5)	102 (10.5)	1798 (16.6)	53.3 (26.2)	0.67 (31.2)
		1000 QD (evening)	8	NF	—	6753N	01-089-AR-01	14.7 (24.1)	85 (10.0)	1728 (12.5)	57.4 (14.9)	0.39 (19.7)
		1000 BID (6pm,6am)		F	Depakote	6215	86-695-AY-22	3.7 (41.0)	98 (10.2)	1747 (10.5)	54.7 (13.9)	0.60 (12.3)
M95-330	SD	500	15	NF	—	6127N	07-194-AR-01	14.3 (40.0)	31.4 (34.2)	857 (39.3)	-	-
		500		NF	—	6128N	06-193-AR-01	11.8 (27.1)	32.3 (26.9)	876 (40.3)	-	-
		500		NF	Depakote	6215	95-434-AA-21	9.2 (45.3)	49.0 (19.0)	976 (31.2)	-	-

Values are mean with % CV in parentheses.
SD=single dose, MD=multiple dosing, F=fasting and, NF=nonfasting.
Δ AUC 0-∞ after single dosing and 0-24 after multiple dosing.
† Small scale runs of the to-be-marketed formulation.
* — :Depakote ———— formulation, Depakote=Depakote delayed-release tablets.

NDA 20-782
Drug Name: Depakote[R] — (divalproex sodium ——— 500 mg tablets)
Sponsor: Abbott laboratories
Indication: Epilepsy
Type of submission: NDA Amendment (B2)
Date of submission: May 21, 1998
Reviewer: Rae Yuan, Ph.D

The sponsor has submitted this amendment in response to a tele-conference between FDA and the sponsor, in which our concerns on the performance of the Depakote ——— product — were discussed. In the original NDA 20-782, a multiple dosing bioequivalence study (Study M95-376) was conducted in healthy volunteers. The subjects received — under fasting and fed condition, and the delayed release product (DR) under fasting condition. Under fasting condition, Cmin of — product was significantly lower than that of the DR product, though AUC of the two products were equivalent. The plasma concentration of — under fasting condition in two subjects (subjects #5 and #10), were consistently lower than the other two regimens throughout the sampling time (Refer review dated April 10, 1998). However, in the same study, — product administered under fed condition was shown to be equivalent to the DR product under the fasting condition (The ratio of fed:fasting was 1.03, 90% C.I. was 0.858-1.25).

The sponsor hypothesize, in this amendment, that gastrointestinal transit time is the key factor for absorption of this — product. In individuals with abnormally short small intestinal transit time, such as subjects #5 and #10, the extent of absorption of the — product is lower. Food helped to prolong the GI transit time and thereby increases the bioavailability of the —drug. Because it was believed that food did not affect pharmacokinetics of DR product (NDA 18-723). — product under fed condition was expected to be equivalent to DR product under the same condition. Therefore, the sponsor proposes to modify the — product labeling so that the product will be required to be taken with food.

Study F93-236 submitted in the NDA 18-723 assessed the effect of food on DR product. Results indicated that Cmin and AUC were about 13% and 8% higher, respecitively, for fed condition than fasting condition (The ratio of the two was 1.13; 90% C.I. was 1.072-1.193). Assuming DR product under fasting condition in the two food effect studies had exactly the same performance, Cmin of — product under the fed condition could still be 10% lower that that of DR product under the same condition. This implies that bioequivalence may not be achieved if both products were administered with food. More over, it should be noted that the food used in study M95-376 is median fat breakfast, which consisted of 43% fat, 20% protein, 76% carbonhydrates, and had a total of 664 calories. The effect of low fat food on the — product has not been studied, and hence not known.

In study M95-401 where most patients were coadministered Carbamazepine with Depakote under unrestricted diet condition, bioequivalence of — and DR was

established. This study appears to support the notion that — and DR products of Depakote are bioequivalent regardless of the considerations in food intake. However, chronic dosing of Carbamazepine can decrease the motility of GI tract (reference: Carbamazepine poisoning: protracted course with development of intestinal atony and hepatic toxicity, *Wien Klin Wochenschr* 1994, 106(1): 27-29). Thus, Carbamazepine in this study may have changed the absorption of Depakote, in addition to its influence on Depakote metabolism. Hence, the results of Depakote — performance in this polytherapy cannot be extrapolated to Depakote monotherapy.

In summary, for Depakote monotherapy, study F93-236 indicated that DR product had 13% higher Cmin under fed condition than under fasting condition. Study M95-376 indicated that — product had 17% higher Cmin under fed condition than under the fasting condition. The sponsor proposes to compare —product under fed condition to DR product under fasting condition and deems the product equivalent. Such comparison is biased, and therefore, is not acceptable.

Recommendations:

The sponsor had not provided convincing evidence to demonstrate that Depakote — product would be equivalent to DR product had it been tested under the same conditions, i.e. both products given either with food or without food. We acknowledge that food may improve the absorption of —product, possibly, by decreasing the GI transit time. However, due to the lack of direct evidence of bioequivalency test under similar conditions, approval for Depakote — is NOT recommended.

Primary Reviewer: Rae Yuan, Ph.D Rae Yuan 6/2/98

Team Leader: Chandra Sahajwalla, Ph.D Chandra

Date of Signature: 6/2/98

CC list: HFD-120, HED-860 (Sahajwalla, Malinowski, Yuan), CDR (Barbara Murphy)

FOOD Effect on — Depakote
(NDA 20-782, Study M 95-376)

ATTACHMENT P.1

Results =

Regimen	Mean (Standard Deviation), n=14				
	T_{max} (hr)	C_{max} (ug/mL)	C_{min} (ug/mL)	AUC_{0-24} (ug•hr/mL)	DFL
A	13.6 (6.3)*	80.5 (18.6)*	48.2 (17.0)	1592 (402)*	0.523 (0.231)
B	15.9 (4.5)*	85.0 (12.5)*	55.1 (13.3)	1709 (276)	0.432 (0.127)*
C	3.6 (0.9)	99.4 (15.7)	54.1 (13.1)	1789 (332)	0.623 (0.160)

* Statistically significantly different from Regimen C.
Regimen A: Divalproex Sodium — 2x500 mg once daily, fasting.
Regimen B: Divalproex Sodium — 2x500 mg once daily, nonfasting.
Regimen C: Depakote Tablet: 500 mg twice daily, fasting.

Two One-Sided Tests Procedure for Equivalence Assessment, Day 6 AUC

Test	Reference	Relative Bioavailability	
		Point Estimate	90% Confidence Interval
A	C	0.891	0.817 - 0.971
B	C	0.970	0.890 - 1.058
A	B	0.918	0.842 - 1.001

90% C.I. of Cmin (A,C)

$z_1 = \mu - 2.16\,SE$
$0.7 = \mu + 2.16\,SE$
$1.5 = 2 \times 2.16\,SE$
$SE = 0.0914$
$\mu = 0.8695$

$m = 0.868 - 1.771 \times 0.0914$
$= 0.707$

$+ \quad 0.868 + 1.771 \times 0.0914$
$= 1.03$

Ratio of Day 6 C_{max} Central Values

Regimens Tests/Reference	Point Estimate	95% Confidence Interval
A C	0.811	0.742-0.887
B C	0.861	0.788-0.941
A B	0.942	0.862-1.030

Ratio of Day 6 C_{min} Central Values

Regimens Tests/Reference	Point Estimate	95% Confidence Interval
A C	0.847	0.672-1.067
B C	1.026	0.814-1.293
A B	0.825	0.655-1.040

90% C.I
(0.707-1.031)
(0.858-1.25)

$0.814 = \mu - 2.16\,SE$
$1.293 = \mu + 2.16\,SE$
$SE = 0.111$
$\mu = 1.054$

LL $m = 1.054 - 1.77 \times 0.111$
$= 0.858$

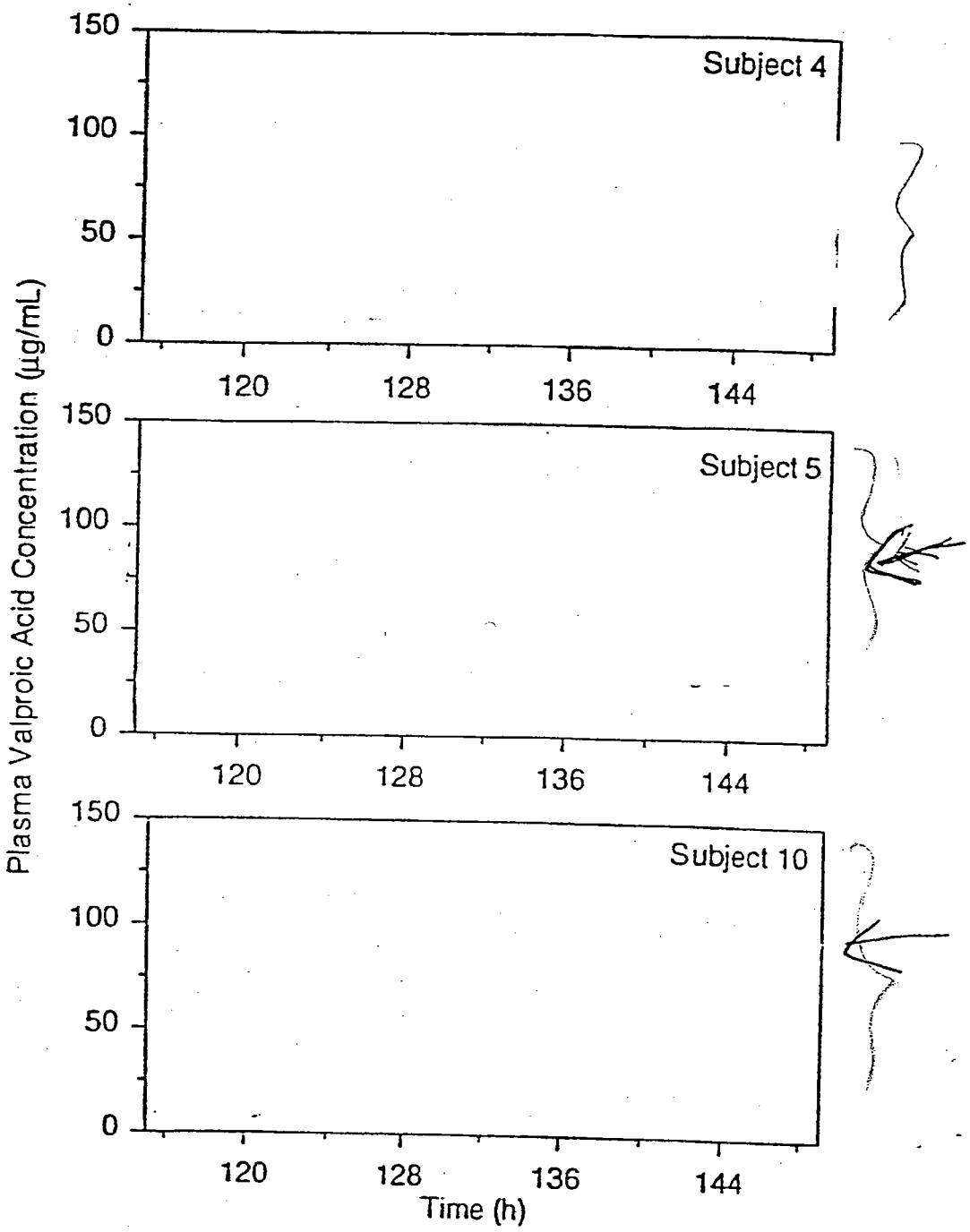
UL $m = 1.054 + 1.77 \times 0.111$
$= 1.25$

Food Effect on ~~-~~. Depakote
(NDA 20-782, study M95-37fb)

ATTACHMENT P.2

Appendix E

Individual profiles



ATTACHMENT P3

Study No. F93-236
R&D/93/714

FOOD Effect on DR Depakote.
(NDA 18-723)

10

Pharmacokinetic Parameters: Day 6								
	Mean (% Coefficient of Variation)							
Regimen	T_{max} (hours)		C_{max} (µg/mL)		C_{min} (µg/mL)		AUC (µg•hr/mL)	
A. Fasting								
am dose	3.3	(71.3)	118.5	(11.6)	74.3	(11.1)	1143	(10.4)
pm dose	4.3	(61.9)	117.6	(11.2)	75.9	(8.3)	1115	(9.1)
24 hours	–	–	123.9	(8.0)	73.4	(11.5)	2258	(8.3)
B. Nonfasting								
am dose	7.8	(31.8)	119.3	(10.7)	86.6	(9.5)	1232	(7.8)
pm dose	7.0	(55.4)	118.0	(11.1)	83.1	(13.7)	1183	(11.4)
24 hours	–	–	123.1	(10.6)	81.1	(12.6)	2415	(9.0)
Regimen A – 750 mg am and 750 mg pm, Fasting Regimen B – 750 mg am and 750 mg pm, Nonfasting								

Mean T_{max} was about 3 to 4 hours for the fasting regimen and about 7 to 8 hours for the nonfasting regimen. There was a greater delay in the onset of absorption for the nonfasting than for the fasting regimen. Mean C_{max} was about the same for both regimens, and the unadjusted C_{min} and AUC means were about 10% and 7% higher, respectively, for the nonfasting regimen. The estimated ratio of means (nonfasting:fasting) for C_{max} (highest plasma concentration after dosing on Day 6), C_{min} (lowest plasma concentration after dosing on Day 6), and AUC_{0-24} and their respective 95% confidence intervals are given below (from Appendix D.2). All of the estimates of the ratios (nonfasting:fasting) of means were greater than 1.0. The differences between regimens in C_{min} and in AUC_{0-24}, although small, were statistically significant (nonfasting > fasting; refer to Appendix D.1).

Ratio of Means and 95% Confidence Intervals			
Estimate of Ratio of Means Regimen B:A		95% Confidence Intervals	
C_{max}	1.01	0.934	1.081
C_{min}	1.13	1.058	1.207
AUC_{0-24}	1.08	1.041	1.131

90% C.I.

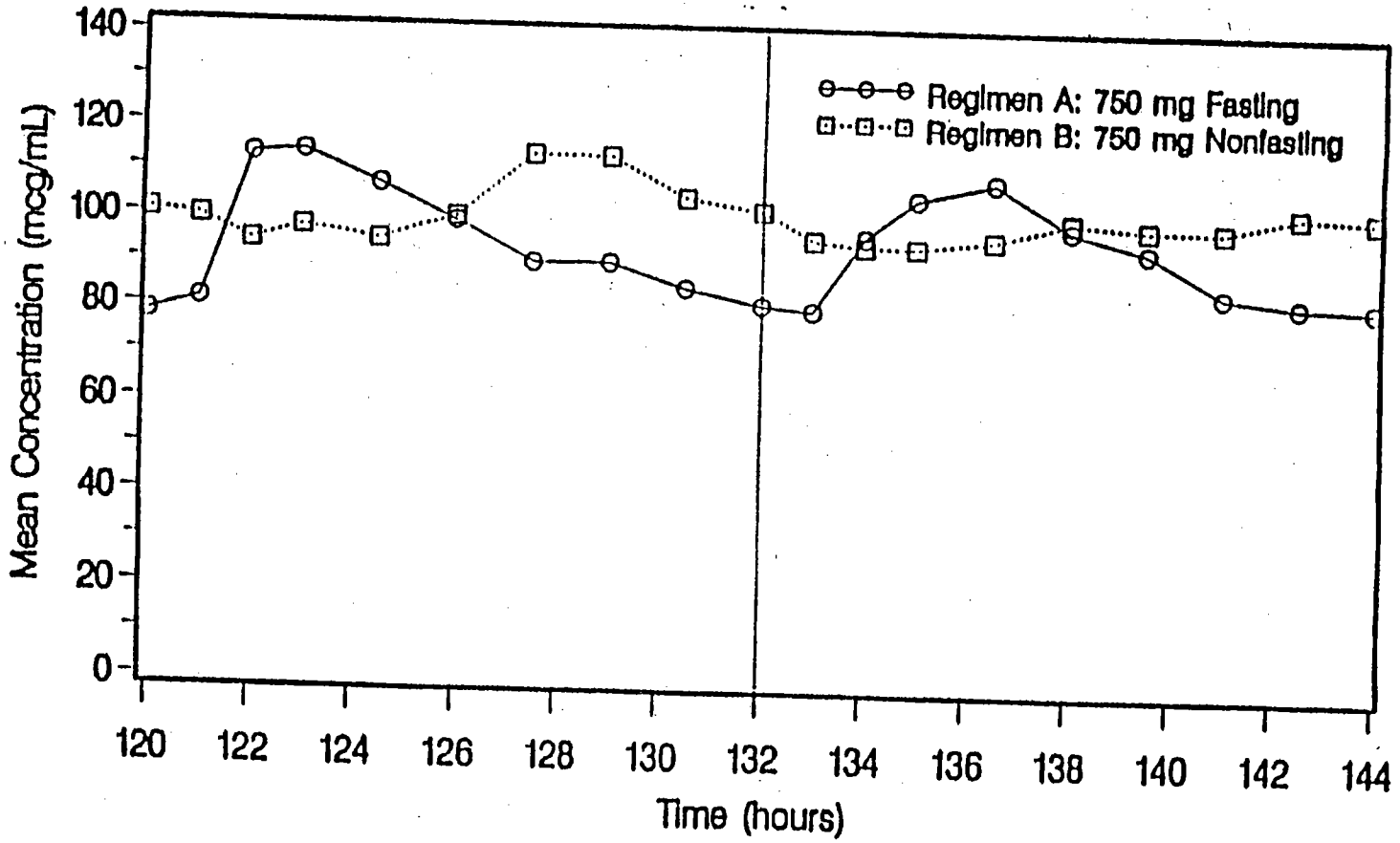
1.072 - 1.193

On Day 6, C_{max} ranged from 109.8 to 138.0 µg/mL for Regimen A and 101.7 to 143.5 µg/mL for Regimen B; C_{min} ranged from 53.9 to 85.3 µg/mL for Regimen A and 64.0 to 96.1 µg/mL for Regimen B; and AUC ranged from 1994 to 2563 µg•hr/mL for

ATTACHMENT P.3

Figure 1

Mean Plasma Valproic Acid Concentrations
Under Fasting and Nonfasting Regimens, Day 6



Food Effect on DR Depakote
(NDA 18-723)

Figure Page 1
Last Figure Page

ATTACHMENT P4

ATTACHMENT P5

Figure 2
Mean "Trough" Plasma Valproic Acid Concentrations
Under Fasting and Nonfasting Regimens