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STUDY DESIGN: This is a double-blind, randomized, placebo-controlled, 2-period crossover study. MK-0966 (75 mg daily) or placebo was administered for 14 days with 4 weeks between periods and the EBT administered on Days -1 and 14 of each treatment period.

RESULTS:

A total of 12 subjects entered and completed the study.

The percentage of administered ^{14}C exhaled is summarized in table 1.

Table 1. Summary Statistics for the Percentage of Administered ^{14}C Exhaled (%)

Day	Treatment	Geometric mean (N=12)	GMR	90% CI for GMR
-1	75 mg MK-0966	3.11 ± 0.708	1.07	(0.99, 1.15)
	Placebo	2.91 ± 0.565		
14	75 mg MK-0966	3.07 ± 0.536	1.08	(0.99, 1.18)
	Placebo	2.84 ± 0.662		

The within-subject CV based on the data (Day -1 and Day 14) for just the placebo treatment period was 9.69%.

CONCLUSIONS:

1. The oral administration of MK-0966 75-mg for 14 days does not significantly alter hepatic CYP3A activity as assessed by the EBT.
2. The precision of the EBT test in this study is acceptable.

STUDY P051. A Randomized, Placebo and Active Comparator-Controlled Dose-Ranging Trial of the Effect of a 12.5% Formulation of MK–0966 in the Treatment of Postoperative Dental Pain

This study examined the dose-response relationship of 12.5-, 25-, and 50-mg doses of MK-0966. This is a double blind, randomized, placebo- and active-comparator-controlled, parallel group study. The number of subjects participated in placebo, 12.5 mg, 25 mg, 50 mg MK-0966, and 550 mg Naproxen sodium (active comparator) treatment groups is 48, 72, 72, 72, and 49, respectively. Ten out of 72 subjects in each MK-0966 treatment group had MK-0966 plasma concentration measurements to assess the relationship between the plasma concentration profile of MK-0966 and the observed analgesic effects over an 8-hour postdose period. The dose-response (efficacy) and safety of treatments are reviewed by the medical officer. This review will focus on the PK/PD relationship of MK-0966.

The mean plasma concentration profiles of MK-0966 treatments are shown in figure 1.

Figure 1. Mean plasma concentration profiles of MK-0966 following 12.5, 25 and 50 mg doses
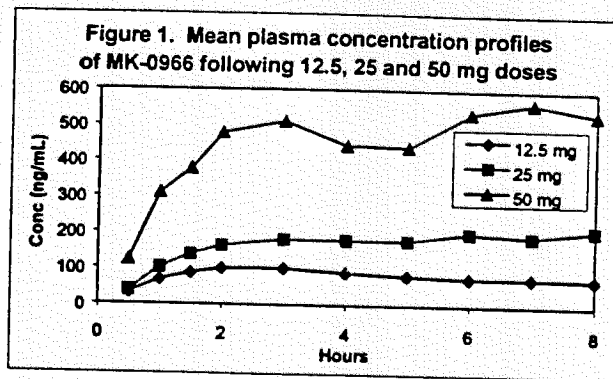
Considering the long half-life (about 10 hours) of MK-0966, the sampling time was not long enough to determine the whole profile. The secondary peaks made the determination of C_{max} difficult. As indicated by the sponsor, the C_{max} value from the individual profiles was not generally obvious for the 25- and 50-mg doses. For many patients, the plasma concentrations appeared to keep increasing up to the 8-hour time point. Therefore, the analysis of the relationship between the C_{max} values and peak analgesic effect was not reliable.

The pharmacodynamic (PD) responses were measured at the same time points as the plasma samples plus 12- and 24-hour measurements. Patients were allowed to take rescue medicine after 1.5 hours (dropouts). The number of patients who had pharamacodynamic measurements decreases with time due to dropouts. For the 10 patients in each dosing group who had PK measurements, the dropout rate was 30%, 30% and 20% at 2 hours, 90%, 60% and 40% at 8 hours for 12.5, 25 and 50 mg dosing group, respectively. Therefore, we have very limited information to establish the PK/PD relationship considering the high variability normally associated with PD response. The sponsor conducted an analysis to assess the correlation between AUC(0.5-8hr) and overall analgesic effect. The results showed that at the 12.5- and 25-mg doses, there was no apparent correlation between AUC and total pain relief (0-8hr) (TOPAR8) or sum of pain intensity difference (0-8hr) (SPID8), and between C_{max} and Peak Pain Relief or Peak PID (correlation coefficients were between -0.32 and 0.23). However, at the 50-mg dose, these pharmacokinetic and pharmacodynamic variables showed moderate-to-strong correlation (correlation coefficients were between 0.47 and 0.73).

Because the analgesic effect is considered more important at earlier time points, the reviewer looked at the relationship between partial AUC (0-1.5hr) and SPID (0-1.5) (Figure 2). The time 1.5 hours was selected because there was no dropout before 1.5


Figure 2. MK-0966 AUC(0-1.5hr) vs. SPID(0-1.5hr)

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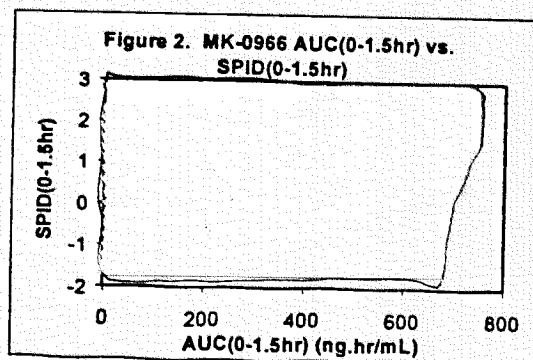
hours. The plot showed that there is no strong correlation between AUC(0-1.5hr) and SPID(0-1.5hr). Based on pervious experience with analgesic drugs, there is normally a delay between the plasma concentration and effect site concentration. Therefore, the assessment of relationship between plasma AUC values and PD response may not be appropriate to assess the PK/PD relationship of the drug. However, limited PK and PD data in this study and unknown PK model for MK-0966 does not allow estimation of this delay, namely the keo value. Therefore, the reviewer tried to assess the PK/PD relationship based on the characteristics of plasma concentration profile of MK-0966.

The mean MK-0966 concentration-time profiles showed that the plasma concentration of MK-0966 did not change much from 2 to 8 hours. Individual data also showed the same trend. Assuming that plasma levels at 4 hours are at "pseudo steady-state", the PK/PD relationship can be assessed by plotting the PID scores versus concentration of MK-0966 at 4 hours, if there is any. Figure 3 is the plot of PID score at 4 hours versus plasma concentration at 4 hours. Zero is used as the PID scores for dropout patients.
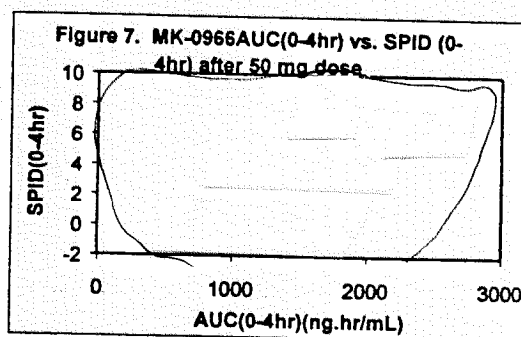

Figure 3. MK-0966 plasma concentrations (4hr) vs. PID (4hr)
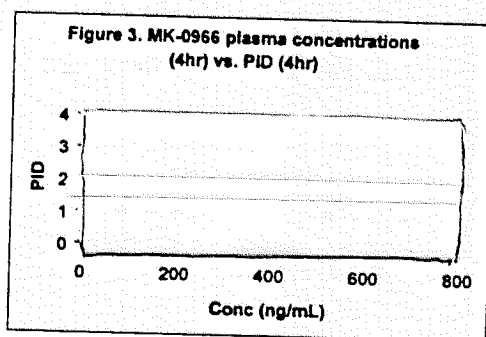
The AUC (0-4hr) and AUC (0-8hr) were also plotted versus SPID (0-4hr) and SPID (0-8hr) (Figures 4 and 5).

Figure 4. MK-0966 AUC(0-4hr) vs. SPID(0-4hr)

Figure 5. MK-0966 AUC(0-8hr) vs. SPID(0-8hr)
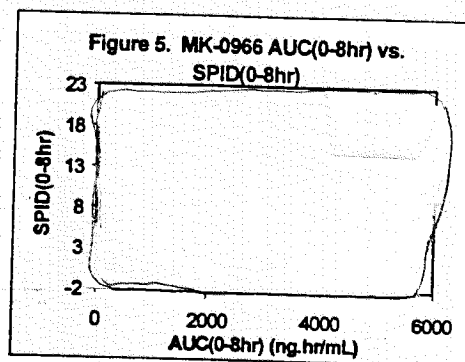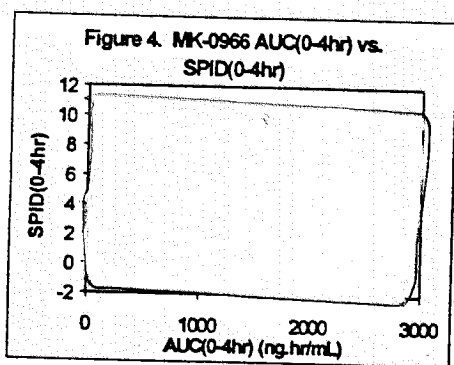
No plasma concentration and effect relationship can be identified from any of the above plots.

However, moderate correlation between plasma levels and pain relief was observed following 50 mg dose as shown in Figures 6 and 7.

Figure 6. MK-0966 AUC(0-1.5hr) versus SPID(0-1.5hr) after 50 mg dose

Figure 7. MK-0966 AUC(0-4hr) vs. SPID (0-4hr) after 50 mg dose
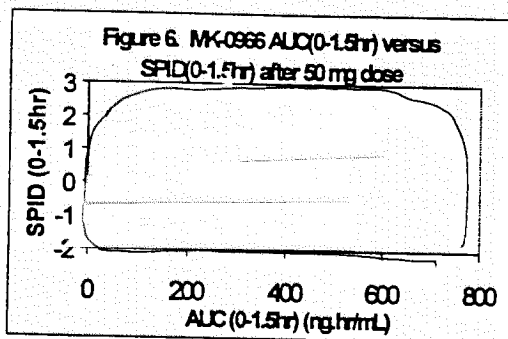
CONCLUSIONS:

Because of limited sample size and variability in the PD variable, PK/PD relationship can not be established from this study. However, the results from patients with both PK and PD measurements suggest that 12.5 and 25 mg dose are not the effective dose for analgesic indication. The 50 mg dose raised MK-0966 plasma concentrations to the level that produce analgesic effect.

STUDY P073. A Partially Open-Label, 3-Part, Randomized, Crossover Study to Investigate the Influence of Altered CYP3A Activity on MK–0966 Pharmacokinetics and of MK–0966 on CYP3A Activity in Healthy Subjects

BACKGROUND: Study P046 investigated the impact of MK-0966 on hepatic CYP3A activity, as assessed during the erythromycin breath test (EBT), prior to and after 14 days of once-daily treatment with 75 mg MK-0966. It was concluded from the study that MK-0966 did not meaningfully alter hepatic CYP3A activity. Nonetheless, given the importance of CYP3A activity for the biotransformation of other drugs, and the intestinal fraction of CYP3A can also contribute substantially to the metabolism of orally administered drugs, a further evaluation of the influence of MK-0966 on CYP3A activity was undertaken in this study utilizing an evaluation of the effect of MK-0966 on oral midazolam pharmacokinetics. Because midazolam metabolism proceeds through both intestinal and hepatic CYP3A, it can be utilized to determine if the intestinal component of CYP3A activity (as compared with hepatic activity alone as tested with the erythromycin breath test) was affected by MK-0966.

In vitro data demonstrated that CYP3A was not likely to be a prominent metabolic pathway for MK-0966. Nonetheless, given the importance of drug interactions produced by inhibitors and/or inducers of CYP3A, it was felt important by the sponsor to demonstrate in humans whether or not classical inhibitors (ketoconazole) or inducers (rifampin) of CYP3A had any meaningful impact on the pharmacokinetics of MK-0966.

STUDY DESIGN: This was a partially open-label, 3-part, randomized, crossover study in which each subject participated in 1 of 3 different investigations: 25 mg MK-0966 or

placebo with midazolam (Part I); 25 mg MK-0966 with and without ketoconazole (Part II); 25 mg MK-0966 with and without rifampin (Part III). Subjects in Part I had CYP3A activity assessed with the oral midazolam hydroxylation test in the presence and absence of 12 days oral MK-0966. Subjects in Part II had MK-0966 kinetics assessed after 11 days of oral dosing in the presence and absence of oral ketoconazole. Subjects in Part III had MK-0966 kinetics assessed after 11 days of oral dosing in the presence and absence of oral rifampin. There was a 21-day washout between the 2 periods in each part of the study and each subject participated in only 1 part of the study.

RESULTS:

A total of 25 subjects (15 men and 10 women) entered, and 23 completed, the study. Subjects that did not completed the study were excluded from the analysis (data were not available).

1. Oral Midazolam – effect of MK-0966 on CYP3A activity

The though levels of MK-0966 indicated that the steady-state was achieved on day 3.

Mean concentration profiles of midazolam following 2 mg doses on Day 11 with MK-0966 or placebo are plotted in figure 1.
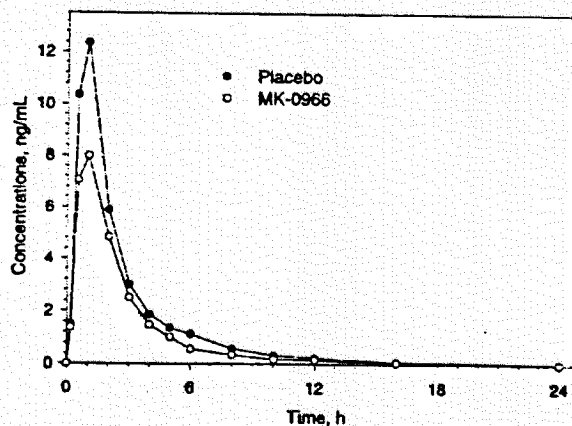

Figure 1

The mean PK parameters of midazoam are summarized in table 1.

Tabie 1. Summary Statistics for Midazolam AUC0-32 hr (ng•hr/mL) and Cmax (ng/mL) Following Administration of a Single 2-mg Oral Dose to Subjects Receiving a 12-Day Course of 25 mg MK-0966 or Placebo

	Treatment	N	Geometric Mean (±SD)	GMR	90% CI for GMR
$AUC_{0-32\ hr}$	MK-0966 + midazolam	8	19.5 (4.5)	0.71	(0.58, 0.88)
	Placebo + midazolam	8	27.4 (6.4)		

		N			
C_{max}	MK-0966 + midazolam	8	8.7 (1.6)	0.71	(0.60, 0.84)
	Placebo + midazolam	8	10.8 (2.3)		
$T_{1/2}$	MK-0966 + midazolam	8	1.25 (0.38)		p-value = 0.558
	Placebo + midazolam	8	1.34 (0.30)		
Amount of metabolite[1]	MK-0966 + midazolam	8	1.31 (0.47)		p-value = 0.962
	Placebo + midazolam	8	1.32 (0.31)		

[1] 1'-hydroxy-midazolam (mg) (major metabolite) recovered in urine

The results indicated that MK-0966 decreased midazolam AUC and Cmax by about 30%. This did not result from any apparent change in the total absorption of midazolam since comparable total urinary excretion of 1'-hydroxy midazolam was found in the presence and absence of MK-0966. In addition, no difference in apparent terminal half-life was evident, suggesting that the observed difference did not arise from a change in systemic metabolism (consistent with the erythromycin breath test data discussed above), but rather, perhaps from increased first-pass metabolism through induction of intestinal CYP3A by MK-0966.

2. Ketoconazole – effect of CYP3A inhibitor on MK-0966 pharmacokinetics

The plasma concentration profiles of MK-0966 given MK-0966 alone or with ketoconazole are plotted in figure 2. Pharmacokinetic parameters are summarized in
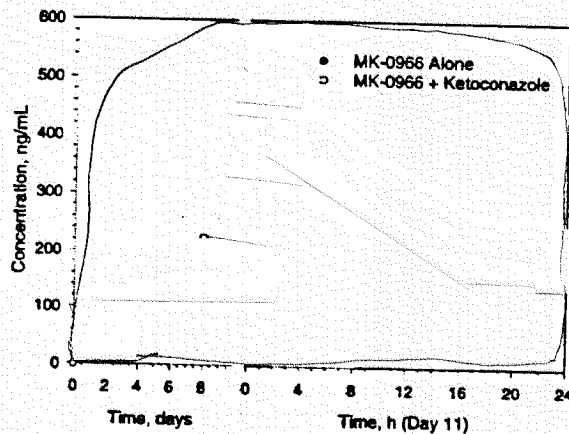

Figure 2

Table 2.

Table 2. Summary Statistics for MK-0966 $AUC_{0-24 hr}$ (ng·hr/mL) and C_{max} (ng/mL) for the MK-0966 Alone and MK-0966 With Ketoconazole Treatments

	Treatment	N	Geometric Mean (±SD)	GMR	90% CI for GMR
$AUC_{0-24 hr}$	MK-0966 + ketoconazole	7	6760 (905)	1.05	(0.92, 1.21)
	MK-0966 alone	7	6430 (861)		
C_{max}	MK-0966 + ketoconazole	7	469 (30)	0.87	(0.82, 0.93)
	MK-0966 alone	7	537 (35)		

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Higher though levels were observed in the treatment of MK-0966 with ketoconazole. However, the comparison of AUC and Cmax values at steady-state indicated that ketoconazole did not affect the PK of MK-0966 significantly. The sponsor indicated that this finding is consistent with in vitro results demonstrating that CYP3A plays a minimal role in the metabolism of MK-0966.

3. Rifampin – effect of CYP3A inducer on MK-0966 pharmacokinetics

The plasma concentration profiles of MK-0966 given MK-0966 alone or with rifampin are plotted in figure 3. Pharmacokinetic parameters are summarized in table 3.
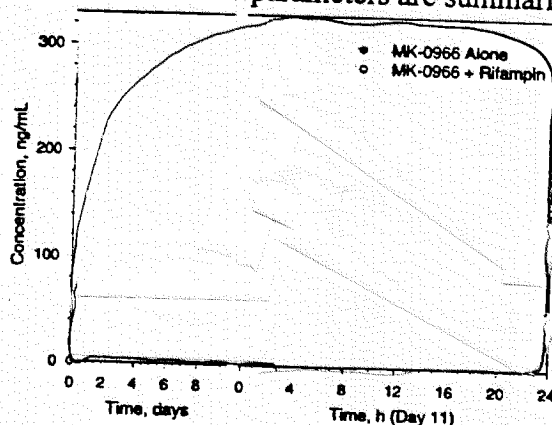

Figure 3

Table 3. MK-0966 $AUC_{0-24 hr}$ (ng•hr/mL) and C_{max} (ng/mL) Summary Statistics for MK-0966 With and Without Rifampin Treatments

	Treatment	N	Geometric Mean (±SD)	GMR	90% CI for GMR
$AUC_{0-24 hr}$	MK-0966 + rifampin	8	2129 (576)	0.50	(0.39, 0.63)
	MK-0966 alone	8	4295 (1161)		
C_{max}	MK-0966 + rifampin	8	222 (74)	0.72	(0.54, 0.97)
	MK-0966 alone	8	306 (103)		

The results showed a significant decrease in both AUC and Cmax values when MK-0966 was given with rifampin. This suggests that when a potent inducer of cytochrome P-450 enzymes is coadministered, the cytochrome P-450 dependent pathways become more important in the metabolic disposition of MK-0966. However, the sponsor indicated that one could not necessarily invoke CYP3A specifically. Although rifampin is one of the most potent inducers of CYP3A, it has also been implicated in the induction of CYP2C9/10/11, CYP2A1, CYP2B1, glucuronosyltransferase, sulfotransferase and glutathione S-transferase. Furthermore, rifampin's effects are not limited to the liver and evidence suggests that its effects may extend to intestinal metabolism. Considering the results of ketoconazole interaction study and in vitro study, the sponsor believes that it is likely that the effect of rifampin on MK-0966 disposition is not mediated through CYP3A, and instead reflects the induction of enzymes other than CYP3A. Although this is possible, the reviewer believes that no solid conclusion can be made at this point. Based on the result of this study, the sponsor suggested treating osteoarthritis patients with 25 mg MK-0966 rather than the usual 12.5-mg starting dose of MK-0966 when it is

given to patients receiving chronic therapy with potent inducers of hepatic metabolism. The reviewer believes that this dose adjustment is acceptable as long as the safety data from clinical trials permit.

It is noticed that the AUC and Cmax values of MK-0966 alone obtained from Part II and Part III are very different (Tables 2 and 3). Inspection of demographic data revealed that such different was likely due to body weight difference between the treatment groups. The steady-state AUC(0-24hr) and Cmax values are plotted in Figure 4 and 5.

Figure 4. Steady-state AUC(0-24hr) versus Body Weight after 25 mg doses
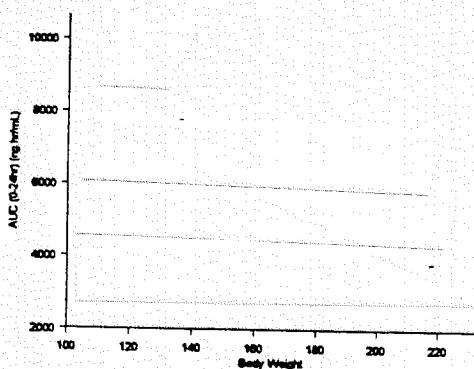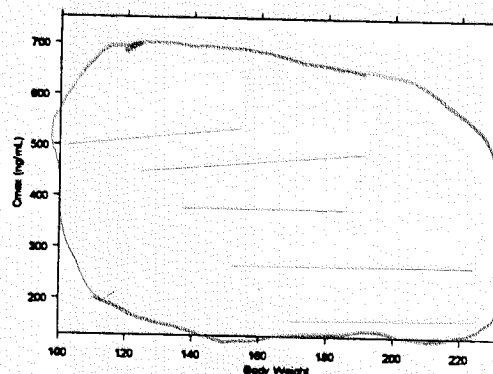
Figure 4. Steady-state Cmax versus Body Weight after 25 mg dose

A strong relationship was observed between AUC and body weight, as well as Cmax and body weight. AUC and Cmax decrease when body weight increases.

CONCLUSIONS:

1. The administration of MK-0966 25-mg orally daily for 12 days caused a decrease in midazolam AUC and Cmax by about 30%. This reduction in AUC and Cmax is most likely due to increased first-pass metabolism through induction of intestinal CYP3A by MK-0966.
2. Inhibition of CYP3A activity by administration of ketoconazole 400 mg daily does not affect MK-0966 disposition, confirming in vitro data that CYP3A is not a dominant metabolic pathway for MK-0966.
3. Induction of hepatic metabolic activity by administration of the inducer rifampin 600 mg daily produces a 50% decrease in MK-0966 plasma concentrations. The dose of 25 mg MK-0966 should be considered for the treatment of osteoarthritis when MK-0966 is coadministered with potent inducers of hepatic metabolism.
4. A strong relationship was observed between AUC and body weight, as well as Cmax and body weight. AUC and Cmax decrease when body weight increases.

STUDY P076. A 2-Part, Open, Randomized Study to determine the Absolute Bioavailability of 12.5- and 25-mg Final Market Image Tablets of MK–0966

BACKGROUND: The absolution bioavailability of MK-0966 had been studied in Study P037. The estimated bioavailability from a comparison of a 50-mg oral and a 1-mg I.V. dose is 122%. The sponsor believed that this unrealistically high value is likely related to nonlinear pharmacokinetics of MK-0966 in this dosing range (higher clearance at lower

dose). To overcome this problem, joint administration of an oral and a tracer I.V. dose is used in this study, since both doses are then subject to the same clearance. Isotopic labeling of one of the doses allows for analytical differentiation by route of administration (oral versus I.V.). Because this approach was dependent upon the use of the ^{13}C label for MK-0966, and isotopic differences may affect the kinetics of enzyme interactions ("isotope effect"), Part I of this study was performed to ensure the absence of altered pharmacokinetics.

STUDY DESIGN: Part I was a single-period study in which an intravenous (I.V.) 1-mg dose of $[^{13}C_7]$MK-0966 was coadministered with an I.V. 1-mg dose of unlabeled MK-0966. Plasma samples were obtained at specified intervals during the subsequent 73 hours after initiation of the infusion. There was a 7-day washout prior to proceeding to Part II. Part II was an open, randomized, 2-period, crossover study in which $[^{13}C_7]$MK-0966 1 mg I.V. was administered along with either MK-0966 12.5- or 25-mg tablets (Formulation C). There was a 2-hour delay from oral dosing to the initiation of the 30-minute I.V. infusion. Subjects received either 12.5 or 25 mg in periods in a balanced fashion. Plasma samples were obtained at specified intervals during the subsequent 121 hours after administration of the tablet during each period. There was a 7-day washout between doses in Part II.

RESULTS: Nine healthy subjects entered and completed Part I. Data for 6 additional healthy subjects were collected in Part II (subject AN 013 withdrew consent before the study was completed).

The plasma concentration profiles after IV (labeled and unlabeled) are shown in Figure 1.

Figure 1. Plasma Concentration Versus Time Profile for Intravenous $[^{13}C_7]$MK-0966 1 mg and MK-0966 1 mg in Healthy Adults (Mean ± SE)

◆ = MK-0966 1 mg
■ = [13C]MK-0966 1 mg
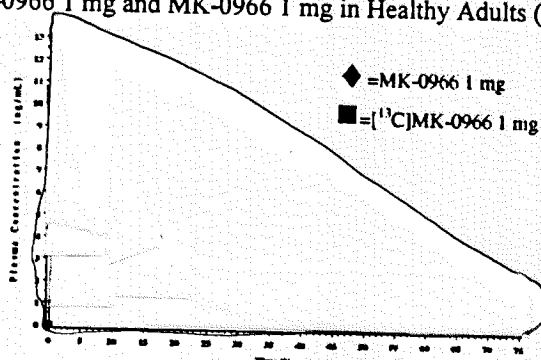
The geometric mean AUC$_{(0-\infty)}$ was 82.5 and 81.7 ng•hr/mL for $[^{13}C_7]$MK-0966 and MK-0966, respectively. The AUC$_{(0-\infty)}$ GMR was 1.01, with a 90% CI of (0.99, 1.03). This result indicated that labeling with a carbon isotope did not affect the disposition of MK-0966. Therefore, $[^{13}C_7]$MK-0966 can be used to evaluate the absolute bioavailability of the MK-0966.
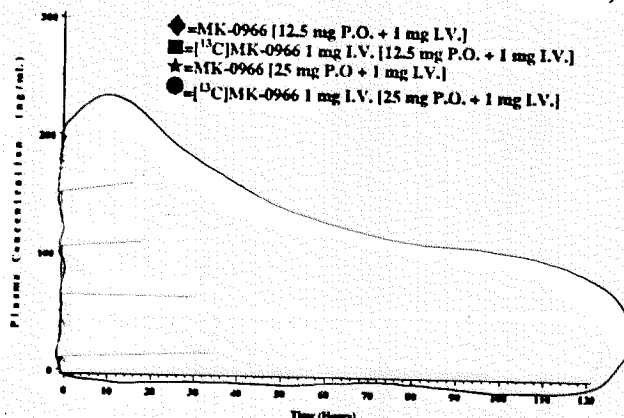
In addition, half-life for each dose and plasma clearance and volume of distribution for the combined 2-mg dose were also evaluated. The mean half-life was 6.3 and 6.1 hours for $[^{13}C_7]$MK-0966 and MK-0966, respectively. A mean plasma clearance of 190.8

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mL/min and volume of distribution of 104.8 L were estimated following infusion of the 2-mg I.V. dose. It is also noticed that the secondary peaks noted previously after oral and I.V. dosing are again evident in the mean as well as individual plasma concentration profiles.

ABSOLUTE BIOAVAILABILITY

The plasma concentration profiles after 12.5 mg and 25 mg oral dose of MK-0966, and 1 mg I.V. dose of $[^{13}C]MK-0966$ are shown in Figure 2.

Figure 2. Plasma Concentration Versus Time Profiles for Oral and Intravenous Formulations of MK-0966 in Healthy Adults (Mean ± SE)

◆=MK-0966 [12.5 mg P.O. + 1 mg I.V.]
■=[^{13}C]MK-0966 1 mg I.V. [12.5 mg P.O. + 1 mg I.V.]
★=MK-0966 [25 mg P.O + 1 mg I.V.]
●=[^{13}C]MK-0966 1 mg I.V. [25 mg P.O. + 1 mg I.V.]

The geometric mean AUC(0-∞) values (N=15) following each dosing are summarized in the following tables.

Table 1. Absolute Bioavailability of 12.5-mg MK-0966 Tablet (90% CI for the Dose-Adjusted AUC(0-∞) Geometric Mean Ratio of the 12.5-mg Tablet Versus the 1 mg I.V.)

Treatment	N	Geometric Mean	GMR of Tablet to I.V.	90% CI for GMR of Tablet to I.V.	Approximately Within-Subject CV (%)
$AUC_{(0-\infty)}$ (ng•hr/mL) Dose-Adjusted to 12.5 mg					
12.5 mg oral	15	1422.8	0.92	(0.89, 0.96)	5.85
[$^{13}C_7$]MK-0966 1 mg (dose-adjusted to 12.5 mg)	15	1538.9			

Table 2. Absolute Bioavailability of 25-mg MK-0966 Tablet (90% CI for the Dose-Adjusted AUC(0-∞) Geometric Mean Ratio of the 25-mg Tablet Versus the 1 mg I.V.)

Treatment	N	Geometric Mean	GMR of Tablet to I.V.	90% CI for GMR of Tablet to I.V.	Approximately Within-Subject CV (%)
$AUC_{(0-\infty)}$ (ng•hr/mL) Dose-Adjusted to 25 mg					
25-mg oral	15	3289.5	0.93	(0.90, 0.96)	4.84
[$^{13}C_7$]MK-0966 1 mg (dose-adjusted to 25 mg)	15	3528.2			

The absolute bioavailability of MK-0966 was 0.92 and 0.93 for the 12.5 mg and 25 mg tablets, respectively. Estimated values for Vss were 105, 91, and 86 L for the total dose of 2-mg, 13.5-mg, and 26-mg, respectively. The mean plasma clearance was 191, 140.7, and 121.4 mL/min for the three different doses.

CONCLUSION:

The absolute bioavailability of MK-0966 tablets (Formulation C) is about 92% and 93% for the 12.5-mg, and 25-mg doses, respectively. Nonlinear pharmacokinetics exists in the dose range of 1 to 50 mg MK-0966.

IV. DISSOLUTION
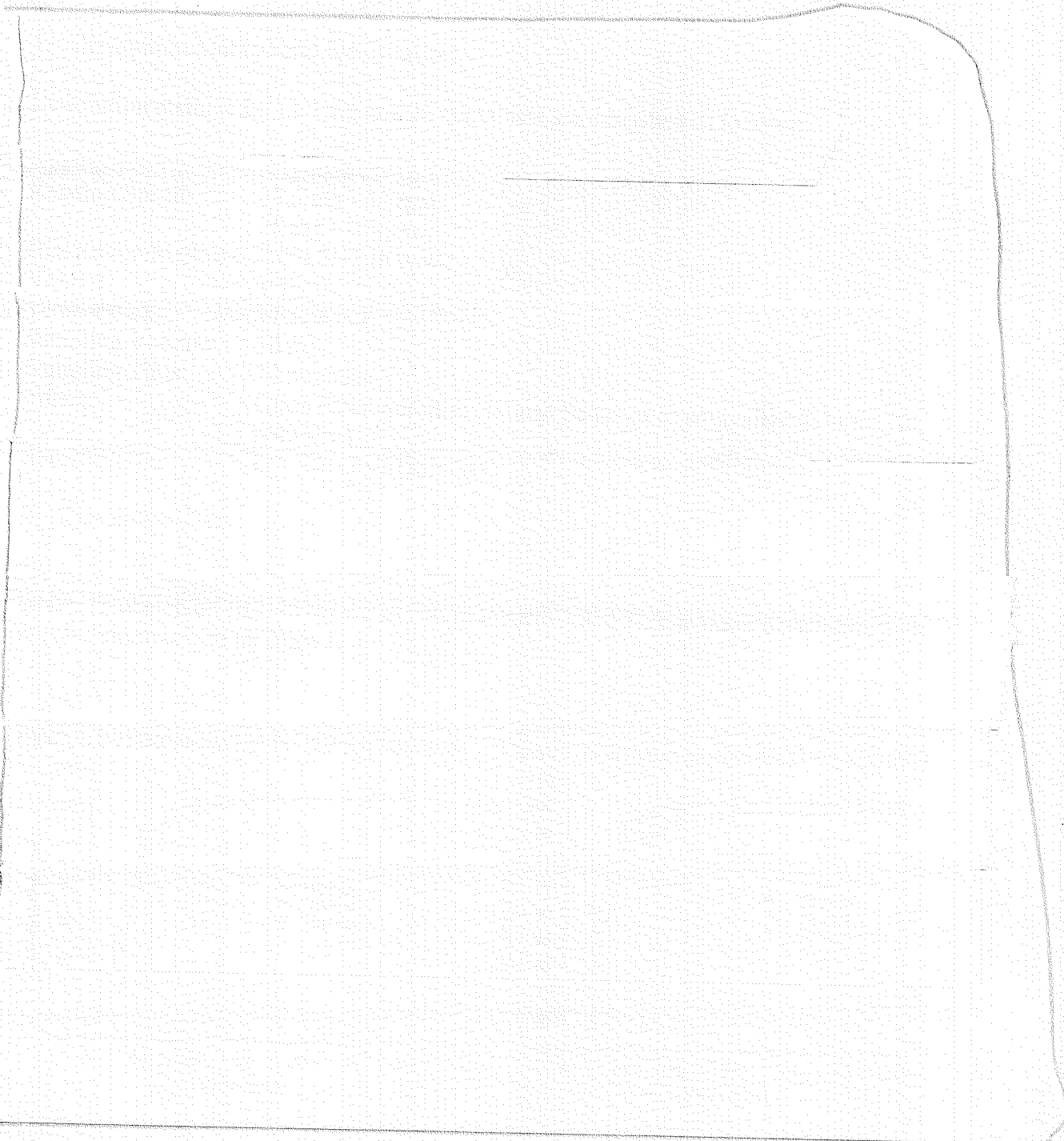
LABELING COMMENTS (need to be sent to the sponsor):

Because of the large number and varied location of the labeling revisions needed, they will not be included in this review, but will be conveyed to the sponsor in toto by the Project Manager once all of the review teams comments have been obtained.

/S/

/ Dan Wang, Ph.D.
Division of Pharmaceutical Evaluation III

FT initialed by E. Dennis Bashaw, Pharm.D /S/ 5/16/99

cc: NDA 21-042 and 21-052 (ORIG)
HFD-550/Div File
HFD-550/PM/Sandy Cook
HFD-880(Wang/Bashaw/Lazor)
HFD-880(Drug File)
CDR: Attn. Barbara Murphy

Appendix I

10 pages
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Appendix IV