frequently prescribed to an older population of patients with diagnoses of congestive heart failure or supraventricular arrhythmias.

The effect of MK-0966 on the pharmacokinetics of a single oral dose of digoxin was examined in a 2-period crossover study in 10 healthy volunteers. MK-0966 75 mg orally or matched placebo (in the alternate period) was administered once daily on Days 1 through 11 of each period. A single open-label oral dose of 0.5 mg digoxin was administered on Day 7 of both periods. The effect of MK-0966 was evaluated based on the plasma concentrations and urinary excretion of immunoreactive digoxin. For other details in study design see pages 15-16 of Appendix II.

Results

MK-0966 75 mg daily had no influence on the plasma concentration-versus-time profiles of immunoreactive digoxin. The plasma concentration-versus- time profiles for immunoreactive digoxin were nearly superimposable for the MK-0966 and placebo treatment periods (Figure 1 attached in the Appendix II on page 17). No significant difference was observed for AUC24 hr, Cmax, Tmax, and t½ (See Table Below). The 90% CI for the AUC GMR (MK-0966 plus digoxin/digoxin plus placebo) was contained within the prespecified clinically meaningful bounds.

	AUC_{∞} (ng·hr/mL)	$AUC_{24\ hr}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
MK-0966 + digoxin	37.94 ± 9.89†	13.93 ± 1.18†	2.82 ± 0.66†	0.5	45.7 ± 12.6§
Placebo + digoxin	36.55 ± 8.22†	13.71 ± 2.52†	2.82 ± 0.65†	0.5	43.4 ± 11.0§
Approximate within-subject CV (%)	11.4	8.9	11.0	--	--
Geometric mean ratio (GMR)‖	1.04	1.02	1.00	--	--
90% CI of GMR	(0.94, 1.14)	(0.94, 1.09)	(0.91, 1.10)	--	--

† Geometric mean ± back-transformed standard deviation.
‡ Median (min, max).
§ Harmonic mean ± Jackknife standard deviation.
‖ (MK-0966/placebo).

Cumulative urinary excretion of immunoreactive digoxin over 120 hours postdose was not significantly different between the placebo and MK-0966 periods (see Table below).

Treatment	N	Mean (SD) µg/120 Hours	p-Value
MK-0966 + digoxin	10	228.2 (30.8)	0.561
Placebo + digoxin	10	235.1 (39.1)	--

No serious adverse effect was noted. Three subjects experienced ECG abnormalities and was the result of digoxin administration and occurred independently of MK-0966 or placebo treatment.

Conclusions

- MK-0966 75 mg once daily for 11 days does not alter the plasma concentration profile and cummulative urinary excretion of digoxin after a single 0.5 mg oral dose, with 90% CIs being within the acceptable limits of 0.80 and 1.25.

Reviewer's Comment

- *The applicant has set the 90% CI acceptance limits as 0.70 and 1.43. However, in this drug interaction study the CIs are between 0.80 and 1.25.*
- *A single dose study with digoxin in healthy volunteers is of minimal clinical and pharmacokinetic significance. The effects on renal tubule and fluid retention is unknown from this study.*

Cimetidine

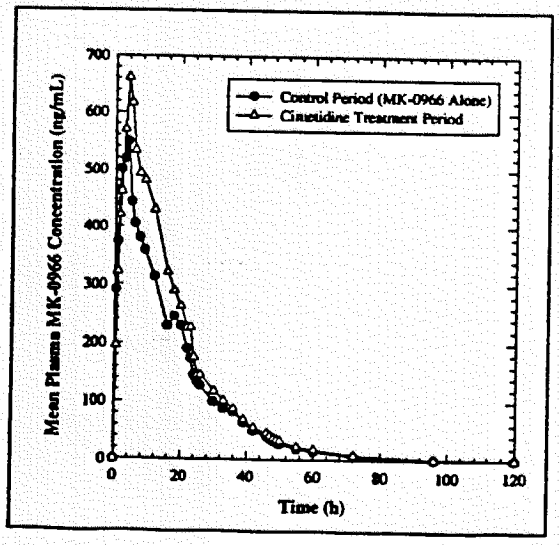
***Study P039**: An open randomized, 2-period, crossover study to investigate the effect of oral Cimetidine on plasma concentrations of MK-966 75 mg in normal volunteers*

The primary objective of this study was to determine whether cimetidine, a frequently used H2 receptor antagonist, alters the plasma concentration profile of MK-0966. By binding to the heme portion of cytochrome P-450 enzymes, cimetidine is associated with the inhibition of metabolism for a variety of drugs. While it is thought MK-0966 is metabolized to some extent by CYP 3A, this study was not designed with cimetidine as a specific probe to assess enzyme inhibition.

This was an open, 2-period crossover study to investigate the influence of oral cimetidine on the pharmacokinetics of MK-0966 in 8 healthy subjects. Cimetidine 800 mg twice daily was administered for 9 days with a concomitant oral dose of 75 mg MK-0966 on Day 5, followed by 120 hours of blood sampling for plasma MK-0966 concentrations. Except for fasting overnight prior to dosing on days when blood samples were obtained, treatments were administered without regard to food. Other details of the study design are given on page18 of Appendix II.

Results

The oral cimetidine when co-administered with MK-0966 increased the MK-0966 plasma concentrations at most time points when compared to MK-0966 alone (see adjacent figure). The concentration-time profiles demonstrated the presence of secondary peaks which have been attributed to the possible combination of enterohepatic recycling and reversible metabolism between MK-0966 and its metabolite L-755,190.



However, the secondary peaks were not observed in all of the individual concentration-time profiles, and when they were observed, the secondary peaks were much less pronounced than in previous studies. Nevertheless, the presence of the secondary peaks did affect the T_{max} values, which ranged from 1.5 to 12 h, especially when the first peak in the concentration-time profile was not the maximum concentration.

All the pharmacokinetic parameters as seen in the table below increased significantly and the 90% CI for the AUC and Cmax did not fall within the (0.80, 1.25) bounds. The applicant has predefined the limits as 0.70 and 1.43.

	$AUC_{(0\text{-}120\ hr)}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
MK-0966 with cimetidine	11757 ± 3166†	657 ± 314†	5.0 ± 3.0‡	10.2 ± 0.97§
MK-0966 alone	9567 ± 3133†	541 ± 222†	3.1 ± 1.1‡	8.8 ± 1.25§
Between-treatment p-value	0.001	0.026	0.081	0.040
Approximate within-subject CV (%)	7.3	13.2		
Geometric mean ratio (GMR)|	1.23	1.21		
90% CI for GMR	(1.15, 1.32)	(1.07, 1.38)		

† Geometric mean ± back-transformed standard deviation.
‡ Mean ± standard deviation.
§ Harmonic mean ± jackknife standard deviation.
| MK-0966 with cimetidine/MK-0966 alone.

Conclusions

- Co-administration with cimetidine increased C_{max} of MK-0966 by 21% and $AUC_{(0\text{-}120\ hr)}$ by 23% and a similar magnitude of increase in t1/2. But no clinical adverse events were reported.
- The 90% CIs for the parameters were not within the bounds of 0.80 and 1.25, showing a shift towards the upper boundary.

Reviewer's Comment

The 90% CIs for the parameters were not within the bounds of 0.80 and 1.25, but the applicant has set his limits to 0.70 and 1.43 and claims that the CIs were within the acceptable limits of no meaningful clinical effect. However, it should be noted that the usual daily dose of cimetidine is 800 mg daily and in this study the subjects have been given 800 mg twice daily for 9 days. The dose of MK-0966 in this study is 75 mg as compared to the clinically recommended doses of 12.5 to 25 mg. Hence, the marginal shift of limits towards the upper boundary may not imply a clinically meaningful difference. However, caution should be advised in the label. The OTC dose of cimetidine is 200 mg twice daily. This marginal increase should not effect its OTC use.

Warfarin

A large number of drugs affect the pharmacokinetics and/or pharmacodynamics of

warfarin. The consequences of decreased or increased anticoagulation in subjects on warfarin therapy are clinically important. The metabolic pathway suspected to be responsible for the biotransformation of R(+) warfarin includes CYP3A4, unlike that considered responsible for S(-) warfarin, which involves 2C9. The effect of MK-0966 on Warfarin was examined in two double blind, placebo controlled, crossover trials. The first study included a single dose of warfarin and the second study utilized a chronic administration of individualized warfarin doses.

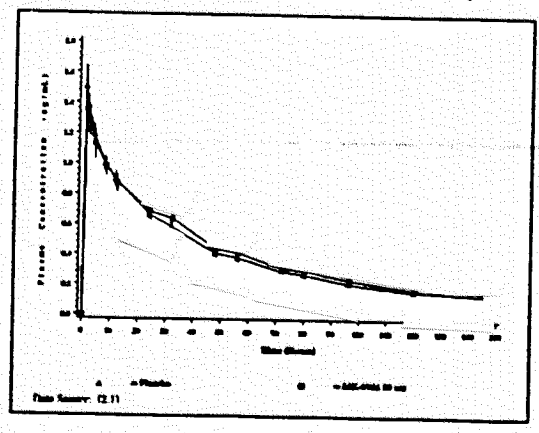
Single dose of Warfarin

Study P053: *An double-blind, randomized, placebo controlled, 2-period, crossover study to investigate the effect of oral 50 mg MK-0966 on pharmacodynamics and pharmacokinetics of Warfarin.*

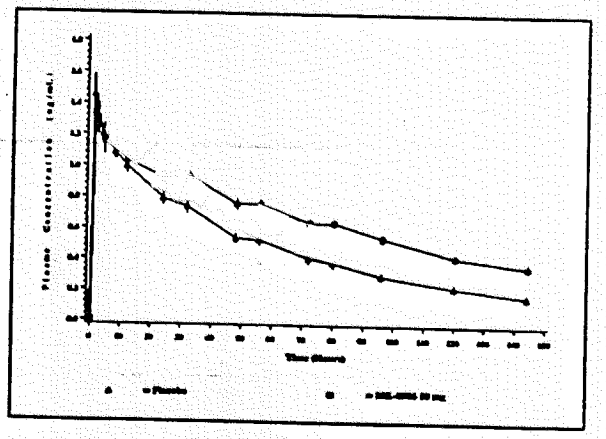
This study investigated the effect of MK-0966 (50 mg daily for 12 days) on the pharmacokinetics and pharmacodynamics of a single oral 30-mg dose of warfarin on Day 7. Warfarin pharmacodynamics were assessed by the AUC of the prothrombin time International Normalized Ratio (INR) and maximum INR (INRmax). Blood samples for prothrombin time and warfarin assay were taken prior to and through 144 hours following the warfarin dose. Other details of study design are given on page 19-20 of Appendix II.

Results

Pharmacokinetic parameters were evaluated for both R(+) and S(-) enantiomer of warfarin for both the single and multiple dose administration. The mean warfarin plasma concentrations through 144 hours post-administration are displayed in figures (a) and (b) for the two enantiomers of warfarin after a single dose of 30 mg warfarin. The plasma concentrations of the R(+) enantiomer were higher with the concomitant administration of MK-0966 than with the placebo (see figure 'b' below).



(a) Warfarin S(-) enantiomer



(b) Warfarin R(+) enantiomer

The summary statistics of the parameters for warfarin enantiomers after a single dose are tabulated below,

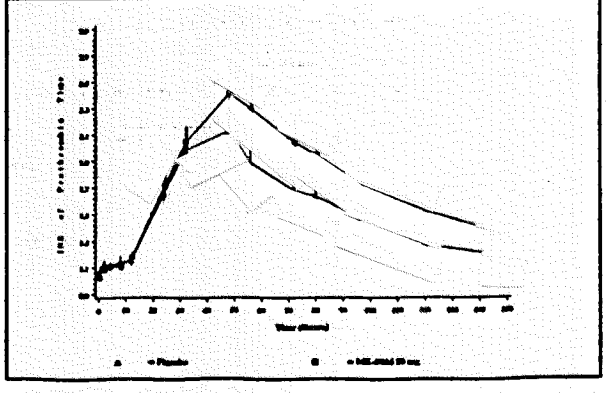
Warfarin enantiomer	Pharmacokinetic parameter	Treatment	Geometric Mean	GMR MK/Pl	90% CI	p-value
S(-)	AUC144 hr,µg.hr/ml	MK-0966 placebo	56.3 54.2	1.04	(0.98,1.11)	0.292
	AUC0-∞,µg.hr/ml	MK-0966 placebo	66.1 63.6	1.04	(0.97,1.12)	.0370
N=12	Cmax, µg/ml	MK-0966 placebo	1.4 1.5	0.92	(0.80,1.05)	0.266
R(+)	AUC144 hr,µg.hr/ml	MK-0966 placebo	97.4 70.6	1.38	**(1.29, 1.48)**	**<0.001**
	AUC0-∞,µg.hr/ml	MK-0966 placebo	139.6 84.0	1.66	**(1.51, 1.82)**	**<0.001**
	Cmax, µg/ml	MK-0966 placebo	1.4 1.5	0.96	(0.89,1.04)	0.408

The difference between the R(+) enantiomer AUC $_{0-\infty}$ between treatments was more pronounced than that observed for AUC $_{0-144}$. Although a significant difference was observed between the MK-0966 and placebo treatments in AUC $_{0-144}$ and AUC $_{0-\infty}$ for the R(+) enantiomer of warfarin, no notable difference ($p \geq 0.266$) was observed in C_{max} between the two treatments with respect to both the R(+) and S(-) enantiomers. The median Tmax value was 1.0 hour for both enantiomers regardless of the concomitant treatment (MK-0966 or placebo). There was no statistical difference between the t1/2 for the S(-) enantiomer for the MK-0966 and placebo treatment (49.2 and 47.8 hours, respectively, p=0.705). However, a longer t1/2 was observed for the R(+) enantiomer when MK-0966 was administered as compared to the placebo treatment (78.1 and 52.6, respectively, $p<0.001$). Enantiomer R(+) is pharmacologically less active than S(-) enantiomer. The S(-) form exhibits 4 to 6 times more anticoagulant activity than R(+) enantiomer, but generally has a more rapid clearance. The CL of R(+) warfarin is generally half that of S(-) warfarin. However, these forms are not interconvertable.

Warfarin pharmacodynamics were assessed by the AUC of the prothrombin time International Normalized Ratio (INR) and maximum INR (INRmax). The summary statistical comparison is provided in the table below.

Parameter	Treatment	Geometric Mean	GMR (MK-0966/Pl)	90% CI	P-value
AUC144 hr of INR of Prothombin time	MK-0966 Placebo	244.1 219.2	1.11	(1.04,1.19)	0.017
Maximum promthrombin time INR	MK-0966 Placebo	2.4 2.1	1.11	1.01, 1.21)	0.071

The figure shows the mean prothrombin time INR over the 144 hours post warfarin administration on Day 7.



Five laboratory adverse experience of increased ALT and two of increased AST

was observed, but all the values were less than 2.5 times the upper limit of normal.

Conclusions

- The results of the present study suggest the potential for an interaction between MK-0966 and warfarin. A small increase in the pharmacodynamic effect of warfarin (anticoagulation) based on the increase in INR $AUC_{(0\text{-}144hr)}$ and INR maximum by approximately 11% occurred in the MK-0966 treatment period relative to the placebo period. Therapy with 50 mg MK-0966 with warfarin requires monitoring of prothrombin time and possibly reductions in warfarin dose.
- There was no change in the plasma S(-) warfarin $AUC_{(0\text{-}144hr)}$ or C_{max}, the plasma R(+) warfarin $AUC_{(0\text{-}144hr)}$ increased during the MK-0966 treatment by approximately 38%, without significant change in C_{max}. There was no change in the plasma half-life of the S(-) warfarin, but that of the R(+) warfarin increased by approximately 47% (from ~53 to ~78 hours). It is likely that these increases in the R(+) isomer pharmacokinetics were responsible for the observed change in the warfarin pharmacodynamics. This effect may be increased with multiple dosing.

Multiple dose of Warfarin

Study P075: *An double-blind, placebo controlled, 2-period, crossover study to investigate the effect of 25 mg oral MK-0966 on pharmacodynamics and pharmacokinetics of Warfarin at steady state*

The major metabolic pathways reported to be responsible for the biotransformation of (R) warfarin include CYP3A4 and CYP1A2, with potential contributions from other CYP450 isoforms. Whereas the dominant isoform responsible for metabolism of (S) warfarin is CYP2C9. Clinical investigations with MK-0966 using the erythromycin breath test and midazolam as metabolic probes, as well as in vitro investigations, did not identify MK-0966 as an important inhibitor of CYP3A4. Additionally, MK-0966 is not a potent inhibitor of CYP1A2 in vitro (Ki>100 μM).

A 2-period, crossover, multiple dose study was conducted to assess the effects of 25 mg MK-0966 on warfarin pharmacodynamics (Average 24hr INR) at steady state. There was an open run-in period (R) of up to 28 days during which all subjects took 5 mg warfarin on Days R1 through R4, followed by a dose titration to a steady-state INR value of 1.4 to 1.7 according to frequently measured INR values. The choice of warfarin dose on any given day was dependent upon the investigator's assessment of the subject's INR response. Prior to the start of MK-0966/placebo treatment, the INR must have been stable (within target range and varying by ≤0.2) for 3 consecutive days. It was intended that subjects not attaining this goal within 28 days would be dropped from the study. Following the run-in period, the stable daily dose of warfarin was continued throughout a 2-period double-blind portion of the study in which 25 mg MK-0966 or placebo was co-administered daily with the warfarin for 21 days in each period. The INR was monitored closely throughout each period. There was no washout period between the final dose of the first treatment period and the first dose of the second treatment period. A 24-hour

blood sampling interval for prothrombin time (converted to INR) and pharmacokinetics of R(+) and S(-) warfarin were conducted on Day 21 of each period. Other details of study design is given on page 21 of Appendix II.

Results

Comparable to the single dose warfarin study, the plasma profile of the S(-) enantiomer was similar during concomitant administration of warfarin with either MK-0966 or placebo. The plasma concentrations of the R(+) enantiomer were higher following concomitant administration of MK-0966 with warfarin when compared to placebo with warfarin. The statistical summary for the pharmacokinetic and the pharmacodynamic parameter is shown in the table below.

Warfarin enantiomer	Pharmacokinetic parameter	Treatment	Geometric Mean	GMR MK/Pl	90% CI	p-value
S(-)	AUC24 hr,µg.hr/ml	MK-0966 placebo	8.42 8.40	1.00	(0.96, 1.04)	0.954
N=12	Cmax, µg/ml	MK-0966 Placebo	0.56 0.56	1.00	(0.94, 1.06)	0.828
R(+)	AUC24 hr,µg.hr/ml	MK-0966 placebo	18.92 13.54	1.40	**(1.30, 1.50)**	**<0.001**
	Cmax, µg/ml	MK-0966 placebo	1.02 0.77	1.32	**(1.23, 1.42)**	**<0.001**
pharmaco-dynamics	Average 24 hr INR (Day 21)	MK-0966 placebo	1.64 1.51	1.08	(1.02, 1.15)	**0.036**

These results are consistent with the single dose studies. The 90% CIs for the parameters for the R(+) enantiomer is not contained with the acceptance limit of 0.80 and 1.25. The applicant has prespecified the acceptable limits as 0.75 and 1.33. The trough INR values on Days 17 to 22 were greater at each time point during the MK-0966 treatment period as compared with the placebo period but the difference was never greater than 0.02. The difference (8%) in Average$_{24\ hr}$ INR for the MK-0966 (1.64 ± 0.24) and placebo (1.51 ± 0.21) treatment periods was statistically significant (p=0.036), though it fell between the 90% CI.

Only 1 subject was discontinued from the study due to an increase in INR greater than 2.5 following randomization (AN 007). This occurred immediately following the completion of Period 1, during which he was treated with MK-0966. At the end of the run-in period, his INR was 1.68 but increased immediately afterward to 2.33 (38.7% increase) predose on Day 1 of Period 1 prior to the initiation of MK-0966. The change from the predose Day 1 INR value (2.33) to his maximum INR level in Period 1 (2.73) occurring at 12 hours postdose on Day 21 was 17%, compared with the nearly 40% increase that occurred prior to any study treatment.

The mechanism of this interaction of MK-0966 and warfarin is not known. The (R+) enantiomer of warfarin is four- to six-fold less potent as an anticoagulant than the (S-) enantiomer. The elimination half-life of warfarin is long and its pharmacologic activity is complex because of the indirect nature of the warfarin response that involves the decreased synthesis of various clotting factors that are eliminated at different rates. With

a single large dose of warfarin, most of the early effect on INR is due to the decay of the factor with the shortest half-life, Factor VII (6 hours). The other vitamin K-dependent factors, II (50 hours), IX (24 hours) and X (36 hours) decay more slowly and may not be as accurately reflected in the acute response. Nonetheless, the results after the single-dose warfarin study with 50 mg MK-0966 were generally similar to those after 25 mg once daily MK-0966 (8%) with a somewhat greater increase in anticoagulant effect seen after 50 mg MK-0966 (11%).

Conclusions

- The SS pharmacokinetics of S(-) warfarin did not change, where as the R(+) enantiomer showed a 40% increase in AUC24hr.
- The steady state Average24hr INR increases by 8% during co-administration with warfarin 25 mg once daily for 21 days.
- Based on the pharmacokinetic and pharmacodynamic data, monitoring of the prothrombin time should be considered when MK-0966 is administered to patients on stable warfarin therapy.

Antacids

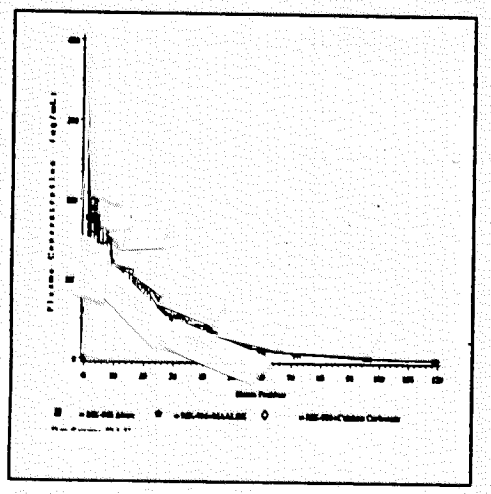
Study P052: *A 4-period, single dose study in elderly subjects to investigate the effect of antacids on the plasma concentration profile of MK-0966*

The two antacid products used in this study are (1) magnesium hydroxide plus aluminum hydroxide, (MAALOX™, Ciba Self Medication,Inc.), and (2) calcium carbonate. Although both types of antacids were available as liquid and solid dosage forms, the liquid suspension of each was administered in this study. The liquid suspensions remove the variables of chewing, disintegration, and dispersion. The oral dose of MK-0966 was 25 mg and I.V. dose was 1 mg. The 1mg intravenous (I.V.) dose is the largest available dose to be administered conveniently due to the extremely limited solubility of MK-0966. An I.V. dose was included so that the absolute bioavailability of could be estimated. The dose of MAALOX™, 20 mL, was selected from the product labeling. The maximum recommended single dose is 4 teaspoonfuls or 20 mL, which has the acid neutralizing capacity of approximately 53 mEq. The dose of the calcium carbonate suspension, 10 mL, was selected as a dose providing an acid neutralizing capacity (50 mEq) similar to the selected dose of MAALOX™.

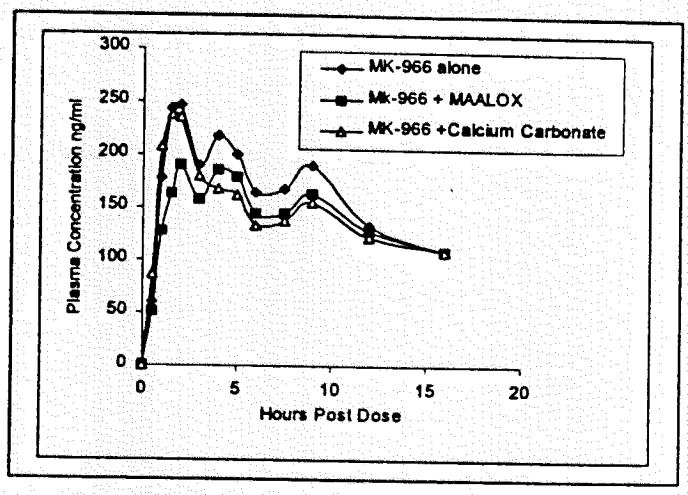
This was a 4-period study in 12 elderly subjects. In the first 3 periods, a single 25-mg oral dose of MK-0966 tablet was given alone or in combination with either of two different antacids in a balanced crossover fashion. In the fourth period, MK-0966 was administered to all subjects as a single 1-mg I.V. dose. Blood samples were taken starting on Day 1 through 120 hours post dose for the oral dose and pre-dose through 48 hours from the end of infusion for the I.V. dose. For other details of study design see page 22 of the Appendix II.

Results

Figure (a) and (b) display the mean plasma concentration profile across for each treatment group.



(a) Complete profile



(b) The first 16 hours expanded for the three treatments

The summary statistics for the pharmacokinetic parameters for the three treatments is shown in the table below.

Treatment	$AUC_{(0-\infty)}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
MK-0966 25 mg + mag & alum (MAALOX™, Ciba Self-Medication, Inc.)	4501.2 ± 1299.9*	219.5 ± 94.2†	3.0	13.4 ± 2.8§
MK-0966 25 mg + calcium carbonate	4226.9 ± 2142.1†	228.1 ± 142.2†	1.5	13.4 ± 3.3§
MK-0966 25 mg alone	4870.4 ± 1578.0†	276.8 ± 95.8†	2.0	14.0 ± 4.4§
Approximate within-subject CV (%)	17.87	22.57		
Geometric mean ratio (MK-0966 + mag & alum (MAALOX™/MK-0966)	0.92 (0.81, 1.05)‖	0.79 (0.68, 0.93)‖		
Geometric mean ratio (MK-0966 + calcium carbonate/MK-0966)	0.87 (0.77, 0.98)‖	0.82 (0.70, 0.97)		

† Geometric mean ± back-transformed standard deviation.
‡ Median (min, max).
§ Harmonic mean ± jackknife standard deviation.
‖ 90% CIs for the GMR.

The dose-adjusted (to 25 mg) MK-0966 $AUC_{(0-\infty)}$ GMR (25-mg oral tablet relative to 1 mg I.V.) was 1.39, with a 90% CI of (1.29, 1.51).

The p-values for the pharmacokinetic parameters for the two antacid treatments in comparison to MK-0966 alone are tabulated below. The 90% CIs are provided in the Table above.

Treatment	AUC0-∞ (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)	T1/2 (hr)
MK-0966 + MAALOX	0.292	**0.021**	0.252	0.564
MK-0966 + Calcium carbonate	**0.066**	**0.049**	**0.082**	0.556

These results show that the 90% CI for the GMR for MK-0966+Calcium carbonate did not fall with the acceptance limits for AUC0-∞ and there was significant difference between these treatments (p=0.066). The applicant however, has prespecified the limits to be 0.77 and 1.43. There was a significant difference in Cmax between MK-0966 with MAALOX™ as well as with calcium carbonate as compared to MK-0966 alone and the 90% CI fell outside the range.

Absolute Bioavailability of MK-0966 in Elderly

The geometric mean dose-adjusted (to 25 mg) MK-0966 $AUC_{(0-\infty)}$ for the 25-mg oral and 1-mg I.V. doses was 4812.7 and 3457.8 ng•hr/mL, respectively. The dose-adjusted MK-0966 $AUC_{(0-\infty)}$ GMR (25-mg oral dose relative to the 1-mg I.V. dose) was 1.39, with a corresponding 90% CI of (1.29, 1.51); thus, estimated absolute bioavailability of oral MK-0966 was greater than 100% (see table below). These results are thought to result from a deviation from linearity for MK-0966 pharmacokinetics at lower doses due to increase in CL at lower doses (see study P039 in Dr. Wang's review). Previous examination of the pharmacokinetic linearity following oral administration of either Formulation C (as tested in the present study) or earlier formulations suggested that plasma clearance of MK-0966 is greater at doses below 25 mg. This nonlinearity is blunted at higher doses due to decreased bioavailability of MK-0966 tablets. In both the present study in the elderly and the previous study in younger volunteers, an I.V. dose of 1 mg was utilized as a reference to estimate absolute oral bioavailability. In both cases, this resulted in dose-adjusted ratios of AUCs greater than 1.0, which is clearly not a good estimate of bioavailability.

Treatment	N	Geometric Mean $AUC_{(0-\infty)}$ (ng•hr/mL)[§]	Between-Subject SD[†]	GMR (Tablet to I.V.)	90% CI for GMR (Tablet to I.V.)	Within-Subject CV (%)[‡]
25-mg tablet	12	4812.7	1559.3	1.39	(1.29, 1.51)	10.70
1 mg I.V.	12	3457.8	1313.6			

[†] Back-transformed from the log scale.
[‡] Log scale within-subject SD (RMSE)*100.
[§] Dose-adjusted to 25 mg and potency normalized.

Data Source: [2.1.1]

A comparison between the $AUC_{(0-\infty)}$ of MK-0966 in healthy elderly (65 years of age or older) to the healthy young subjects following administration of a single oral dose of MK-0966 (dose adjusted to 50 mg) showed a 34% increase in the AUC of elderly subjects. The $AUC_{(0-\infty)}$ means shown below the is back-transformed least square mean from log-scale using ANOVA model.

Population (Protocol)	Dose	N	Adjusted Mean†	GMR‡	90% CI for GMR (Elderly/Young)	Between-Population p-Value	Between-Subject CV (%)§
Healthy elderly (052)	25 mg	12	10302	1.34	(1.17, 1.53)	0.001	25.2
Healthy young	25 or 50 mg	50	7719				

† Back-transformed least square mean from log-scale using the ANCOVA model (ng•hr/mL).
‡ Geometric mean ratio (elderly/young) using the adjusted means.
§ Root mean square error on the log scale x 100; CV=coefficient of variation.

Data Source: [2.1.1 to 2.1.5]

Conclusions

- There was a 13% decrease in $AUC_{(0-\infty)}$ of MK-0966 following calcium carbonate as compared toMK-0966 alone, approaching significance of p=0.066
- C_{max} was approximately 20% lower when 25 mg MK-0966 was administered with either antacid.
- The dose adjusted ratio of AUCs (oral/I.V.) was 1.39. These results are thought to result from a deviation from linearity for MK-0966 pharmacokinetics at lower doses.

Reviewer's Comment

- *There was a decrease in the AUC (by 13%) and Cmax (by 18%) of MK-0966 when administered with Calcium carbonate and a 21% decrease in Cmax when co-administered with MAALOX in the elderly. This decrease may be considered relevant to the acute analgesia use of MK-0966. Labeling recommendations should be made accordingly.*

Benazepril

***Study P054:** A double-blind, randomized, placebo controlled, 3-period, crossover study to investigate the effect of oral MK-0966, indomethacin, placebo on the antihypertensive response to Benazepril in patients with mild to moderate hypertension.*

NSAIDs such as indomethacin and ibuprofen, which are nonspecific COX inhibitors, have been reported to decrease the effectiveness of angiotensin-converting enzyme (ACE) inhibitors as well as other antihypertensive agents. It was considered important to determine whether a specific COX-2 inhibitor would have effects similar to NSAIDs on renal function, serum electrolytes and antihypertensive efficacy. An MK-0966 dose of 25 mg was selected for this study. Indomethacin was selected as the comparator for this study because it is known to be a potent nonspecific COX-1/COX-2 inhibitor and also has been found in clinical trials to attenuate the antihypertensive effect of ACE inhibitors. The dose selected (75 mg once daily in a sustained release formulation) is a commonly used dose of this agent and has elevated blood pressure in the presence of an ACE inhibitor in previous trials. Benzapril was selected as the widely accepted and clinically effective ACE inhibitor in the dose range of 10-40 mg.

41 patients were individually stabilized (diastolic blood pressure [DBP] 100 mm Hg) on once-daily benazepril prior to entering the 3-period crossover portion of the trial. 25 patients were administered 10 mg, 11 were on 20 mg, 5 on 30 mg and 2 on 40 mg benzapril. They remained on the same dose of benazepril throughout the 12 weeks of the study. Each 4-week treatment period, consisting of co-administration with MK-0966, indomethacin, or placebo, followed the previous period with a 1-week washout interval. End points were monitored on the last day (Day 28) of each 4-week treatment period. Other details are given on page 23 of Appendix II.

Results

The primary efficacy endpoint was the 24-hour mean DBP measured by ABPM (ambulatory blood pressure measurement) in patients with mild-to-moderate hypertension. Similar efficacy endpoints were also computed for the systolic blood pressure readings and for the mean arterial pressure (MAP) values. Inferential test for the primary hypothesis was carried out by using the upper limit of the 90% confidence interval (CI) (equivalent to the 1-sided 95% confidence limit) to detect no clinically meaningful increase in the mean 24-hour mean DBP in MK-0966 as compared with placebo. Posterior probability was computed for the event that the mean increase from placebo in 24-hour mean DBP in MK-0966 is less than 5 mm Hg.

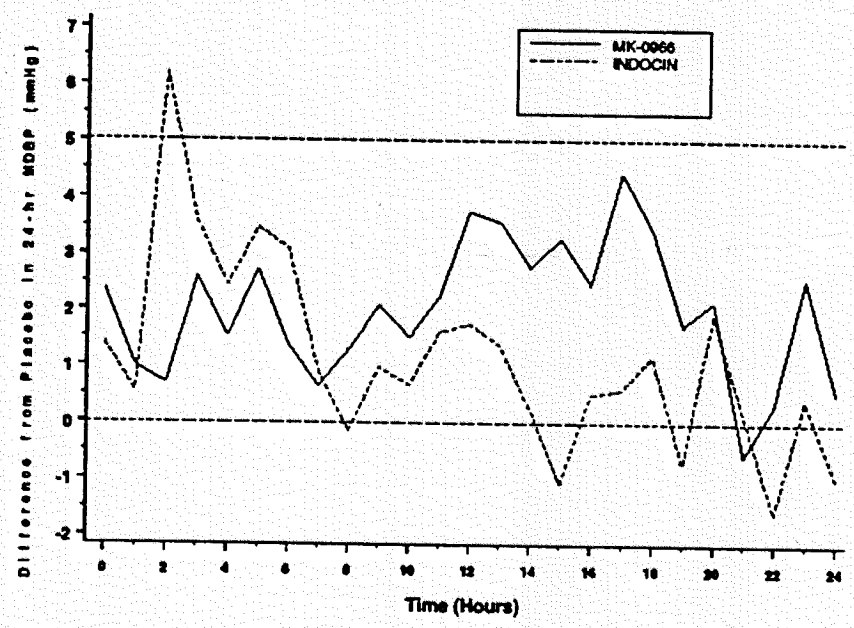
Diastolic Blood Pressure

No clinically meaningful increase from placebo was observed for MK-0966 in the 24-hour mean diastolic ABPM (i.e., the upper limit of the 90% CI for mean increase was less than 5 mm Hg). Also, there is more than 99% posterior probability that the true mean increase from placebo in the MK-0966 mean 24-hour DBP is less than the clinically significant increase of 5 mm Hg. No clinically meaningful increase from placebo was observed in indomethacin in 24-hour mean diastolic ABPM. Also, no statistical significance was observed in the overall treatment effect obtained from the ANOVA model. The mean DBP values are tabulated below.

Between-Treatment Comparisons of 24-Hour Mean DBP (mm Hg)

Treatment	N	Mean	Different From Placebo		Different From Indomethacin	
			Mean	90% CI	Mean	90% CI
24-Hour Mean DBP						
MK-0966	36	85.7	1.9	(0.3, 3.6)	0.8	(-0.9, 2.4)
Indomethacin	36	84.9	1.1	(-0.5, 2.8)	.	.
Placebo	36	83.8	.	.	.	.
Posterior probability (true mean of MK-0966 minus placebo < 5 mm Hg) = 0.999. Root Mean Square Error (RMSE) = 4.2, overall treatment p-value = 0.124.						

Hourly Mean Difference From Placebo in Diastolic ABPM



Systolic Blood Pressure and Mean Arterial Blood Pressure

Based on the ABPM, the systolic blood pressure and mean arterial pressure (weighted average of systolic and diatolic measurements based on ABPM) revealed small increases on MK-0966 and indomethacin. Mean increases in 24-hour mean systolic blood pressure (SBP) versus placebo (90% CI) were 4.5 (2.2, 6.8) mm Hg for MK-0966 and 2.0 (-0.3, 4.4) mm Hg for indomethacin. Mean increases in MAP versus placebo (90% CI) were 2.8 (1.0, 4.6) mm Hg for MK-0966 and 1.4 (-0.4, 3.2) mm Hg for indomethacin. The between treatment comparison for 24-hr mean SBP and MAP (mm Hg) are tabulated below.

Treatment	N	Mean	Difference From Placebo		Difference From Indomethacin	
			Mean	90% CI	Mean	90% CI
24-Hour Mean SBP						
MK-0966	36	139.9	4.5	(2.2, 6.8)	2.5	(0.1, 4.7)
Indomethacin	36	137.4	2.0	(-0.3, 4.4)	.	.
Placebo	36	135.4	.	.	.	.
RMSE = 5.9, overall treatment p-value = 0.006.						
24-Hour Mean MAP						
MK-0966	36	103.8	2.8	(1.0, 4.6)	1.4	(-0.5, 3.1)
Indomethacin	36	102.4	1.4	(-0.4, 3.2)	.	.
Placebo	36	101.0	.	.	.	.
RMSE = 4.6, overall treatment p-value = 0.033.						

Data Source: [4.6]

Changes in Serum Electrolytes (Potassium, Sodium, and Calcium)

No significant effects associated with treatments were observed (see Table 1 on page 24,Appendix II)

Body Weight

No statistically significant change was observed in body weight across treatments.

Heart Rate

A small but statistically significant decrease in heart rate for both MK-0966 and indomethacin as compared with placebo occurred during the study and was likely associated with the small increase in blood pressure. Following 4 weeks of placebo treatment, the 24-hour mean (SE) heart rate was 78.7 (1.5) beats per minute (bpm). After 4 weeks of MK-0966 and indomethacin the values were 73.5 (1.4) and 74.7 (1.5) bpm, respectively.

Conclusions

- Twenty-five milligrams MK-0966 administered in combination with an ACE inhibitor for 4 weeks is associated with a small attenuation of the antihypertensive effect (average increase in 24-hour mean MAP 2.8 mm Hg [90% CI; 1.0, 4.6]). The magnitude of the increase in blood pressure with MK-0966 is similar to that found with indomethacin 75 mg and is comparable to that generally reported for NSAIDs. This interaction should be given consideration in patients taking MK-0966 concomitantly with ACE inhibitors. Although the effect is marginal with a 25 mg dose of MK-0966, but could be more concerning for higher doses of MK-0966.
- MK-0966 25 mg once daily is not associated with any clinically meaningful effects on serum electrolytes, including potassium and sodium, in hypertensive patients treated with 10 to 40 mg benazepril once daily.

<u>Aspirin</u>

Study P063: *A double-blind, randomized, placebo controlled, parallel group study to assess the effect of MK-0966 on the anti-platelet effects of low dose aspirin in healthy volunteers*

The purpose of this study was to determine whether there was any influence of MK-0966 on the anti-platelet actions of low-dose aspirin. Because of the structural similarities of the two COX isoforms, and because of the evidence that other COX-2-specific inhibitors bind to the active site of COX-1 (without causing inactivation of COX-1), there was a theoretical concern that MK-0966 could sterically inhibit aspirin-mediated acetylation of COX-1, without itself having any direct inhibitory effect on COX-1.

Serum thromboxane B_2 (TXB_2), generated ex vivo during the process of spontaneous clotting of whole blood, was included in this study, since it is predominantly platelet derived, and since blockade of platelet COX-1 activity (resulting in reduced thromboxane formation) inhibits platelet function. Thus, many clinical studies of anti-platelet therapy that work through the COX system have measured ex vivo serum TXB_2 as a marker for in vivo platelet inactivation. In addition, platelet function was also investigated by performing ex vivo platelet aggregation studies.

The dose of aspirin used in this study, 81 mg (a "baby" aspirin), is the lowest dose commonly prescribed for prophylaxis of cardiovascular events in present clinical practice. Using this low dose increased the likelihood that any competitive effects of MK-0966 that diminish the anti-platelet effects of aspirin would be detected.

This study was designed to assess whether there was any influence of MK-0966 on the pharmacodynamic actions of low-dose aspirin, rather than to assess a pharmacokinetic interaction. However, a separate in vitro study demonstrated that MK-0966 has no effect on the protein binding of salicylic acid in human plasma, making it unlikely that plasma protein binding interaction occurs in vivo.

This was a double-blind, randomized, placebo-controlled, parallel-group study in 24 healthy volunteers. There were 2 treatment groups, and subjects received double-blind tablets of either MK-0966 or matching placebo, according to a randomized allocation schedule. All subjects received open-label aspirin 81 mg.
One treatment group (N=12) received MK-0966 50 mg daily for 10 days (Days 1 to 10), and beginning on Day 4, through Day 10, received an open-label dose of 81 mg aspirin daily (seven doses).
A second treatment group (N=12) received placebo daily for 10 days (Days 1 to 10), and beginning on Day 4, through Day 10, received an open-label dose of 81 mg aspirin daily (seven doses).

Blood samples for serum TXB_2 and platelet aggregation were collected within 72 hours prior to the initiation of dosing, predose on Day 1 (prior to initiation of MK-0966 or placebo therapy), Day 4 (prior to initiation of aspirin therapy), and predose and 4 hours postdose on Day 10, as a measure of anti-platelet effects. Platelet aggregation studies were performed with arachidonic acid and collagen as agonists. Platelet aggregation was measured as percent light transmission for two agonists: 1 mM of arachidonic acid and 1 g/mL of collagen. The inhibition of platelet aggregation was calculated by taking the difference of the post-administration of treatment (Day 4 predose, Day 10 predose, and Day 10, 4 hours postdose) from Day 1, predose baseline value and dividing by baseline times 100. Arachidonic acid was predefined as the primary platelet aggregation agonist for purposes of data analysis. Subjects must have had a platelet aggregation study (arachidonic acid) that showed no substantial inhibition (65% aggregation) within 72 hours prior to first dosing in order to participate.

Results

Thromboxane B_2

The percent change from baseline TXB_2 for each day by time point is plotted in the Figure. Percent inhibition of the TXB_2 on Day 10, 4 hours post-dose, for the aspirin with MK-0966 and aspirin -alone treatments, was 98.37 and 98.36%, respectively. The percent inhibition in ex vivo generated serum TXB_2 from Day 1