Summary Statistics of TXB_2 Percent Inhibition From Baseline by Time Point

Day	Time (Hours)	Treatment	N	Mean	Median	Min, Max	Between-Subject SD		
Baseline (ng/mL)									
1	0	MK-0966	12	302.83	259.90		128.54	.	.
		Placebo	12	250.31	239.65		83.36	.	.
Day	Time (Hours)	Treatment	N	Mean*	Median*	Min, Max*	Between-Subject SD†	Within-Group p-Value‡	Within-Group 90% CI
Inhibition From Baseline (%)									
4	0	MK-0966	12	6.79	-1.99		26.19	0.373	(-6.77, 18.62)
		Placebo	12	-4.94	-9.89		10.30	0.133	(-10.70, 0.51)
Inhibition From Baseline (%)									
10	0	MK-0966 + Aspirin§	12	97.22	96.70		65.65	<0.001	(96.09, 98.02)
		Aspirin	12	96.99	97.00		35.80	<0.001	(96.38, 97.50)
Inhibition From Baseline (%)									
10	4	MK-0966 + Aspirin§	12	98.37	97.87		78.98	<0.001	(97.55, 98.92)
		Aspirin	12	98.36	98.02		67.64	<0.001	(97.67, 98.84)

* Back-transformed from the log scale.
† SD on the log scale * 100.
‡ Within-group p-value versus no inhibition.
§ Note that concomitant therapy with aspirin began on Day 4.

Data Source: [2.1]

Summary Statistics for Percent Inhibition From Baseline Platelet Aggregation Using 1 mM of Arachidonic Acid as Agonist

Day	Time (Hours)	Treatment	N	Mean	Median	Min, Max	Between-Subject SD		
Baseline Platelet Aggregation¶									
1	0	MK-0966	12	77.9	78.0		6.5	.	.
		Placebo	12	78.3	78.0		4.2	.	.
Day	Time (Hours)	Treatment	N	Mean	Median	Min, Max	Between-Subject SD	Within-Group p-Value†	Within-Group 90% CI
Inhibition From Baseline (%)									
4	0	MK-0966	12	0.83	0.63		6.69	0.674	(-2.63, 4.30)
		Placebo	12	4.05	0.59		9.43	0.165	(-0.84, 8.93)
Inhibition From Baseline (%)									
10	0	MK-0966 + Aspirin‡	12	93.78	93.29		2.23	<0.001	(92.63, 94.94)
		Aspirin	12	92.13	92.91		3.00	<0.001	(90.57, 93.68)
Inhibition From Baseline (%)									
10	4	MK-0966 + Aspirin‡	12	93.73	94.32		1.78	<0.001	(92.81, 94.66)
		Aspirin	12	93.54	93.55		1.73	<0.001	(92.64, 94.44)

* Within-group p-value versus no inhibition.
† Note that concomitant therapy with aspirin began on Day 4.
‡ Measured as percent light transmission.

Data Source: [2.2]

Summary Statistics for Percent Inhibition From Baseline Platelet Aggregation Using 1 µg/mL of Collagen as Agonist

Day	Time (Hours)	Treatment	N	Mean	Median	Min, Max	Between-Subject SD		
Baseline Platelet Aggregation¶									
1	0	MK-0966	12	77.8	77.5		4.7	.	.
		Placebo	12	79.3	79.0		4.3	.	.
Day	Time (Hours)	Treatment	N	Mean	Median	Min, Max	Between-Subject SD	Within-Group p-Value†	Within-Group 90% CI
Inhibition From Baseline (%)									
4	0	MK-0966	12	2.79	2.00		10.19	0.363	(-2.49, 8.07)
		Placebo	12	13.66	1.89		25.49	0.090	(0.45, 26.88)
Inhibition From Baseline (%)									
10	0	MK-0966 + aspirin‡	12	78.31	80.78		16.24	<0.001	(69.89, 86.73)
		Aspirin	12	79.61	84.38		17.84	<0.001	(70.36, 88.86)
Inhibition From Baseline (%)									
10	4	MK-0966 + aspirin‡	12	86.84	89.43		8.60	<0.001	(82.38, 91.29)
		Aspirin	12	90.84	91.84		4.94	<0.001	(88.28, 93.40)

* Within-group p-value versus no inhibition.
† Note that concomitant therapy with aspirin began on Day 4.
‡ Measured as percent light transmission.

Data Source: [2.2]

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-042 & 21-052 SUBMISSION DATES: 11/23/98
PRODUCT: Vioxx (rofecoxib) Tablets, 12.5 mg & 25 mg 3/10/99, 3/16/99, 3/18/99
Vioxx (rofecoxib) Suspension, 12.5 mg/5 mL & 25 mg/5 mL
SPONSOR: Merck
P.O. Box 4, West Point, PA 19486
TYPE OF SUBMISSION: Original REVIEWER: Sue-Chih Lee, Ph.D.

Background

This review covers pharmacokinetic studies on special populations (renal insufficiency and hepatic insufficiency patients), bioequivalence (Formulation C tablets vs. Formulation B tablets; and suspension vs. tablets) and food effect. The review of other pharmacokinetic studies were conducted and presented separately by Drs. Dan Wang and Veneeta Tandon. The overall synopsis and recommendation are included in Dr. Dan Wang's review.

Table of Contents:

Review

SPECIAL POPULATIONS

Patients with Hepatic Insufficiency

Study Title: An Open-Label, Randomized, 2-Period, Crossover Study to Investigate the Influence of Hepatic Insufficiency on the Pharmacokinetics of MK-0966 (Protocol #057)

The objectives of this study were (1) to compare plasma concentrations and pharmacokinetic parameters of MK-0966 following administration of single oral and intravenous doses of MK-0966 in patients with mild-to-moderate hepatic insufficiency and healthy subjects and (2) to

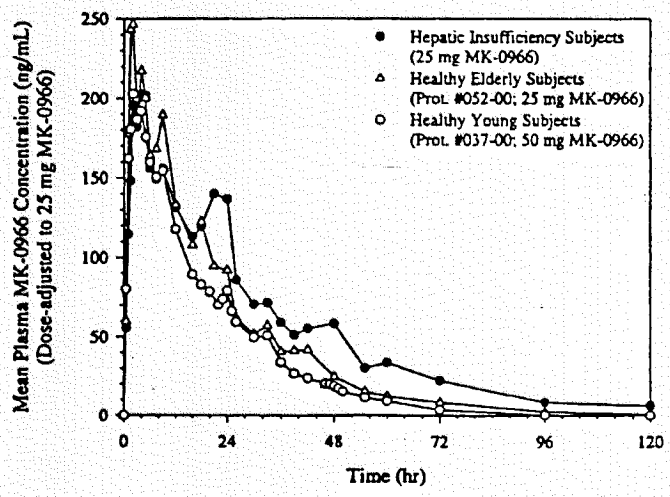
estimate the oral bioavailability of MK-0966 in hepatic insufficiency patients. This is a two-period crossover study in which eight patients (4 mildly & 4 moderately impaired as defined by the Child-Pugh classification system) received, under fasted conditions, a single 25-mg dose of MK-0966 in one period and a 1-mg IV dose of MK-0966 in the alternate period. A 14-day washout separated the periods. Plasma samples, collected for 120 hours following the oral dose and the end of the 30-minute intravenous infusion, were analyzed for MK-0966. Detailed study design is given in Appendix III.

Pharmacokinetic data from healthy subjects receiving 50-mg (Studies 037 & 043) and 25-mg (Studies 048 & 052) doses of MK-0966 were potency normalized and dose adjusted to 25 mg and pooled for comparison. ANCOVA model including the factors of population, age, sex, race, weight and height was used to compare the PK parameters between healthy subjects and hepatically impaired patients. ANOVA model containing sequence, subject within sequence, period and treatment as factors was used to compare the dose-adjusted parameters between the oral formulation and IV dose.

Hepatic insufficiency patients vs. healthy subjects:

(A) MK-0966 25 mg oral dose:

Mean plasma concentration-time profile for mild-to-moderate hepatic insufficiency patients is shown in the figure below along with the profiles for healthy subjects (Study 052: elderly; Study 037: young). One patient with moderate hepatic insufficiency (Subject 001) was found to have very high plasma levels (~3x of average of the 8 subjects). The individual parameter values are given in Appendix III. The adjusted mean parameter values for these patients (obtained from ANCOVA model) are presented in the table below along with the values for healthy subjects (pooled data from 4 studies: #037, 043, 048 & 052). The AUC geometric mean ratio (hepatic insufficiency/healthy) was 1.32 with a corresponding 90% CI of (1.07, 1.62), while the ratio for Cmax was 1.11 with a 90% CI of (0.88, 1.41). Tmax and T1/2 were higher in hepatic impairment patients when compared to healthy subjects (median Tmax: 4.0 hrs vs. 3.0 hrs; T1/2: 13.4 hrs vs. 11.3 hrs).



Mean Parameter Values: Mild-to-Moderate Hepatic Insufficiency Patients (25 mg Oral Dose) vs. Healthy Subjects

Population	Dose	$AUC_{0-\infty}$ (ng.hr/mL)		Cmax (ng/mL)	
		Mean[1]	GMR[2] (90%CI)	Mean[1]	GMR[2] (90% CI)
Hepatic Insufficiency (n=8)	25 mg	5449	1.32 (1.07-1.62)	247	1.11 (0.88-1.41)
Healthy (n=47)	25 or 50 mg	4143		222	

[1]Adjusted mean from ANCOVA analysis after dose adjustment to 25 mg

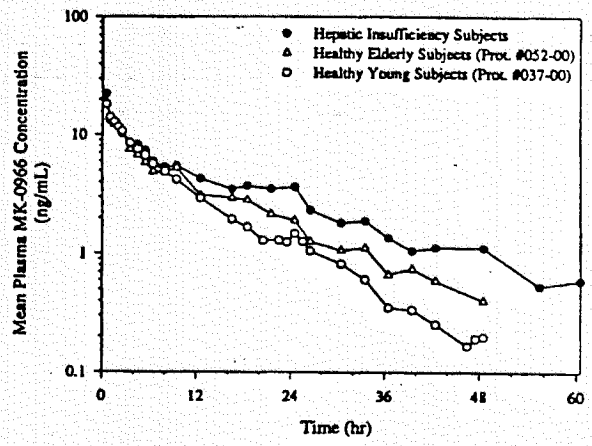
[2]Geometric mean ratio (hepatic insufficiency/healthy)

[3]Pooled inter-subject CV: 29.4% (AUC); 33.2% (Cmax)

Note: In a later analysis by the sponsor, pooled data for healthy subjects also included study 076. The analysis results yielded a GMR (hepatic insufficiency/healthy) of 1.29 (90% CI: 1.08-1.54) for AUC and 1.04 (90% CI: 0.88-1.21) for Cmax.

(B) 1 mg IV Dose:

Hepatic insufficiency (mild-to-moderate) patients had higher mean plasma concentrations than healthy subjects after 1 mg IV dose. (See figure below.) As presented in the table below, the adjusted mean AUC(0-∞) based on the ANCOVA model for the 1-mg I.V. administration was 167 and 140 ng.hr/mL for the patients with hepatic insufficiency and for the healthy subjects (Protocols 037 and 052), respectively. The AUC(0-∞) geometric mean ratio (hepatic insufficiency/healthy) based on the adjusted means was 1.19, with a corresponding 90% CI of (0.86, 1.64). In hepatically impaired patients, the adjusted mean T1/2 was longer (11.1 hrs vs. 9.9 hrs), mean clearance lower (100 mL/min vs. 119 mL/min) and Vd_{ss} was comparable (98 L vs. 93 L). These differences in magnitude did not rise to statistical significance at an α level of 0.05. (*Reviewer's note*: The power for detecting a 20% difference was not given.)



Mean Parameter Values: Hepatic Insufficiency Patients (1 mg IV Dose) vs. Healthy Subjects

Parameter	Population [Ref.]	Mean[1]	GMR (H.I./Healthy)	90% C.I. for GMR	p-Value
AUC_{∞}, ng·hr/mL	Hepatic Insufficiency	167	1.19	(0.86, 1.64)	0.366
	Healthy*	140			
Clearance, mL/min	Hepatic Insufficiency	100	–	–	0.365
	Healthy	119			
V_{dss}, L	Hepatic Insufficiency	98	–	–	0.496
	Healthy	93			
$t_{1/2}$, hr	Hepatic Insufficiency	11.1‡	–	–	0.601
	Healthy [P037; P052]	9.9‡			

[1]Geometric mean. ‡Harmonic mean. *Data for healthy subjects from Protocol #037 & 052

Bioavailability of Formulation C (25-mg) tablets in hepatic impairment patients:

Based on the data obtained from the 1 mg IV dose and the 25-mg oral dose, the absolute bioavailability for the tablets in hepatic impairment patients was calculated to be 1.36 (90% CI: 1.19-1.55). Again, the nonlinearity at low dose range resulted in an unrealistic value for absolute bioavailability. This value was comparable to those calculated for healthy subjects.

Conclusion: Following a 25-mg oral dose, mild-to-moderate hepatic impairment patients had a 30% higher AUC and approximately 10% higher Cmax when compared to previous studies in

healthy subjects. (Following a 1-mg IV dose, these hepatic impairment patients had a 20% higher AUC than healthy subjects.) The sponsor concluded that clinically important pharmacokinetic differences were not apparent between the healthy and hepatic insufficiency populations and that no dose adjustment is necessary for the hepatically impaired patients.

Reviewer's comments:

1. In the ANCOVA analysis, data were pooled from studies using both 25-mg and 50-mg doses. This would be appropriate if dose proportionality between the two doses have been established.

2. The sponsor indicated that, because of the small sample size (4 mildly impaired & 4 moderately impaired), possible gross differences in pharmacokinetic parameters due to severity of hepatic dysfunction could not be addressed. It was concluded that clinically important pharmacokinetic differences were not apparent between the healthy and hepatic insufficiency populations. However, two moderately impaired patients did have significantly higher (≥ 2-fold of group average) plasma concentrations and one subject (#001) with moderate hepatic impairment had very high plasma levels (3-fold of group average). It is noted that Subject 001 also had a history of Hepatitis C which might contribute to reduced hepatic function not reflected by the Child-Pugh score. In any case, this study raises concern that moderate hepatic impairment may result in significantly higher plasma concentrations requiring dose adjustment. Therefore, it is necessary that the sponsor conduct a new study in moderate hepatic impairment patients with increased sample size (n≥10). Since age, weight and other factors may confound the results, the sponsor is encouraged to conduct the study with matching healthy subjects. The detailed scoring (i.e. scores for ascites, prothrombin time, etc.) for each individual patients should be provided in summary tables. In addition, patients with a history of hepatitis should be excluded. Until the results of such a study are available, the use of rofecoxib in moderate hepatic insufficiency patients is not recommended.

Upon our request, the sponsor later analyzed separately the data for mild and moderate hepatic impairment patients. The results are given in the table below. These results indicated that mean AUC and Cmax in mildly impaired patients were similar to those in healthy subjects. Since high variability in AUC and Cmax was observed in moderately impaired patients, we consider it necessary that the sponsor conduct a new study in this group of patients as described above.

Mean Parameter Values: Hepatic Impairment (25 mg Oral Dose) vs. Healthy Subjects

Population	AUC		Cmax	
	Mean[1] (ng.hr/mL)	GMR[2] & 90% CI	Mean[1] (ng/mL)	GMR[2] & 90% CI
Mild Hepatic Insufficiency	4215	1.01 (0.77-1.31)	227	1.02 (0.74-1.40)
Moderate Hepatic Insufficiency	7098	1.69 (1.31-2.19)	269	1.21 (0.89-1.65)
Healthy Subjects[3]	4190	-	223	-

[1]Adjusted geometric mean from ANCOVA analysis

[2]Geometric mean ratio (hepatic impairment patients vs. healthy subjects)

[3]Data from pooled studies (N=47)

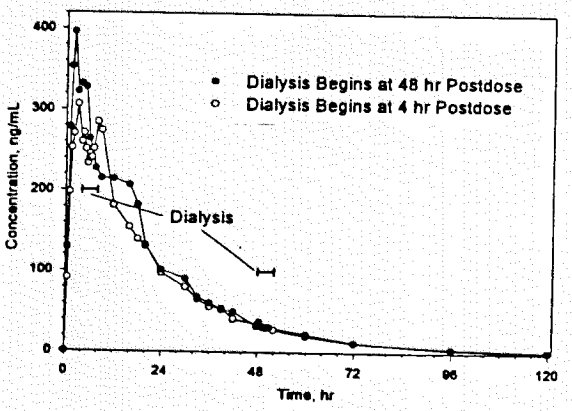
Patients with Renal Insufficiency

Study Title: An Open-Label, Three-Part, Oral Study to Investigate the Pharmacokinetics, Safety, and Tolerability of MK-0966 in Patients With Renal Insufficiency (Protocol #064)

The objectives of Parts I and II were to determine the influence of renal insufficiency and of hemodialysis on the plasma pharmacokinetics of MK-0966. (Note: This was to be a 3-part study but part III was not carried out because it was deemed unnecessary.)

Effect of hemodialysis on the pharmacokinetics of MK-0966: In Parts I and II, single 50-mg oral doses of MK-0966 were administered to 6 hemodialysis patients. In Part I, the dose was administered 48 hours prior to hemodialysis to examine the plasma profile of MK-0966 in the absence of hemodialysis. In Part II, doses were administered 4 hours prior to a 3-hour hemodialysis session to examine the contribution of dialysis to the elimination of MK-0966 in these patients. A washout period of at least 1 month was allowed between Parts I and II. Plasma (collected for 120 hours postdose) and dialysate samples were analyzed for MK-0966. Additionally, the binding of MK-0966 to plasma proteins was examined in these subjects to ascertain how it might be affected by renal impairment. More information on the study design is given in Appendix III.

Examination of the mean plasma concentration profiles (see figure below) from Parts I and II and the corresponding pharmacokinetic parameter values shows that although the C_{max} was 18% lower for the 4 hours postdose hemodialysis treatment, the AUCs and other parameter values were similar between treatments. Geometric mean ratios (90% CI) were 0.91 (0.79, 1.06) for AUC (dosed 4 hours predialysis/48 hours predialysis) and 0.82 (0.74, 0.91) for C_{max}. For both regimens, median T_{max} was 3.0 hrs, mean $t_{½}$ was 12-13 hrs and clearance of MK-0966 by hemodialysis was approximately 40 mL/min. When patients had hemodialysis 4 hours postdose, only 4.0±1.2% of dose was recovered in dialysate, leading to the conclusion that hemodialysis 4 hours postdose had little effect on the plasma pharmacokinetics of MK-0966.

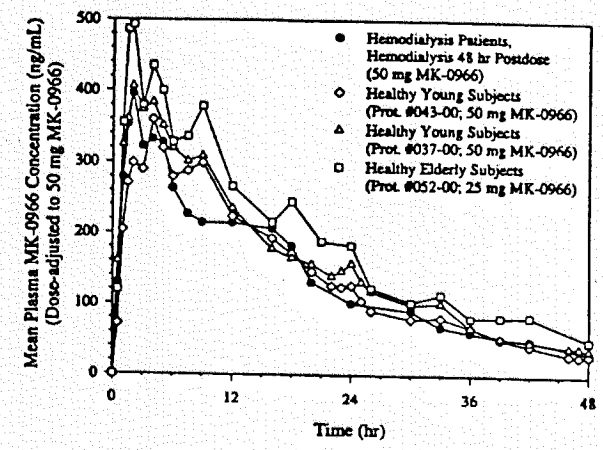


Parameter	Timing of Hemodialysis Relative to Dosing	Geometric Mean	Between-Subject SD	GMR (4 Hours /48 Hours)	(90% CI of GMR)	p-Value
AUC_{∞}, ng•hr/mL	4 hours 48 hours	6326 6927	3663 4393	0.91	(0.79, 1.06)	0.269
C_{max}, ng/mL	4 hours 48 hours	325 395	111 144	0.82	(0.74, 0.91)	0.014
T_{max}, hr	4 hours 48 hours	3.0† 3.0†	(2.0, 9.0)‡ (2.0, 5.0)‡	–	–	0.642
$t_{½}$, hr	4 hours	13.3§	4.7	–	–	0.055

	48 hours	12.1§	4.7			
Dialysis clearance, mL/min	4 hours	45	7	--	--	--
	48 hours	38	21			

† Median. ‡ (Min, max). § Harmonic mean.

Effect of renal insufficiency on the pharmacokinetics of MK-0966 (hemodialysis patients vs. healthy subjects): Presented in the figure below are mean profiles from subjects dosed 48 hours before the start of dialysis in this study and from healthy subjects (for Studies 037, 043 & 052 only). Parameter values between renal insufficiency patients and healthy subjects (Studies 037, 043, 048, 052 & 076) were compared using ANCOVA model that included population, age, sex, race, weight and height as factors. The analysis results showed that renal insufficiency patients had lower AUC (↓15-20%) and Cmax (↓12%) when compared to the pooled healthy subjects. Therefore, the pharmacokinetic behavior of MK-0966 is similar between the renally impaired and healthy subjects. In addition, no difference in the plasma protein binding of MK-0966 was found between hemodialysis patients (85.9±4.8% for the concentration range of 50-500 ng/mL) and healthy subjects (85.6%; from previous studies).



In light of the results in patients with end-stage renal disease, the sponsor did not evaluate the kinetics of the drug in patients with mild-to-moderate renal insufficiency. In conclusion, end-stage renal insufficiency requiring hemodialysis has little effect on the plasma pharmacokinetics of MK-0966, including protein binding. Therefore, dosing adjustments are not necessary for patients with any degree of renal insufficiency.

Mean Parameter Values: Hemodialysis Patients vs. Healthy Subjects

Parameter	Population	Geometric Mean[1]	GMR (Hemodialysis /Healthy)	(90% CI of GMR)	p-Value
AUC_{∞}, ng•hr/mL	Hemodialysis patients	7059	0.85	(0.69, 1.04)	0.195
	Healthy subjects[2]	8310			
AUC_{48}, ng•hr/mL	Hemodialysis patients	6501	0.81	(0.66, 1.00)	0.096
	Healthy subjects[3]	8008			
C_{max}, ng/mL	Hemodialysis patients	406	0.88	(0.73, 1.06)	0.271
	Healthy subjects[2]	461			
T_{max}, hr	Hemodialysis patients	3.0†	--	--	0.838
	Healthy subjects[2]	2.8†			

[1]Adjusted mean values from ANCOVA after dose adjustment to 50 mg; †Median.
[2]Studies 037, 043, 048, 052 & 076 used in the analysis
[3]Studies 037, 043, 048 & 052 used in the analysis (Study 076 not included)

Conclusions:

- There is no clinically important difference in pharmacokinetics of MK-0966 between renal insufficiency patients and healthy subjects. Since the drug is primarily eliminated by metabolism, this is as expected.
- Hemodialysis 4 hours postdose resulted in a reduction of 9% in AUC and 18% in Cmax as compared to hemodialysis 48 hours postdose.
- Binding of MK-0966 to plasma proteins is unaffected by renal insufficiency.
- No adjustment of MK-0966 dose is necessary for patients with renal insufficiency or for patients on hemodialysis.
- Single 50-mg doses of MK-0966 are well tolerated in patients with renal insufficiency and/or on hemodialysis.

Reviewer's comment:
The intersubject variability for AUC in hemodialysis patients as determined from this study is larger than that for healthy subjects. However, the small sample size of hemodialysis patients (n=6) may contribute to the high variability observed.

Race

To assess the possible differences in the pharmacokinetic parameters among race categories, the sponsor performed a combined analysis pooling the pharmacokinetic data from several studies (Protocol #037, 043, 048, 052, 070 and 076) involving three doses (12.5, 25 and 50 mg). A summary of the demographic data for these studies is presented on page 16 of the Appendix. An ANCOVA model with factors of race, gender, age, weight and height was used to analyze the parameters (dose adjusted $AUC_{0-\infty}$ and Cmax, Tmax and T1/2). Mean Tmax values were 3.9, 3.3 and 3.5 hours, and mean half-life values were 10.9, 10.9 and 9.8 hours for Black, Hispanic and Caucasian, respectively. There was no significant difference in mean Cmax among Black, Hispanic and Caucasian populations (see Table below). Higher mean AUC values were observed in Blacks (15%) and Hispanics (9%) when compared to Caucasians.

Mean Pharmacokinetic Parameter Values Among Races

Race	$AUC_{0-\infty}$		Cmax	
	Mean[1] (ng.hr/mL)	GMR[2] & 90% CI	Mean[1] (ng/mL)	GMR[2] & 90% CI
Black (n=29)	8294	1.15 (1.02-1.29)	451	0.99 (0.90-1.09)
Hispanic (n=35)	7875	1.09 (0.97-1.22)	452	0.99 (0.90-1.10)
Caucasian (n=46)	7227	-	456	-

[1]Adjusted geometric mean from ANCOVA analysis
[2]Geometric mean ratio (Black or Hispanic vs. Caucasian)

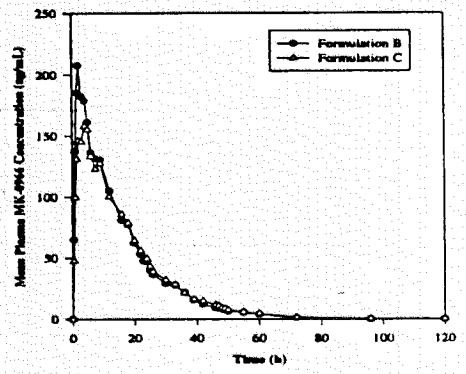
COMPARATIVE BIOAVAILABILITY/BIOEQUIVALENCE STUDIES

Comparative Bioavailability: Formulation C (25 mg) vs. Formulation B (25 mg)

Study Title: A 2-Period, Balanced, Single-Dose, Crossover Study in Healthy Subjects to Investigate the Comparative Bioavailability of Two Tablet Formulations (Protocol 036; Vol. 1.70)

The objective of this study was to assess the comparative bioavailability of 2 tablet formulations: Formulation B (25 mg MK-0966; tablet weight:) and Formulation C (to-be-marketed formulation; 25 mg MK-0966; tablet weight:). A single 25-mg dose of Formulation B or C was administered under fasted conditions in each of 2 periods in a crossover fashion with a 7-day washout. Blood samples for plasma MK-0966 were collected over 120 hours postdose. A total of 12 healthy subjects (2F & 10M) participated and completed the study. Detailed study design is given in Appendix III.

As shown in the figure, Formulation B has higher mean plasma concentrations than Formulation C up to 6 hours postdose. The pharmacokinetic parameter values for both formulations are listed in the table below. The geometric mean ratio expressed as Formulation C/Formulation B was 0.94 (90% CI: 0.90-0.98) for $AUC_{0-\infty}$ and 0.78 (90% CI: 0.68-0.90) for Cmax. Both formulations gave a median Tmax of 2.0 hours. The half-life as estimated from this study was approximately 8.5 hrs.



Parameter Values for Formulations B and C

	$AUC_{0-\infty}$ (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
Formulation B, 25 mg	3175.3 ± 764.4	222.1 ± 57.6	2.0	8.5 ± 3.2
Formulation C, 25 mg	2984.8 ± 756.8	174.2 ± 43.2	2.0	8.7 ± 2.6
Within Subject CV (%)	~ 6.1	~ 18.4	-	-
Geometric Mean Ratio (GMR)	0.94	0.78	-	-
90% CI of GMR	0.90 – 0.98	0.68 – 0.90	-	-

$AUC_{0-\infty}$ and Cmax: Geometric mean ± back-transformed standard deviation
Tmax: Median (Range); T1/2: Harmonic mean; GMR: Formulation C/Formulation B

Conclusion: The extent of absorption as determined by $AUC_{0-\infty}$ for Formulations B and C were comparable (90% CI for GMR: 0.90-0.98). Formulation C, however, had a lower Cmax and did not pass the bioequivalence criteria (90% CI: 0.68-0.90). The sponsor indicated that the efficacy of Formulation C would be examined in subsequent clinical trials.

Comparison of Three Formulations:
25 mg Tablet, 12.5 mg/5 mL suspension, and 25 mg/5 mL suspension

Study Title: A 3-Period, Balanced, Single-Dose, Crossover Study in Healthy Subjects to Investigate the Comparative Bioavailability of Tablet and Suspension Formulations of MK-0966 (Protocol #048; Vol. 1.75)

Suspension formulations were developed to provide dosing alternatives to patients who may have difficulty swallowing tablets. This study is a pilot study to examine the bioavailability of two suspension formulations as compared to that of the to-be-marketed tablet formulation (Formulation C). It is a single-dose, 3-period, randomized, crossover study in which one tablet or 5 mL of a suspension was administered in each of 3 periods with a 10-day washout between

periods. Blood samples for plasma MK-0966 were collected over 120 hours postdose. A total of 12 healthy subjects (8F & 4M) participated and completed the study. Detailed study design is given in Appendix III.

The parameter values were normalized to a 25-mg dose. (See Table below.) Geometric mean ratios of dose-adjusted parameters (suspension/tablet) for AUC were 0.85 (90% CI: 0.80-0.90) and 0.97 (90% CI: 0.91-1.02) for the 12.5-mg/5 mL and the 25-mg/5-mL suspension formulations, respectively. The corresponding C_{max} ratios were 1.04 (90% CI: 0.88, 1.24) and 0.89 (90% CI: 0.75, 1.06), in the same order. T_{max} and $t_{½}$ were comparable between formulations.

Dose-Adjusted (to 25 mg) Parameter Values

Formulation	$AUC_{0-\infty}$ (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
12.5 mg Suspension	3590.2 ± 887.1	248.9 ± 100.9	2.0	9.2 ± 1.7
25 mg Suspension	4082.4 ± 852.3	212.5 ± 53.8	2.0	9.9 ± 2.4
25 mg Tablet	4230.0± 1138.3	238.3 ± 98.4	3.0	9.6 ± 1.7

$AUC_{0-\infty}$ & Cmax: Geometric mean ± back-transformed standard deviation
Tmax: Median (Range)
T1/2: Harmonic mean

Conclusions:

- The 12.5-mg/5-mL and 25-mg/5-mL suspensions were not bioequivalent to the 25-mg tablet because the 90% CI for Cmax was out of the 80-125% range.
- When both suspensions are compared to the 25-mg tablet, the dose-adjusted Cmax of the 12.5-mg/5-mL suspension more closely approximates that of the 25-mg tablet than that of the 25-mg/5-mL suspension, possibly due to higher variability in Cmax and small sample size.
- The lower bioavailability of the 12.5-mg/5-mL suspension may reflect the slight departure from linearity at lower doses previously observed.
- When administered in single doses, the tablet (25 mg) and 2 suspensions (12.5 mg/5 mL and 25 mg/5 mL) are well tolerated.

Reviewer's Comment: The results from this pilot study were used to better design the following definitive study.

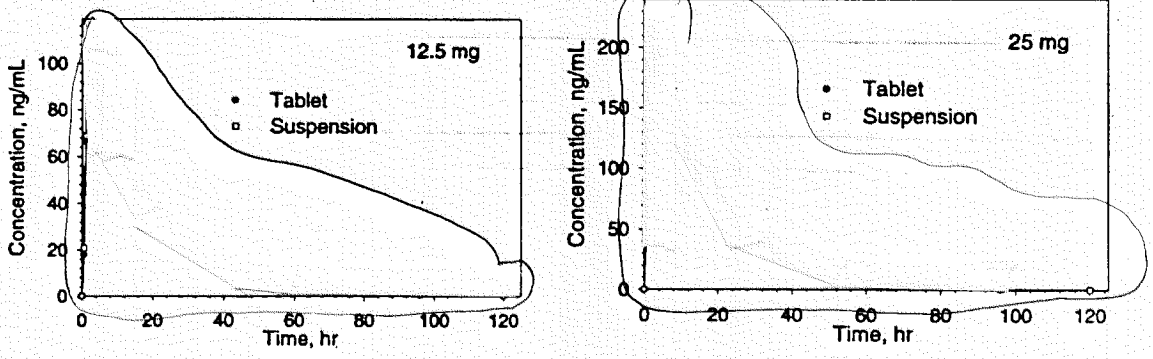
Bioequivalence of Suspension Formulations (12.5 mg/5 mL suspension & 25 mg/5 mL suspension) to Tablet Formulations (12.5 mg & 25 mg) and Food Effect

Study Title: A 2-Part, Open, Balanced, Crossover Study in Healthy Subjects to establish the Bioequivalence of MK-0966 Tablet and Suspension Formulations (#070; Vol. 1.85)

This study was conducted to examine (1) the bioequivalency of suspension formulations to the to-be-marketed tablet formulations and (2) the food effect on the 25-mg tablets. The study had two parts. Part I was a 2-period, crossover study in which a single dose of the 12.5-mg tablet or 12.5-mg/5-mL suspension was administered in the fasted state to 24 healthy subjects (12M & 12 F). Part II was a 3-period, crossover study in which a single dose of the 25-mg tablet (fasting), 25-mg/5-mL suspension (fasting), or 25-mg tablet (with standard high fat breakfast) was

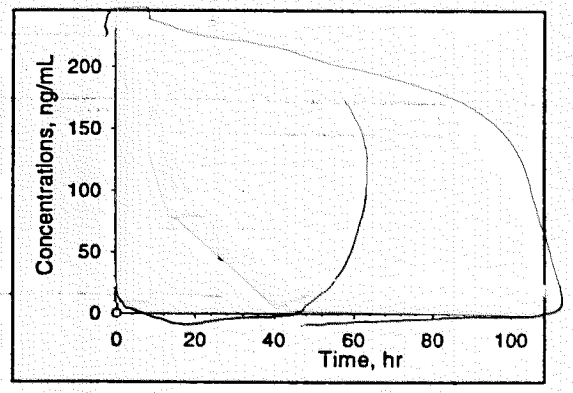
administered to another group of 24 healthy subjects (12M & 12 F). In all periods of both parts, blood samples were collected for plasma MK-0966 concentrations at intervals over 120 hours post-dose. There was a 7-day washout between doses of MK-0966. Detailed study design is given in Appendix III.

Suspension vs. Tablet: The mean plasma concentration time profiles for suspensions closely followed those of tablets for both strengths (12.5 mg & 25 mg) as shown in the figures below. Multiple [redacted] were observed as in previous studies.



The geometric mean AUC and Cmax for both suspension and tablet formulations at both strengths are presented in the table below. The 90% confidence intervals for the geometric mean ratios (GMR; ratio as suspension/tablet) were within the 80-125% range. Both the 12.5 mg tablet and 12.5 mg/5 mL suspension (Part I study) had a median Tmax of 2.0 hrs (Mean: 2.4 hrs for tablet and 2.5 hr for the suspension). In the Part II study, the median and mean Tmax were 2.0 and 2.5 hours, respectively, for the 25mg/5 mL suspension and 3.0 and 3.9 hours, respectively, for the 25 mg-tablet. The terminal half-life was determined to be approximately 10 hours at both doses.

Food effect for the 25-mg tablet:
Compared to the fasted state (see figure; filled circles), the plasma concentrations of MK-0966 under fed conditions (see figure; open circles) in general were delayed and reached a higher Cmax. The geometric mean parameter values are listed in the table above. The 90% confidence intervals were calculated for the geometric mean ratios and were within the range of 80-125% for both AUC and Cmax. In general, Tmax delayed for about 2 hours when the tablet was administered with high fat breakfast.



	$AUC_{(0-\infty)}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Part I				
12.5-mg/5-mL suspension	1778±945[†]	113±39[†]	2.0	10.2±2.9[§]
12.5-mg tablet	1907±847[†]	122±39[†]	2.0	10.5±3.0[§]
Geometric mean ratio (12.5-mg/5-mL suspension/12.5-mg tablet)	0.93 (0.89, 0.98)[‖]	0.92 (0.85, 1.00)[‖]		
Approximate within-subject CV (%)[¶]	10.1	16.2		
Part II				
25-mg/5-mL suspension	3635±1153[†]	213±86[†]	2.0	9.4±3.0[§]
25-mg tablet (fed)	3948±1249[†]	244±64[†]	5.0	9.4±2.2[§]
25-mg tablet	3799±1365[†]	217±72[†]	3.0	9.9±2.7[§]
Approximate within-subject CV (%)	8.5	18.5		
Geometric mean ratio (25-mg/5-mL suspension/25-mg tablet)	0.96 (0.92, 1.00)[‖]	0.98 (0.90, 1.08)[‖]		
Geometric mean ratio (25-mg tablet [fed]/25-mg tablet [fast])	1.04 (1.00, 1.08)[‖]	1.13 (1.03, 1.23)[‖]		

[†] Geometric mean ± back-transformed standard deviation.
[‡] Median (min, max).
[§] Harmonic mean ± jackknife standard deviation.
[‖] 90% CIs for the GMR.
[¶] CV=Coefficient of variation

Conclusions:

- 12.5-mg/5-mL suspension vs. 12.5-mg tablet: Bioequivalent
  90% CI: 89-98% (AUC); 85-100% (Cmax) .
  Tmax: similar (2.0 hrs vs. 2.0 hrs)
- 25-mg/5-mL suspension vs. 25-mg tablet: Bioequivalent
  90% CI: 92-100% (AUC); 90-108% (Cmax)
  Tmax was shorter for the suspension (2.0 hrs vs. 3.0 hrs.)
- Food effect for 25-mg tablet: Effect on Cmax and AUC not clinically important.
  90% CI: 100-108% (AUC); 103-123% (Cmax)
  Tmax was delayed for 1 to 2 hours.

Reviewer's Comments:

1. The ANOVA model for Part II study did not include sequence as a factor. Upon this reviewer's request, the sponsor provided results from re-analysis that separated subject into sequence and subject within sequence as factors in the model. The results indicated a significant sequence effect. However, based on the Guidance on Statistical Procedures for Bioequivalence Studies, the design of this study falls into the circumstances in which the study can be qualified. Therefore, the sponsor is not required to conduct a new study. The sponsor indicated that the re-analysis gave the same geometric mean ratios and confidence intervals as those obtained from previous analysis.

2. Food effect was studied for the 25 mg-tablets only. According to the current Food Effect Guidance, a study is needed for the suspension formulation as well. The sponsor should commit to conduct a Phase IV food effect study for the suspension.

/S/

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. /S/ 5/10/99

CC:
NDA 21-042, 21-052
HFD-550 (Div.File)
HFD-550 (CSO/Cook)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

APPENDIX III

(Studies 036, 048, 057, 064 & 070)

Clinical Pharmacology/Biopharmaceutics Study Summary Sheet

NDA/IND#	SUPPL/AMEND. #		SUBMISSION DATE:		VOLUME:	
21042			23 Nov. 98			
Study Type:	Pharmacokinetics		Study 036			
Study Title:	A 2-Period, Balanced, Single-Dose, Crossover Study in Healthy Subjects to Investigate the Comparative Bioavailability of 2 Tablet Formulations of MK-0966					

CLINICAL INVESTIGATOR(s)	SITE(s)	ANALYTICAL INVESTIGATOR	SITE
		Merck	West Point, PA

SINGLE DOSE:	X	MULTIPLE DOSE:	NA	WASHOUT PERIOD:	7 Days
CROSS-OVER	X	PARALLEL	NA	OTHER DESIGN:	NA

FASTED	X	FOOD STUDY		FDA HIGH FAT BREAKFAST	NA
If fasted, how long (hrs.)?	8 hrs predose	Meals consistant in each period		NA	NA

SUBJECT BREAKDOWN											
Normal	X	Patients	NA	Young	X	Elderly	NA	Renal	NA	Hepatic	NA

	SUBJECT TYPE						GROUP		N=	12	M=	10	F=	2
Weight	Mean	81.4 Kg	M	Range	70.3	88.9	Group		N=	NA	M=	10	F=	NA
Age	Mean	33.1 Yr	M	Range	22	44	Group		N=	NA	M=	10	F=	NA
	SUBJECT TYPE						GROUP		N=	2	M=	NA	F=	2
Weight	Mean	69.4 Kg	F	Range	69.0	69.9	Group		N=	NA	M=	NA	F=	2
Age	Mean	40.0 Yr	F	Range	36	44	Group		N=	NA	M=	NA	F=	2

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
MK-0966 25 mg (25%)	25	Tablet	25 mg	MR-3285	NA
MK-0966 25 mg (12.5%)	25	Tablet	25 mg	MR-3359	NA

SAMPLING TIMES	
Plasma	predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 12, 16, 18, 20, 22, 23, 24, 25, 26, 30, 33, 36, 39, 42, 46, 47, 48, 49, 50, 55, 60, 72, 96, and 120 hours postdose
Urine	NA
Feces	NA

ASSAY METHOD:	
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Pharmacokinetics