STUDY P003. A Double-Blind, Randomized, Placebo-Controlled, Rising Single (Part 1) and Multiple (Part 2) Oral Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of L-748,731 in Healthy Elderly Male and Female Volunteers

This study was to assess the safety, tolerability and pharmacokinetics of MK-0966 following rising single and multiple oral doses of 250 mg, 500 mg and 750 mg MK-0966. These dose levels are much higher than those intended for clinical use (25 and 50 mg). This study is reviewed for gender effect and age effect on PK of MK-0966. (This study may not need to be included in the review)

This was a double-blind, randomized, placebo-controlled, rising single (Part 1, 20 subjects) and multiple (Part 2, 10 subjects) oral dose study in healthy elderly men and women (age ≥ 65 yrs). In Part 1, 8 men and 8 women received single doses of MK-0966 250, 500, and 750 mg, and 3 men and 1 woman received placebo in 3 separate treatment periods. There was at least a 2-week interval between treatment periods in Part 1. In Part 2, 4 men and 4 women received single daily doses of MK-0966 125 mg for 7 days, followed by 250 mg for 7 days, followed by 375 mg for 4 days, and 1 man and 1 woman received placebo for 18 consecutive days. The final dosing interval in Part 2 was discontinued on Day 18 prior to the scheduled completion on Day 21 because of clinical adverse effects (nausea and vomiting) in one subject.

Plasma samples were taken up to 120 hours following single doses and trough levels were obtained after multiple doses. However, samples from multiple dosing were not assayed. Therefore, pharmacokinetics of MK-0966 was only assessed after single dose administration in this study. Following multiple dosing, only safety was evaluated.

RESULTS:

1. Dose proportionality

Consistent with study P002, $AUC_{(0-120h)}$ increases with dose in a less than dose proportional manner. The mean dose-adjusted $AUC_{(0-120h)}$ values for 250 mg, 500 mg and 750 mg doses are 51.0, 39.8 and 35.1 µg.h/mL, respectively.

2. Gender effect

Geometric mean (N=8) AUC_{0-120}, Cmax and 90% CI about the AUC_{0-120} and Cmax GMR (female/male) for each dose are summarized in the following table.

Summary Statistics for AUC_{0-120h} (µg.hr/mL) and Cmax (ng/mL) by Treatment Separated by Gender

Dose (mg)	Gender	AUC_{0-120}	GMR_{AUC}	90% CI_{AUC}	Cmax	GMR_{Cmax}	90% CI_{Cmax}
250	Female	55	1.15	0.91 – 1.46	1302	1.09	0.87 – 1.35
	Male	47			1198		
500	Female	74	0.87	0.67 – 1.13	1711	1.01	0.81 – 1.26
	Male	85			1696		
750	Female	109	1.07	0.79 – 1.43	2534	1.34	1.00 – 1.80
	Male	102			1891		

In elderly people, the maximum gender difference observed was 15% higher AUC in females at 250 mg dose and 34% higher Cmax in females at 750 mg dose level. The terminal half-life ($t_{1/2}$) values were also compared at each dose. No statistically significant difference in $t_{1/2}$ was found.

3. Age effect

The geometric mean AUC_{0-24h} and Cmax values were compared for the elderly subjects and young subjects (study P002) at 250 mg dose level. The results were summarized in the following table.

Summary Statistics for Healthy Elderly Subjects Versus Healthy
Young Subjects at the MK-0966 250-mg Single Dose

	N	Geometric Mean	Min, Max	Between-Group SD	Between-Group p-Value	GMR[†]	90% CI for GMR
MK-0966 AUC_{0-24} (µg·hr/mL)							
Elderly Men and Women	16	20.6		0.280	0.0642	1.30	(1.03, 1.64)
Young Men	6	15.9					
MK-0966 C_{max} (µg/mL)							
Elderly Men and Women	16	1.3		0.309	0.0503	1.36	(1.06, 1.76)
Young Men	6	0.9					
MK-0966 T_{max} (Hours)							
		Median[‡]		SE			
Elderly Men and Women	16	23.9		1.92	0.021	--	--
Young Men	6	4.0		0.00			

[†] The ratio was elderly/young.
[‡] Since the data was rank-transformed, the median is reported.
[§] One subject was an outlier with a T_{max} of 24 hours; he was removed from the summary table above, but analyses done with and without this subject were consistent.

It is observed that the systemic exposure of MK-0966 was _____ higher in elderly subjects than young subjects.

CONCLUSIONS:

The $AUC_{0-120\ hours}$ showed a less than dose-proportional increase in the dose range of 250 to 750 mg. Moderate increase in $AUC_{0-120\ hours}$ (_____) and Cmax (_____) was observed in elderly females compared to elderly males at 250 mg dose and 750 mg dose, respectively. Across comparison between studies P002 and P003 indicated that the systemic exposure of MK-0966 was about _____ in elderly subjects than young subjects.

STUDY P005. A Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Biochemical Selectivity of L-748,731 With Multiple-Dose Administration to Healthy Male Volunteers

The objectives of this study were to (1) evaluate the safety and tolerability of 13 daily oral doses of MK-0966 administered over a 14-day period; (2) obtain steady-state plasma pharmacokinetic data for MK-0966 and compare the area under the plasma concentration versus time curve (AUC) $AUC_{0-\infty}$ following a single dose with the plasma $AUC_{0-24 hours}$ following multiple doses administered once daily; (3) obtain evidence of sustained biochemical selectivity by measurement of the effect of multiple doses of MK-0966 on ex vivo lipopolysaccharide (LPS)-induced whole blood prostaglandin E_2 (PGE_2), serum thromboxane B_2 (TXB_2), and bleeding time; (4) analyze urine for MK-0966 and potential metabolites, change in urine 6-beta-hydroxycortisol (6-β-OH cortisol)/cortisol ratio, and creatinine clearance following multiple doses of MK-0966; (5) assess the effect of multiple-dose administration of MK-0966 on blood pressure and body weight. This review will focus on pharmacokinetic aspect of the study.

This was a randomized, double-blind, placebo-controlled, staggered incremental dose, parallel-group study in 4 panels (A, B, C, and D). Each panel was comprised of 8 healthy young men; within each panel, 2 subjects received placebo and 6 subjects received MK-0966. MK-0966 dose levels were 25, 100, 250, and 375 mg. All doses were taken orally once daily in the morning on Day 1 and Days 3 to 14; a dose was not administered on Day 2. Dosing was followed by a standard breakfast (a Belgian waffle and 240 mL of orange juice), except on Days 1 and 14 when subjects fasted until 4 hours postdose due to pharmacokinetic sampling. Plasma samples for drug assay were collected on Day 1 predose (baseline) and 1, 1.5, 2, 4, 6, 8, 11, 14, 24, 30, 36, and 48 hours postdose; on Days 7, 9, 11, 12, and 14 predose (trough); and on Day 14 at 1, 1.5, 2, 4, 6, 8, 11, 14, 24, 36, 48, and 96 hours postdose. Urine samples were collected but not assayed for MK-0966.

RESULTS:

1. Pharmacokinetics

Thirty-two men were scheduled to enter the study, however, 1 subject (AN 014) failed to report to the clinic at the start of the study and he was not replaced [3.8]. Therefore, Panel B had only 5 subjects who received MK-0966 instead of 6 subjects as in other three panels.

Mean (±SE) plasma concentration versus time profiles following single (Day 1) and multiple (Days 7, 9, 11, 12 and 14) doses are in Figure 1. Secondary peaks in plasma drug concentration observed in another multiple-dose study (P003) were also observed in this study.

Figure 1. Mean Concentration of MK-0966 in plasma following administration of Single and Multiple Oral Doses to Healthy Man
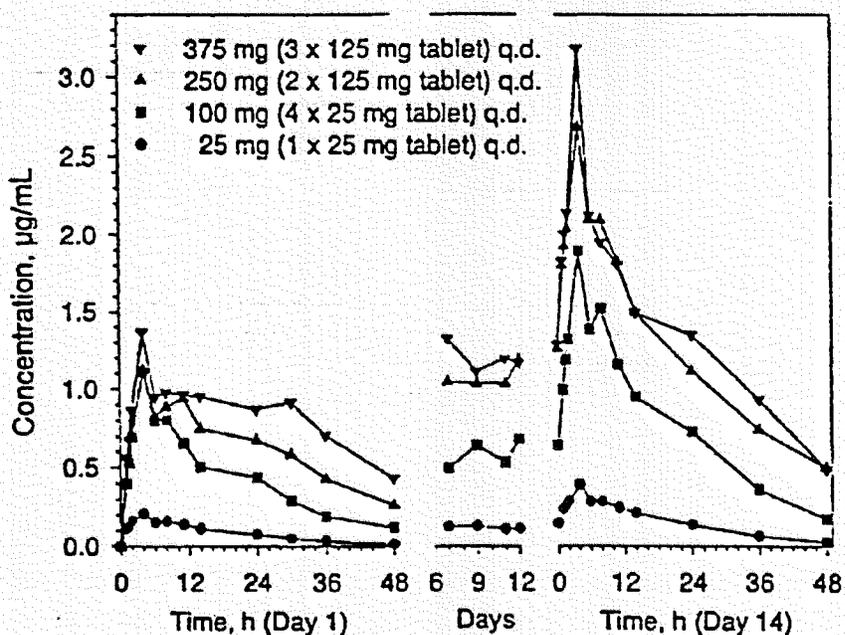
1) Dose proportionality

The geometric mean of dose adjusted (to 25 mg) MK-0966 $AUC_{0-48\ hours}$ on Day 1 were 3798, 4887, 2936, and 2538 ng•hr/mL for the 25-, 100-, 250-, and 375-mg doses, respectively. Dose proportionality was not obtained. The highest dose adjusted $AUC_{0-48\ hours}$ for 100 mg may suggest non-linear pharmacokinetics, while lower $AUC_{0-48\ hours}$ values for 250- and 375- mg doses may be caused by low solubility of the drug substance. The dose-adjusted $AUC_{0-48\ hours}$ values for the 250- and 375-mg dose groups were not significantly different from one another.

2) Attainment of Steady-State

Trough concentrations of MK-0966 were similar between Days 7, 9, 11, 12, and 14 for all treatments (p>0.200), indicating that steady state was achieved for each treatment within 4 days of multiple-dose administration (note that Day 3 began the continuous multiple-dose portion of the study) (Figure 1).

3) Accumulation

It is noticed in the study design that MK-0966 was given under fasting condition for the first and last doses (Days 1 and 14), while given with food for the doses on Days 3 to 13. It is learned from study P002 that food increases the absorption of MK-0966 by about 100% at 250- mg dose level. Therefore, the food effect, if any, might confound with the determination of accumulation factor. However, from the trough levels (Figure 1), it appears that the effect food is not significant for the treatments studied. Otherwise, the

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trough levels on Day 14 would be lower than those measured on previous days when MK-0966 was given with food. The lack of food effect observed in this study might be due to the low fat breakfast (a Belgian waffle and 240 mL of orange juice) used in this study. In study P002, MK-0966 was given with a standard high fat breakfast, which increased the absorption of MK-0966 by increasing the solubility of the drug.

The geometric mean values of MK-0966 $AUC_{0-24\ hours}$ and Cmax on Days 1 and 14, and their geometric mean ratios (GMR) are summarized in Table 1. The accumulation ratios were similar across all doses (p>0.200) for $AUC_{0-24\ hours}$.

Table 1. The geometric mean of MK-0966 AUC_{0-24} (ng·hr/mL) on Days 1 and 14 across treatments

		25 mg	100 mg	250 mg	375 mg
AUC_{0-24} (ng·hr/mL)	Day 1	2941	14376	18479	22035
	Day 14	5427	26238	40634	42009
	GMR	1.85	1.83	2.20	1.91
Cmax (ng/mL)	Day 1	203	1102	1139	1332
	Day 14	382	1832	2649	3169
	GMR	1.88	1.66	2.33	2.38

The median Tmax is about 4 hours across the dose range studied both after single dose and at steady-state. The accumulation half-life values were calculated for each dose group.

4) Terminal half-life ($t_{1/2}$) on Days 1 and 14

The terminal $t_{1/2}$ values were difficult to estimate because of the presence of secondary peaks observed in the plasma drug concentration curves. In addition, the duration of sampling was insufficient to fully characterize the terminal elimination phase. The terminal $t_{1/2}$ values calculated based on available data for each dose at Days 1 and 14 and summarized in Table 2.

Table 2. Summary of MK-0966 terminal $t_{1/2}$ (hours) on Days 1 and 14

	25 mg	100 mg	250 mg	375 mg
Day 1				
Day 14				

The terminal $t_{1/2}$ values increase with dose suggesting non-linear pharmacokinetics in this dose range.

2. Effect on CYP 3A

The urinary excretion of free cortisol and 6-β-OH cortisol was measured. The sponsor indicated that the ratio of 6-β-OH cortisol/cortisol was to be used to screen MK-0966 for any potential to alter CYP 3A-mediated metabolism of cortisol. The ratio of urine 6-β-OH cortisol/cortisol has been proposed as a measurement of hepatic (and maybe renal)

CYP 3A activity. The 6-β-OH cortisol/cortisol ratio values at baseline (Day-1) and the end of the treatment (Day 14) are summarized in Table 3.

Table 3. The 6-β-OH cortisol/cortisol ratio values (SD) on Day-1 and Day 14

	Placebo (N=6)	100 mg (N=5)	250 mg (N=6)	375 mg (N=6)
Day 1	7.1 (3.3)	7.9 (3.9)	8.0 (2.5)	10.6 (2.6)
Day 14	8.4 (2.7)	11.5 (5.8)	9.1 (6.1)	8.3 (1.8)

The statistical analysis showed that there was no statistically significant difference between treatment groups on both Day 1 and Day 14. Therefore, no effect of MK-0966 on urine 6-β-OH cortisol/cortisol ratio was evident after 12 consecutive once-daily doses of up to 375 mg MK-0966. These data suggest no important induction of hepatic/renal CYP 3A-mediated metabolism using endogenous cortisol as a probe.

CONCLUSIONS:

Dose proportionality was not obtained following the administration of 25-, 100-, 250-, and 375-mg doses of MK-0966 indicated by their corresponding $AUC_{0-48\ hours}$ values on Day 1. Negative deviation from linearity was observed at both low (25 mg) and high (250 and 350 mg) dose levels. Steady-state was achieved within 4 days of multiple dosing. The accumulation ratio ranged from _____ based on AUC values. The accumulation $t_{1/2}$ values were about 20 hours except for the 250- mg dose (26 hours). The terminal $t_{1/2}$ increases from 9 hours at 25- mg dose to 20 hours at 375 mg dose level. The increase in $t_{1/2}$ along with the negative deviation from linearity at lower dose indicated non-linear pharmacokinetics of MK-0966 in this dose range.

Similar 6-β-OH cortisol/cortisol ratio values at baseline (Day-1) and the end of the treatment (Day 14) and across treatment groups suggest no important induction of hepatic/renal CYP 3A-mediated metabolism using endogenous cortisol as a probe.

STUDY P012. An Open, Oral Single-Dose, 4-Period Study in Healthy Subjects to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of ^{14}C-MK–0966 in Solution

The objectives of this study is to (1) investigate metabolism and the routes of elimination of MK-0966 in healthy subjects following an oral dose of ^{14}C-MK-0966 in solution; (2) demonstrate mass balance for ^{14}C-MK-0966 in humans; (3) estimate intrasubject variability of MK-0966 by comparing the plasma concentration profile (maximum concentration [C_{max}], area under the curve [AUC], and time to maximum concentration [T_{max}]) of MK-0966 after 2 separate administrations in solution, and (4) estimate the relative bioavailability of a tablet formulation of MK-0966 compared to a solution.

This was an open, 2-part, 4-period study. Part 1: During the first period, all 12 subjects received a solution of MK-0966; 6 subjects received orally 125 mg ^{14}C-MK-0966 (~100

microcuries) and 6 subjects received 125 mg unlabeled MK-0966 as a solution in polyethylene glycol (PEG), followed by collections of blood, urine, and stool. Part 2: In Periods 2, 3, and 4, the same 12 subjects were randomized in crossover fashion to receive a second oral dose of 125 mg in the PEG solution or 2 separate administrations of a 125-mg tablet of unlabeled MK-0966 followed by collection of blood samples. There were 7 to 10 days between doses in all periods. All doses were given after an overnight fasting.

RESULTS: All 12 subjects completed the study and were included in the analysis.

1. Relative bioavailability

The MK-0966 plasma levels for solution and tablet were shown in Figure 1.

Figure 1. Mean (n=24) Concentrations of MK-966 in Plasma Following Administration of Single 125-mg Oral Doses in Solution or as Tablets
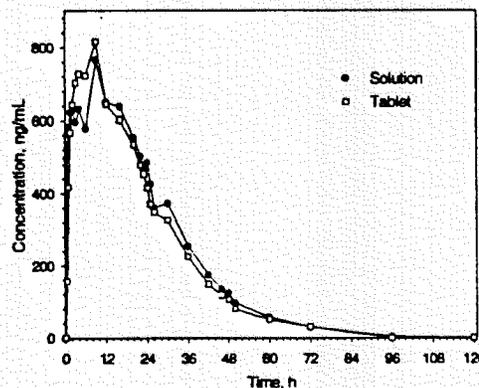
The summary statistics for the MK-0966 PK parameters was shown in Table 1.

Table 1. Summary statistics for the MK-0966 pharmacokinetic parameters.

Pharmacokinetic Parameter	Treatment	Geometric Mean[†]	Intersubject SD	Intrasubject SD	Pooled Intrasubject SD	GMR (Tablet/ Solution)	95% CI for GMR	p-Value
AUC_∞, µg•hr/mL	Tablet	21.1	5.9	3.0	3.4	0.95	(0.87, 1.04)	0.287
	Solution	22.2	5.7	3.7	--	--	--	--
C_{max}, ng/mL	Tablet	904	234	168	163	1.11	(0.99, 1.24)	0.070
	Solution	817	265	157	--	--	--	--
T_{max}, hr	Tablet	9.0[‡]	6.2	6.7	6.4	--	--	0.902
	Solution	9.0[‡]	5.0	6.0	--	--	--	--
$t_{1/2}$, hr	Tablet	11.1[§]	2.5	--	--	--	--	0.009
	Solution	12.3[§]	2.6	--	--	--	--	--

[†] Grand mean for both administrations (N=24).
[‡] Median.
[§] Harmonic mean.

The results showed that the MK-0966 solution and tablet are bioequivalent with similar t_{max} and $t_{1/2}$. In this study, 125 mg MK-0966 as both a PEG solution and a tablet

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(25% drug/excipient ratio: Formulation A) were each administered twice to the same subjects. Within-subject variability for AUC $_{[0-\infty]}$ and C_{max} was relatively small and comparable for both the tablet (CV=14.1%, 18.2% for AUC$_{[0-\infty]}$ and C_{max}) and solution (CV=16.5%, 18.7% for AUC$_{[0-\infty]}$ and C_{max}), permitting a pooled estimate of intrasubject variability (CV) of 15.3% for AUC$_{[0-\infty]}$ and 18.5% for C_{max}.

2. Plasma radioactivity and MK-0966, and mass balance

The plasma profiles of radioactivity and MK-0966 after a single oral dose of radiolabeled MK-0966 solution are shown in Figure 2.

Figure 2. Mean (n=6) Concentrations of MK-966 and Radioactivity in Plasma Following Administration of a Single 125-mg Oral Dose in Solution
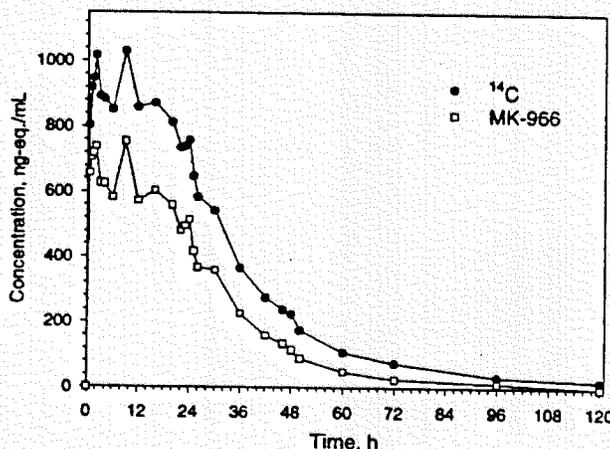
The results indicated that parent drug accounts for the majority of radiolabeled material in the circulation (approximately two-thirds) (Table 2). Furthermore, the ratio of parent drug to metabolite(s) is fairly constant, with the two curves mirroring one another throughout most of the sampling interval. As indicated by the sponsor, this could result from either a reversible process of transformation for MK-0966 and metabolites(s) or rate-limiting formation of metabolite(s). The sponsor also indicated that the amounts of radioactivity were insufficient to establish the identity of the radiolabeled species circulating in plasma.

Table 2. Summary Statistics for mean AUC(0-∞) (μg-eq•hr/mL) and C_{max} (ng-eq/mL) of Plasma Radioactivity and MK-0966

	MK-0966	Radioactivity	GMR	90% CI for GMR
AUC(0-∞) (N=6)	22.2	36.6	0.63	0.61 – 0.65
C_{max} (N=6)	814	1095	0.74	0.70 – 0.79

The mean recovery of radioactivity over 7 days after the single oral dose of radiolabeled MK-0966 solution was 71.5% of the dose in urine, 14.3% of the dose in feces and, a total 85.8% of the dose. The corresponding 90% CIs as a percent of the dose recovered were (65.5, 77.4), (12.4, 16.1), and (79.7, 91.8), respectively. This result along with relative bioavailability of the tablet to the solution indicated that MK-0966 tablet is well absorbed.

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3. Metabolism

Examination of the metabolic pattern of radiolabeled MK-0966 revealed that the main metabolic pathway is the reduction of the double bond on the dihydrofuranone ring of the drug to the cis-dihydro and trans-dihydro derivatives in the ring-open (hydroxyacid) and ring-closed (lactone, cyclized from their respective acid during isolation) forms, which accounted for a total of _____ of the radioactive dose as recovered in urine over the first 24 hours postdose. An additional _____ of the dose was recovered as the glucuronide of the hydroxy derivative, L-755,190. Based on _____ MK-0966 and L-755,190 _____ each of the radioactivity recovered from urine. There are also additional three unidentified metabolites. Table 3 summarized the metabolite information quantitively. The structure of identified metabolites is shown in Figure 3.

CONCLUSIONS:

The MK-0966 125- mg tablet is bioequivalent to the solution formulation. About 85% of the dose were recovered from the urine and feces following 125- mg oral dose of solution. In plasma, parent compound accounted for about 2/3 of the radioactivity. The plasam radioactivity and MK-0966 suggested a possible reversible process of transformation for MK-0966 and metabolites(s) or rate-limiting formation of metabolite(s). Major metabolism pathways were identified to be reduction and glucuronization.

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Table 3. Quantitation of metabolites as percent of total radioactivity and as percent of dose in 0-24 hr urine following oral administration of [^{14}C]MK-0966 at 125 mg (100 μCi) as a solution in PEG-400 to six healthy male subjects.

| Metabolites	Retention Time (min)	0-24 Urine[a]	
		% of Total ^{14}C	% of Dose
Unknown-1[b]	10.1	6.5	2.4
Unknown-2[b]	12.6	2.2	0.8
cis-Dihydro-MK-0966[c] (hydroxy acid)	15.6	16.5	6.1
L-755,190 Glucuronide[d]	16.0	8.8	3.3
cis-Dihydro-MK-0966[c] (lactone)	24.4	6.6	2.4
trans-Dihydro-MK-0966[c] (lactone)	26.3	33.3	12.4
Unknown-3[b]	17.2	4.6	1.7
L-755,190[b]	23.6	0.3	0.1
MK-0966[b]	27.6	1.1	0.4
Total		79.9	29.7

[a]The mean percent of dose excreted in the 0-24 hr urine interval is 37.1%.
[b]The percent of total radioactivity was obtained from radiochromatograms using an in-line radiochemical detector (n=6).
[c]The percent of total radioactivity was estimated from histograms obtained during characterization of the isolated crude metabolite mixture.
[d]The percent of total radioactivity was obtained by subjecting the isolated crude metabolite mixture to β-glucuronidase treatment and quantitating the amount of L-755,190 formed.

Figure 3. Structures of MK-0966 and its metabolites in human urine.
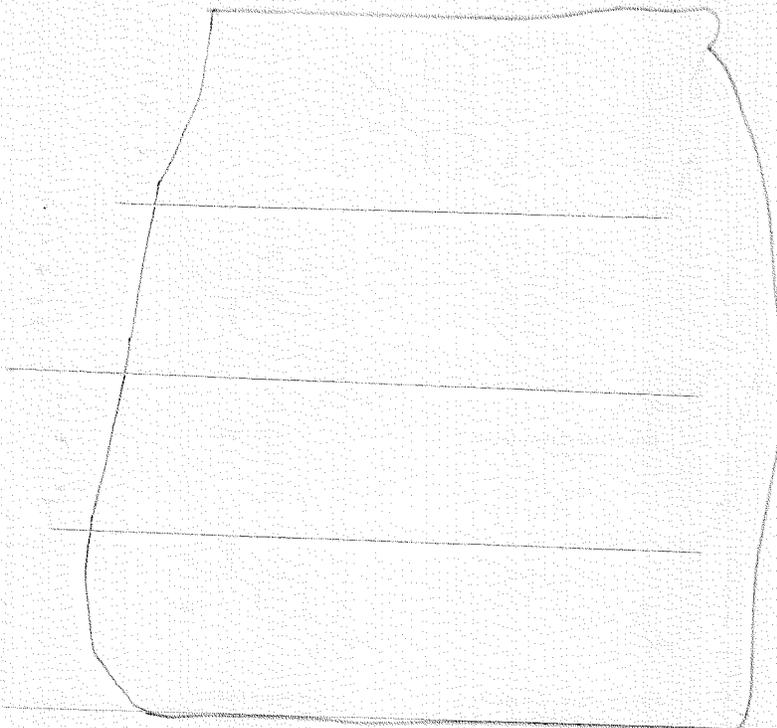
STUDY P018. An Open Study to Investigate the Biliary Excretion of MK–0966 and its Metabolites Following Single Oral Doses of ^{14}C-MK–0966 in Patients Having a Surgically Implanted T-Tube or L-Tube

It is observed from previous studies that plasma profiles of MK-0966 following oral administration to human subjects consistently show the appearance of secondary peaks. These peaks were thought to be possibly attributable to enterohepatic recycling. This interpretation was supported by extensive enterohepatic recycling seen in rats. The present study was performed to test the hypothesis that enterohepatic circulation of MK-0966 in humans was responsible for the secondary peaks.

Four patients who had undergone elective gallbladder surgery and who had a drainage tube for bile inserted into the common bile duct during surgery (L-tube, Vishneusky's choledoch drainage), were given single oral 142-mg doses of $[^{14}C]$MK-0966 (100 µCi) (nominal dose of 125- mg). To estimate the efficiency of bile collection, subjects were administered a single I.V. doses of indocyanine green (ICG) (0.5 mg/Kg) two hours before administration of MK-0966. Indocyanine green, a marker for bile flow, is exclusively eliminated from the body *via* biliary excretion. Bile, blood, urine and stool samples were collected over the succeeding 120 hours for examination of contents of total radioactivity and of MK-0966, and for identification of metabolites.

RESULTS:

All 4 patients completed the study and were included in the analysis of the study. The overall recoveries of ICG averaged 86% of the quantity administered indicating efficient bile collection.

1. Biliary excretion

The mean recoveries from urine, feces and bile were listed in Table 1.

Table 1. Overall recoveries of radioactivity, MK-0966 and L-755,190 following oral dose of ^{14}C-MK-0966

	Urine	Feces	Bile	Total	MK-0966 in bile (µg-eq)	L-755,190 in bile (µg-eq)
Radioactivity (mg-eq)	40.8	70.7	2.6	114.2	18.8	27.6
Percent of the dose	29%	50%	1.8%	81%	0.013%	0.020%

It is observed that recoveries in bile of either MK-0966 or a metabolite, L-755,190, capable of reversible transformation with MK-0966 in rats, were _____ even though collection of bile was nearly complete. These results clearly show that excretion of either compound in bile is negligible and that enterohepatic recycling plays no significant role in the pharmacokinetics of MK-0966. In fact, excretion of radioactivity in bile _____ of dose, demonstrating that biliary involvement is minimal in the disposition of MK-0966 and its metabolites. Therefore, the origin of _____ is apparently due to a mechanism other than enterohepatic recycling, although its nature remains unknown.

2. Absorption of MK-0966

It is also observed from Table 1 that only 29% of the radioactivity were recovered from the urine, whereas 71.5% of orally dosed radiolabeled material was recovered in healthy subjects (Study P012). This comparison reveals that the apparent absorption of MK-0966 was substantially less in the cholecystectomized patients than in the healthy volunteers. Also, plasma AUC and C_{max} values for MK-0966 and radioactivity were lower in these patients (Table 2).

Table 2. Mean AUC and C_{max} values for MK-0966 and radioactivity in healthy subjects and cholecystectomized patients

	AUC (µg.eq.h/mL)		C_{max} (µg.eq/mL)	
	MK-0966	Radioactivity	MK-0966	Radioactivity
Healthy subjects	22.9	35.3	0.814	1.095
Cholecystectomized patients	5.8	18.4	0.188	0.425

Additionally, MK-0966 accounted for approximately 65% of the AUC for radioactivity in the healthy subjects but only for 32% in the cholecystectomized subjects. Examination of fecal excretion of radioactivity, which was substantially greater in this study than in healthy subjects, showed that it could all be accounted for as unchanged drug. The following is the sponsor's interpretation of the above observation. The sponsor indicated that these data all suggested diminished absorption of MK-0966 in these patients. The discrepancy in MK-0966 absorption between cholecystectomized patients and healthy subjects may be due to bile facilitating the absorption of MK-0966. Since the cholecystectomized patient's bile is being diverted away from the intestine due to the L-tube, absorption of MK-0966 may be compromised in these circumstances. Additionally, the bowel function in general in postoperative patients may influence absorption. However, food itself might also facilitate the absorption of MK-0966. These postoperative patients likely had less oral intake of nutrients then would normal subjects. Alternatively, dissolution of the tablets used in this study was slower than observed with tablets used in other studies. This difference might have also contributed to the lowered absorption. The reviewer believes that the sponsor's interpretation is reasonable.

CONCLUSION:

Excretion of MK-0966 and L-755,190 in bile is negligible and the   of MK-0966 plasma concentration-time profile are apparently not produced by enterohepatic recycling of either compounds. The absorption of MK-0966 in cholecystectomized patient was much lower than that in healthy subjects probably because of bile facilitating the absorption of MK-0966.

STUDY P021. Part I: An Open, 5-Period Study of MK–0966 to Assess Dose-Proportionality and Compare Different Formulation Profiles in Healthy Male Volunteers. Part II: An Open, 4-Period Study of MK–0966 to Assess Dose-Proportionality Profiles in Healthy Female Volunteers at Similar Doses

In all studies reviewed previously, Formulation A was used. The objectives of this study were to investigate the dose proportionality of MK-0966 in a newly developed tablet formulation, compare the single-dose pharmacokinetics of MK-0966 (Formulation B) between males and females, and compare the plasma concentration profiles between the old (Formulation A,   MK-0966) and new (Formulation B,   MK-0966) tablet formulations.

There are two parts in the study. Part I: An open-label, balanced, 5-period, crossover study in male subjects in which Formulation B tablets of MK-0966 at dose strengths of 10, 50, 125, and 250 mg, and the Formulation A 125-mg tablet, were administered orally and followed by a series of blood samples and urine collections over 5 days. There was a washout interval of 7 to 10 days between doses. Part II: A 4-period crossover study in female subjects, identical in design to Part I except the Formulation A tablet was not included.

RESULTS:

Mean plasma concentration profiles in males and females following four MK-0966 tablet strengths of Formulation B and 125- mg tablet of Formulation A are shown in Figure 1.

A. Men   B. Women

Figure 1
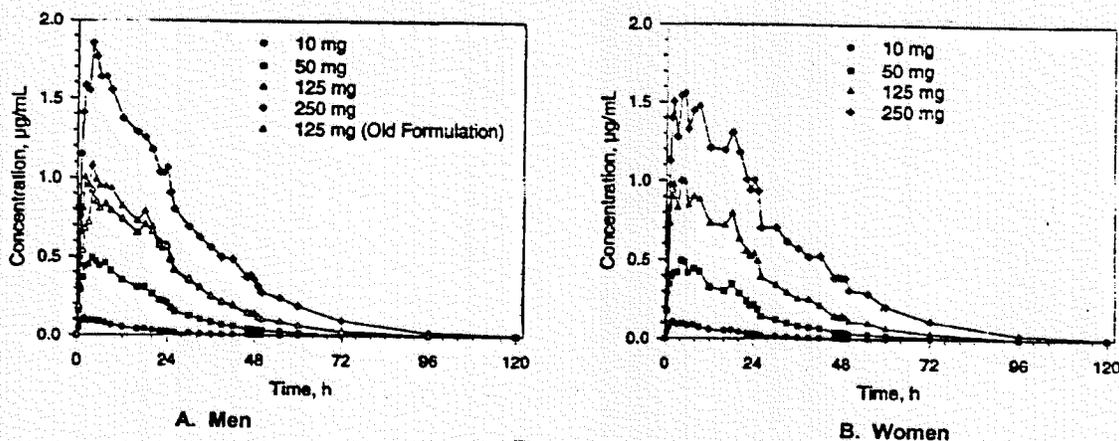
1. Dose proportionality

The 90% CIs of dose-adjusted (to 10 mg) $AUC_{0-120\,hr}$ and Cmax GMRs for all pairs of doses of MK-0966 are summarized in Tables 1 and 2.

Table 1. GMRs and 90% Confidence Intervals for Dose-Adjusted (to 10 mg) AUC (All Pairs of Doses of MK-0966 Formulation B)

Comparison	GMR	90% Confidence Interval of GMR
Male		
50 mg vs. 10 mg	1.33	(1.24, 1.42)
125 mg vs. 10 mg	1.31	(1.22, 1.40)
250 mg vs. 10 mg	1.26	(1.17, 1.35)
125 mg vs. 50 mg	0.98	(0.92, 1.06)
250 mg vs. 50 mg	0.95	(0.88, 1.01)
250 mg vs. 125 mg	0.96	(0.90, 1.03)
Female		
50 mg vs. 10 mg	1.24	(1.16, 1.31)
125 mg vs. 10 mg	1.18	(1.11, 1.25)
250 mg vs. 10 mg	1.13	(1.07, 1.20)
125 mg vs. 50 mg	0.95	(0.90, 1.01)
250 mg vs. 50 mg	0.92	(0.86, 0.97)
250 mg vs. 125 mg	0.96	(0.90, 1.02)
250 mg vs. 125 mg	0.96	(0.90, 1.02)

GMRs of the higher dose to the lower dose.

Table 2. GMRs and 90% Confidence Intervals for Dose-Adjusted (to 10 mg) Cmax (All Pairs of Doses of MK-0966 Formulation B)

Comparison	GMR	90% Confidence Interval of GMR
Male		
50 mg vs. 10 mg	0.88	(0.78, 1.00)
125 mg vs. 10 mg	0.78	(0.68, 0.88)
250 mg vs. 10 mg	0.69	(0.61, 0.79)
125 mg vs. 50 mg	0.88	(0.77, 1.00)
250 mg vs. 50 mg	0.78	(0.69, 0.89)
250 mg vs. 125 mg	0.89	(0.78, 1.01)
Female		
50 mg vs. 10 mg	0.88	(0.79, 0.99)
125 mg vs. 10 mg	0.73	(0.65, 0.82)
250 mg vs. 10 mg	0.55	(0.49, 0.62)
125 mg vs. 50 mg	0.83	(0.74, 0.93)
250 mg vs. 50 mg	0.63	(0.56, 0.70)
250 mg vs. 125 mg	0.75	(0.67, 0.85)

GMRs of the higher dose to the lower dose.

The AUC geometric means increased in linear manner over 50 to 250-mg dose range for both males and females. The 10-mg dose showed a negative deviation from linearity, which is consistent with the results from dose proportionality studies conducted for Formulation A.

The Cmax geometric means showed a less than dose proportional increase across the 10- to 250-mg range in both males and females. An increasing pattern for Tmax was observed with the increase in the MK-0966 dose for both males and females.

In the males, harmonic mean values of effective $t_{1/2}$ for the 10-, 50-, 125-, and 250-mg doses were 9.0, 11.7, 13.5, and 16.0 hours, respectively; those for the females were 9.6, 12.1, 14.9, and 19.0 hours, respectively. Thus, $t_{1/2}$ values tended to increase with increasing dose in both males and females.

2. Gender difference

The comparison of PK parameters in males versus females is shown in Table 3.

Table 3. Male Versus Female Comparison Summary for AUC and Cmax Across the Doses of MK-0966 Formulation B

Treatment	Male N	Male Mean	Male CV	Female N	Female Mean	Female CV	Male vs. Female p-Value	GMR	90% CI
AUC (µg•hr/mL)—Dose Adjusted to 10 mg									
Combined	10	1.95	32.48	8	2.05	14.86	0.213	0.95	(0.86, 1.06)
10 mg	10	1.60	25.83	8	1.81	14.04	0.129	0.89	(0.74, 1.06)
50 mg	10	2.13	31.51	8	2.24	12.57	0.347	0.95	(0.77, 1.17)
125 mg	10	2.10	34.62	8	2.13	15.13	0.454	0.98	(0.78, 1.24)
250 mg	10	2.02	33.56	8	2.05	10.46	0.448	0.98	(0.79, 1.22)
Cmax (ng/mL)—Dose Adjusted to 10 mg									
Combined	10	97.49	30.02	8	95.19	30.75	0.629	1.02	(0.91, 1.15)
10 mg	10	117.58	27.98	8	123.04	19.14	0.351	0.96	(0.78, 1.17)
50 mg	10	103.69	19.29	8	108.59	16.21	0.298	0.95	(0.82, 1.11)
125 mg	10	91.29	37.54	8	90.29	28.55	0.527	1.01	(0.76, 1.34)
250 mg	10	81.17	22.07	8	68.07	21.78	0.945	1.19	(0.99, 1.43)

Geometric mean.
Log scale between-subject SD x 100.
Combined across the doses of Formulation B.

There was no overall gender effect observed for the dose adjusted AUC and Cmax between males and females, although the 90% CIs were out of the limit of 80-125% in some cases.

CONCLUSIONS:

Based on $AUC_{0-120 hr}$, MK-0966 plasma concentrations increase in a linear manner over the 50 to 250-mg dose range while the 10-mg dose showed a negative deviation from the linearity. The Cmax increases with dose in a less than proportional manner over the dose range of 10 to 250-mg dose range. It is observed that Tmax and $t_{1/2}$ values increases with dose.

Pharmacokinetics of MK-0966 are similar in males and females.

Formulation A and B, as 125-mg tablets, are equivalent in term of AUC, but the Cmax of Formulation B is 17% higher than Formulation A (90% CI of 1.03-1.33).