CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 21-042, 21-052
PRODUCT: Rofecoxib tablets and oral suspension
BRAND NAME: VIOXX™
SPONSOR: Merck & Co., Inc.
P.O. Box 4
West Point, PA 19486

SUBMISSION DATE: 11/23/1998
1/7/99, 1/11/99, 1/26/99, 3/12/99,
3/15/99, 3/16/99, 3/17/99, 3/18/99,

REVIEWER: Dan Wang, Ph.D.
TYPE OF SUBMISSION: Original

SYNOPSIS

VIOXX™ (Rofecoxib) is an orally active cyclooxygenase-2 (COX-2) specific inhibitor. It is the second agent submitted in its class. The efficacy of VIOXX™ is thought to be due to its specific inhibition of COX-2. Because VIOXX™ does not inhibit COX-1 within and significantly above the clinical dose range, it is supposed to have a safety profile in the GI tract superior to NSAIDS and similar to placebo, when administered in the clinical dose range. The proposed indications for VIOXX™ are the acute and chronic treatment of the signs and symptoms of osteoarthritis, relief of pain, and treatment of primary dysmenorrhea.

The sponsor submitted two formulations simultaneously: Tablets (NDA 21-042) and an Oral Suspension (NDA 21-052). NDA 21-052 is structured with cross-referencing to NDA 21-042. Information presented in NDA 21-052 is specific to manufacture, testing, packaging and labeling of the drug product.

Thirty-four studies were submitted under the Human Pharmacokinetics and Bioavailability section of the NDA. Among them, 29 studies were reviewed. The medical officer reviewed the other 5 studies. In this submission, rofecoxib was also referred as MK-0966 and L-748,731. These names will be used in the review.

Most of drug interaction studies were reviewed by Dr. Veneeta Tandon. Special population studies and some bioequivance studies were reviewed by Dr. Sue-chih Lee. They are included in separate reviews.

Dissolution method and specification were submitted for the tablet formulation.

RECOMMENDATIONS

1. The applicant has adequately studied the pharmacokinetics of rofecoxib. The submission is acceptable from clinical pharmacology and biopharmaceutics point of view. The pharmacokinetics of rofecoxib is summarized in "Overall Summary of *In Vivo* Pharmacokinetic/Pharmacodynamic Studies".

2. The applicant should be informed of **COMMENT #1** and **LABELING COMMENT.**

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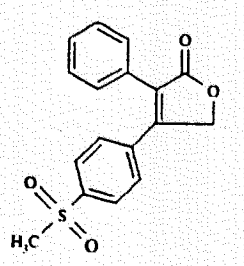
I. BACKGROUND

SPECIFIC INHIBITION OF COX-2

Cyclooxygenase is responsible for the generation of prostaglandins, which are potent biological mediators involved in diverse physiologic functions as well as pathologic conditions. Two isoforms of cyclooxygenase have been identified: COX-1 and COX-2. COX-1 is constitutively expressed and enzymatically active in various tissues, including the stomach, intestines, kidneys and in platelets. Evidence suggests that COX-1 is responsible for prostaglandin-mediated physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 in the gastric mucosa by nonspecific cyclooxygenase inhibitors has been associated with gastric damage. In contrast, COX-2 is constitutively expressed in only a limited number of tissues, including the brain and kidney, and is the inducible isoform of the enzyme that has been shown to be up regulated by pro-inflammatory stimuli. Based on patterns of expression and localization, COX-2 has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. The efficacy of VIOXX™ is due to its specific inhibition of COX-2. Because VIOXX™ does not inhibit COX-1 within and significantly above the clinical dose range, it is supposed to have a safety profile in the GI tract superior to NSAIDS and similar to placebo, when administered in the clinical dose range.

CHEMISTRY AND NOMENCLATURE

The compound 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone, also referred to as MK-0966, L-748,731, and rofecoxib, is a specific inhibitor of the inducible form of Cyclooxygenase. Its empirical formula is $C_{17}H_{14}O_4S$ with a molecular weight of 314.36. It has no chiral centers and presents no optical activity. Its molecular structure is shown below.



MK-0966 is a crystalline solid with a melting point of approximately 209°C. The drug is poorly soluble in most pharmaceutical solvents including water (0.00389 mg/mL), aqueous buffers (<0.008 mg/mL), alcohols (0.41 mg/mL in ethanol), and oils and shows no effect of pH on solubility, consistent with its lack of ionizable groups. It is also poorly wetted and of low polarity. It shows better solubility in hydrophobic organic solvents (28.7 mg/mL in acetonitrile, 19.6 mg/mL in acetone) and polyethylene glycol (10.9 mg/mL in PEG-400, ~7 mg/mL in 10% water/PEG-400).

II. FORMULATION

1. Tablet

The proposed market formulations for MK-0966 tablets are 12.5- and 25-mg doses for osteoarthritis. The proposed compositions of these formulations are listed in Table 1.

Table 1. Final Market Image Compositions

Formulation Type Formulation Strength	Tablet 12.5 mg	Tablet 25 mg	Suspension 12.5 mg/5 mL	Suspension 25 mg/5 mL
MK-0966	12.50 mg	25.00 mg	12.5 mg	25 mg
Lactose				
Xanthan Gum				
Microcrystalline Cellulose				
Hydroxypropyl Cellulose				
Croscarmellose Sodium				
Sorbitol Solution				
Sodium Citrate (Dihydrate)				
Citric Acid (Monohydrate)				
Methylparaben Sodium				
Propylparaben Sodium				
Magnesium Stearate				
Yellow Ferric Oxide				
Strawberry Flavor				
Purified Water USP				
Tablet Weight				

For the studies described in this application, MK-0966 was formulated in tablet strengths of 5, 7.5, 10, 12.5, 25, 50, 125, and 250 mg. The composition of these formulations is presented in Table 3. Tablets of the Final Market Image (FMI) composition manufactured on production scale equipment were supplied for all pivotal clinical studies of safety and efficacy. The FMI formulation for tablets is referred as Formulation C in this application, while other formulations used in earlier development are referred as Formulation A and B (Table 3). In addition, oral and intravenous solutions were developed for use as reference dosage forms in the human pharmacokinetics and bioavailability program (Table 5) and an oral capsule of L-755,190 (the 5-OH metabolite of MK-0966 [P012]) was also developed (Table 6). A summary of the formulation usage in the clinical development program is in Table 7. Tables 3, 4, 5, 6 and 7 can be found in Appendix 1.

2. Suspension

A suspension formulation of MK-0966 was developed to provide flexibility of dosing. The final product is an opaque, white to faint yellow suspension containing either MK-0966, and buffered to (Table 1).

III. ANALYTICAL METHODS

Overall, assay validation data are acceptable.

IV. OVERALL SUMMARY OF *IN VIVO* PHARMACOKINETIC/ PHARMACODYNAMIC STUDIES

1. Absorption and Bioavailability

MK-0966 is well absorbed at the therapeutic dose range of 12.5-mg to 50-mg. The absolute bioavailability of MK-0966 was estimated as for a 12.5-mg tablet and for a 25-mg tablet (Study P076). MK-0966 125 mg tablets and PEG solution are bioequivalent after single dose administration (Study P012). The geometric mean of $AUC_{0-\infty}$ after single dose of 25-mg MK-0966 is and Cmax is (Study P043). The magnitude of AUC and Cmax values are found strongly related to the body weight of subjects studied (Study P073). Median Tmax values ranged from 2 to 4 hours across studies. The Tmax values obtained for MK-0966 may not be related to the rate of absorption because higher secondary peaks were observed in some cases. Intrasubject variability for AUC and Cmax was estimated to be respectively.

a. Food Effect

At the therapeutic dose levels, food had no significant effect on either the Cmax or AUC of MK-0966 when VIOXX tablets were taken with a high fat meal. The time to peak plasma concentration (Tmax), however, was delayed by 1 to 2 hours. However, food (high fat meal) increased the absorption of MK-0966 by when 250-mg dose was given by increasing the solubility of MK-0966.

The food effect on the suspension formulation has not been studied.

b. Antacid

There was 13% and 8% decrease in AUC when MK-0966 was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively.

There was an approximate 20% decrease in C_{max} of MK-0966 with either antacid (Study P052).

c. Cholecystectomized Patient

The absorption of MK-0966 in cholecystectomized patient was much lower than that in healthy subjects probably because of the lack of bile facilitating the absorption of MK-0966 in these patients (Study P018).

2. Dose Proportionality

Dose proportionality was investigated in the dose range of 5 to 375 mg MK-0966. In the therapeutic dose range (12.5 to 50 mg), single dose of MK-0966 is nearly dose proportional with the extent of absorption for 25 and 50 mg dose than 12.5 mg dose, respectively (Study P043). However, significant deviation from dose proportionality was observed at dose levels lower than 12.5 mg (Study P021, P042) due to the nonlinear pharmacokinetics of MK-0966. Much higher clearance and shorter elimination half-lives were observed at those dose levels. Deviation from dose proportionality was also observed at dose levels higher than 100 mg (Study P002, P003, P005, P043) due to low solubility of the drug substance. It is the interplay of these competing process ("capacity limited" metabolism and decrease in bioavailability) that combine to provide dose proportionality at clinical doses.

3. Distribution

The *in vitro* study showed that binding of rofecoxib to human plasma protein is approximately 86.5%. The apparent volume of distribution was 91 and 86 L for 12.5 and 25mg dose, respectively (Study P076).

4. Metabolism and Elimination

MK-0966 is primarily eliminated through metabolism and the metabolites are excreted in the urine. Six metabolites have been identified in man. Metabolism of MK-0966 is primarily through the reduction of double bond on the dihydrofuranone ring mediated by a cytosolic enzyme (Study P012). The principal metabolic products are the *cis*-dihydro and *trans*-dihydro derivatives of MK-0966, which account for nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the glucuronide of the hydroxy derivative, L-755,190, a product of oxidative metabolism. The biotransformation of MK-0966 and L-755,190 is reversible in humans (Study P037). There are also additional three unidentified metabolites.

Cytochrome P450 plays a minor role in metabolism of MK-0966. Inhibition of CYP3A activity by administration of ketoconazole 400 mg daily does not affect MK-0966 disposition (Study P073). However, induction of hepatic metabolic activity by administration of the general 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 comparing to the normal dose of 12.5-mg.

The effect of MK-0966 on CYP3A activity has been evaluated by measuring 6-β-OH cortisol/cortisol ratio (Study P005), erythromycin breath test (Study P046), and interaction with midazolam (Study P073). It was concluded that MK-0966 has no significant effect on hepatic CYP3A activity. However, a 30% increase in midazolam AUC and Cmax suggests an increased first-pass metabolism through induction of intestinal CYP3A by MK-0966.

Secondary peaks were observed in MK-0966 plasma profiles. The origin of such peaks is unknown. The study results show that they are not the results of enterohepatic recycling or reversible biotransformation of MK-0966 and L-755,190 (Study P018, P037).

5. Excretion

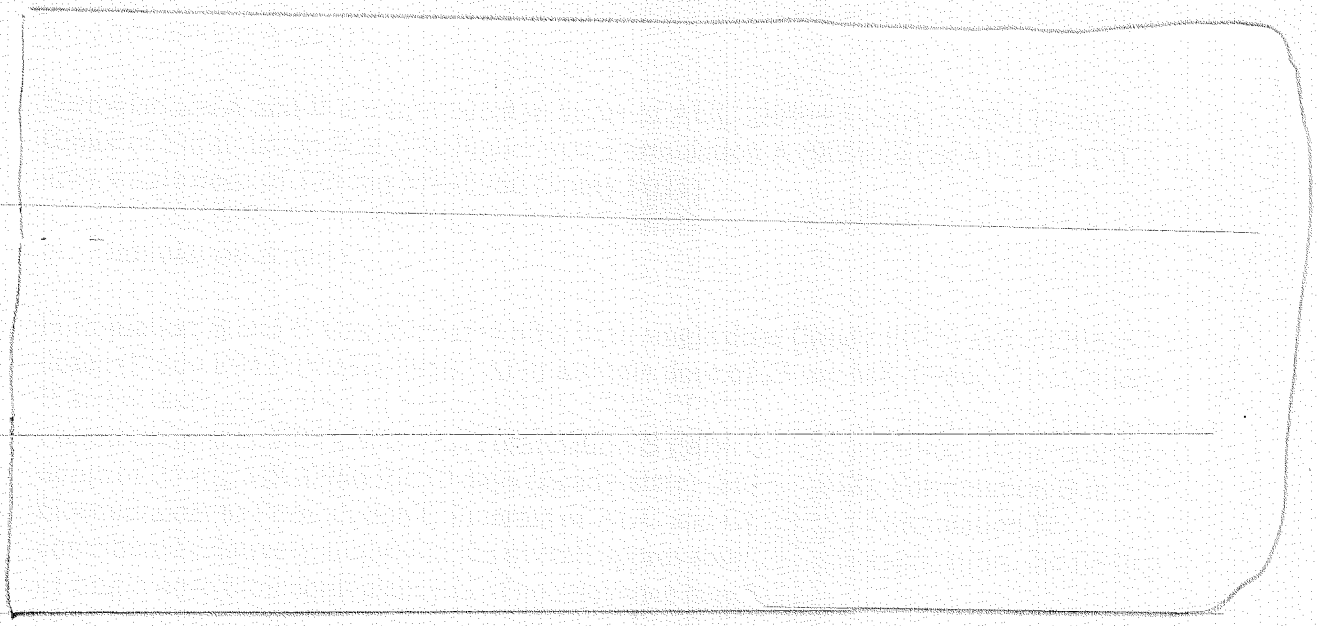
Following administration of a 125-mg radiolabeled oral dose of MK-0966 to healthy subjects, 72% of radioactivity was recovered in urine and 14% in feces (Study P012). Elimination of unchanged MK-0966 through urinary excretion is minimal (~1% of dose).

Due to the nonlinear pharmacokinetic property of MK-0966 (Study P037), the plasma clearance decreased as the total dose of MK-0966 increased. The mean plasma clearance was 141, and 121 mL/min after a single dose of 2.5 and 25 mg MK-0966, respectively (Study P076).

Excretion of MK-0966 and L-755,190 in bile is negligible (Study P018).

6. Multiple Dose

Steady-state concentrations of MK-0966 are reached within 4 days of once-daily administration of 25 mg. Steady-state pharmacokinetic behavior of MK-0966 is generally consistent with that observed following single-dose administrations. MK-0966 accumulates in plasma at steady-state by a factor of approximately following 25-mg daily doses, indicative of an accumulation $t_{1/2}$ of approximately 17 hours.



c. Tablet versus Suspension

The 12.5 mg MK-0966 tablet and 12.5 mg MK-0966 suspension are bioequivalent.

8. Special Populations

a. Geriatric

After single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. While the clinical significance of this increase is unknown, therapy with VIOXX should be initiated at the lowest dose.

b. Pediatric

VIOXX has not been investigated in pediatric patients below 18 years of age.

c. Race

Meta-analysis of pharmacokinetic studies did not detect any significant differences in rofecoxib AUC and Cmax among Blacks, Hispanic and Caucasians.

d. Hepatic Insufficiency

A pharmacokinetic study in mild (Child-Pugh Class I) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. In patients with moderate (Child-Pugh Class II) hepatic insufficiency a trend towards much higher AUC of rofecoxib was observed. Patients with severe hepatic insufficiency have

not been studied. Therefore, the use of VIOXX in patients with moderate to severe hepatic insufficiency is contraindicated.

e. Renal Insufficiency

There is no clinically important difference in pharmacokinetics of rofecoxib between patients with end-stage renal disease and subjects with normal renal function. Hemodialysis 4 hours postdose resulted in a reduction of only 9% in AUC and 18% in Cmax. Therefore, no dosage adjustment is necessary for patients with any degree of chronic renal insufficiency or for patients on hemodialysis.

9. Drug Interactions

In most of the drug interacting studies the applicant has measured plasma levels of the interacting drug and not MK-0966 (with the exception of the Cimetidine and Antacids interaction studies). The metabolites of MK0966 have not been analyzed in these studies.

At a dose of 3 to 6 times higher than that recommended for the treatment of osteoarthritis, MK-0966 significantly increased the methotrexate plasma concentrations in patients with rheumatoid arthritis receiving 7.5 to 15 mg methotrexate per week, as measured by AUC and Cmax. After a dose of 250 mg or 75 mg of MK-0966, the AUC, the $AUC_{(0-24)}$ [redacted] respectively. The renal clearance of methotrexate conversely [redacted] respectively in the two dose groups.

A potential of interaction between MK-0966 and warfarin was demonstrated by a small increase in the pharmacodynamic effect of warfarin based on increased prothrombin time International Normalized Ratio (INR) by approximately 11% and 8% after a single dose of warfarin with subjects on 50 mg MK-0966 and after multiple doses of warfarin and 25 mg of MK0966, respectively.

In patients with mild-to-moderate hypertension, administration of 25 mg daily of MK-0966 with ACE inhibitor (benezapril, 10 to 40 mg) for 4 weeks was associated with a small attenuation of the antihypertensive effect (average increase in 24-hr mean arterial pressure of 2.8 mm Hg) compared to ACE inhibitor alone.

Mk-0966 did not have any clinically important effects on the pharmacokinetics of prednisone/prednisolone or digoxin. However, the digoxin interaction study was done with a single dose of digoxin in healthy volunteers and as such would have minimal clinical relevance in the demonstration of an interaction. MK-0966 increased the plasma concentrations of ethinyl estradiol and norethindrone of oral contraceptive to a small magnitude.

Cimetidine and antacids (magnesium hydroxide/Aluminum hyroxide and Calcium carbonate) had a small effect on the pharmacokinetics of MK-0966, with cimetidine increasing the plasma concentrations and antacids decreasing the levels of MK-0966.

At steady state, MK-0966 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by ex vivo platelet aggregation and serum TXB_2 generated in clotting blood.

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.

Inhibition of CYP3A activity by administration of ketoconazole 400 mg daily does not affect MK-0966 disposition.

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.

10. PK/PD relationship

PK/PD relationship has been evaluated in a postoperative dental pain trial (Study P051) with 30 patients at three dose levels. 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, suggesting that 50 mg is the lowest effective analgesic dose studied.

V. SUMMARY OF INIDVIDUAL STUDIES

STUDY P002. A Double-Blind, Randomized, Placebo-Controlled, Rising Single Oral Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Biochemical Activity of MK-0966 in Healthy Male Volunteers

As stated in the title, the objectives of this study are to: (1) evaluate the safety and tolerability of rising single oral doses of MK-0966 in young, healthy, male volunteers; (2) obtain preliminary plasma pharmacokinetic data following single-dose administration of MK-0966 in the fasted state and following a standardized breakfast; (3) assess the effect of single doses of MK-0966 on serum thromboxane B_2 (TXB_2), ex vivo lipopolysaccharide (LPS)-induced whole blood PGE_2, and bleeding time; and (4) measure urine MK-0966 concentrations following single oral doses. Items (1) and (3) will be reviewed by the medical officer. Urine MK-0966 samples were not analyzed because the sponsor felt that urine samples from a multiple dose study would be more relevant. This review will focus on rising single-dose MK-0966 pharmacokinetics and food effect.

This was a double-blind, randomized, placebo-controlled study. Periods 1 to 8 comprised an alternating-panel, rising single-dose study. Sixteen healthy men were randomly assigned to one of two panels (A or B), 8 per panel. Table 1 shows the detailed design.

Table 1

Dosing Schedule for Panels A and B

	Dose of MK-0966			
	Panel A (N=8)		Panel B (N=8)	
Period	(N=6)	(N=2)	(N=6)	(N=2)
1	5 mg	PBO[†]		
2			10 mg	PBO
3	25 mg	PBO		
4			50 mg	PBO
5	125 mg	PBO		
6			250 mg	PBO
7	500 mg	PBO		
8			1000 mg	PBO
9			250 mg[‡]	PBO

[†] PBO = placebo.
[‡] Administered following a standard breakfast.

There was a minimum 48-hour interval between dosing Panels A and B to allow review of safety laboratory reports from the previous panel. All doses were given in the morning following an overnight fast. There were at least 6 days between consecutive treatments within the same panel. Period 9 (Panel B) was conducted 9 days following completion of Period 8 (Panel B) to assess the food effect. The standardized breakfast consisted of 2 eggs, 2 strips of bacon, 2 pieces of toast with butter, 2 to 4 ounces of hash browns, and 375 mL of whole milk.

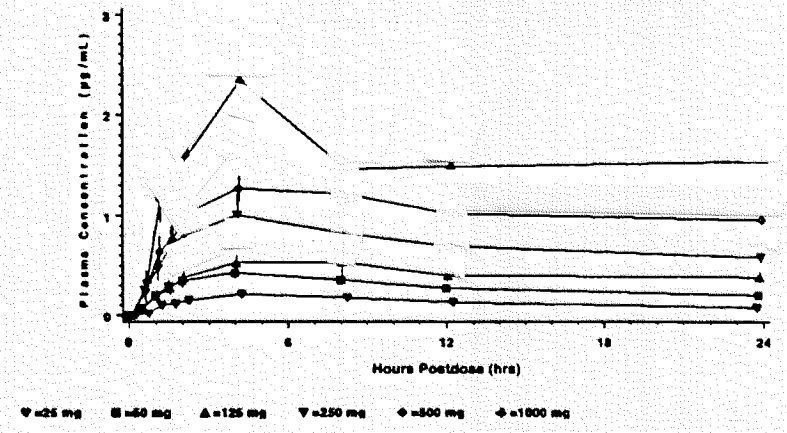
RESULTS:

1) Single dose pharmacokinetics and dose proportionality

All subjects completed the treatment of Period 1 to Period 8. Mean (±SE) plasma concentration-time profiles for 25- to 1000-mg dose levels are in Figure 1.

Figure 1

Mean (± SE) Plasma Concentrations Versus Hours Postdose



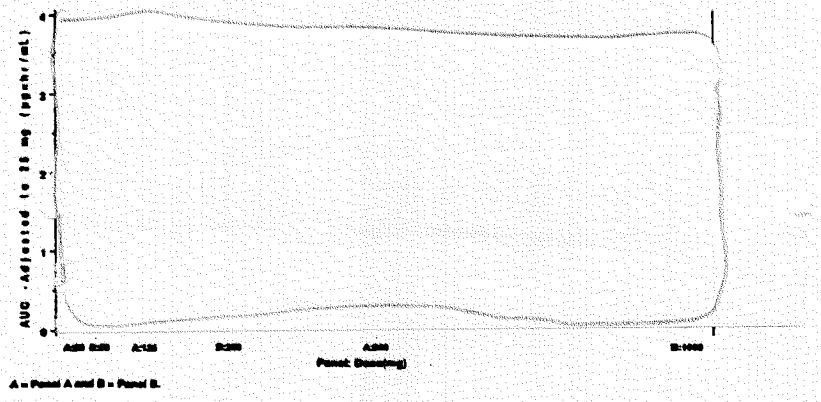
As is evident in Figure 1, the duration of sampling (24 hours) was inadequate to completely characterize the pharmacokinetic behavior of MK-0966, especially relative to any comparisons across dose groups. The interpretability of subsequent analysis of C_{max}, T_{max}, and $AUC_{(0-24)}$ is therefore limited.

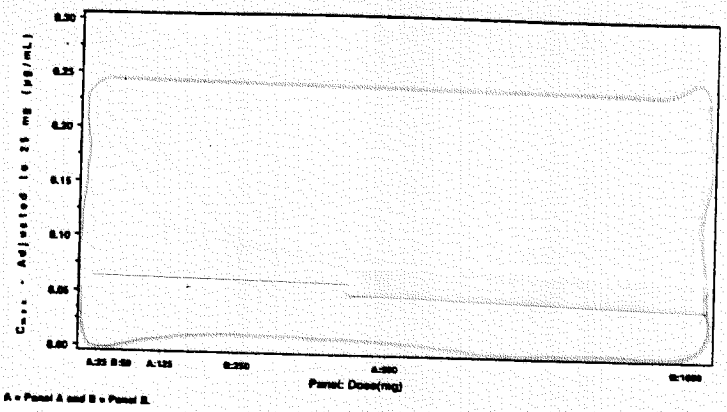
The pharmacokinetic parameters following each treatment are summarized in Table 2.

Table 2. Mean $AUC_{(0-24)}$ (%CV) and C_{max} (%CV) values following 25 to 1000 mg dose of MK-0966

	25 MG	50 MG	125 MG	250 MG	500 MG	1000 MG
$AUC_{(0-24)}$ (µg.h/mL)	3.04(34.2)	6.70(18.2)	9.42(36.3)	15.9(41.3)	23.9(30.0)	37.0(16.2)
C_{max} (µg/mL)	0.21(18.9)	0.44(24.8)	0.54(39.0)	0.92(47.8)	1.35(28.6)	2.41(26.8)
T_{max} (h, median)	4	4	4	4	6	4

The dose adjusted $AUC_{(0-24)}$ and C_{max} values versus dose are plotted below to evaluate dose proportionality of MK-0966.



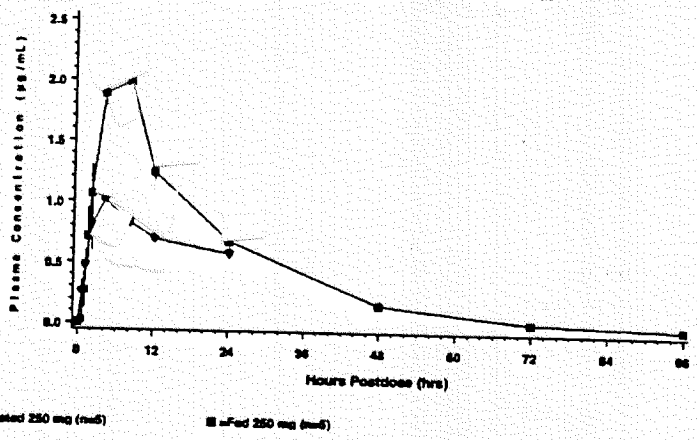


It is observed that both AUC and C_{max} increase with dose but in a less than dose-proportional manner.

2) Food Effect

Food effect was evaluated at 250 mg dose level. In Period 9, one subject did not complete the study and was excluded from the statistical analysis. The mean $AUC_{(0-24)}$ (μg.h/mL) values (N=5) under fasted and fed condition are [redacted] and the mean C_{max} (μg/mL) values (N=5) was [redacted] respectively. It is appeared that the bioavailability increased dramatically under fed condition at 250 mg dose level. This is also clearly observed from the following figure. The T_{max} values in the fasted and fed periods were [redacted] but the difference was not statistically significant.

Mean (± SE) Plasma Concentrations Versus Hours Postdose
250 mg of MK-0966 in Fasted Versus Fed Periods



CONCLUSIONS:

Following single dose of MK-0966 25 mg to 1000 mg, $AUC_{(0-24)}$ and C_{max} increased with dose but in a less than dose-proportional manner. Food increased the absorption of MK-0966 by about [redacted] at 250 mg dose level. Further study is needed to make a definitive conclusion since plasma levels of MK-0966 were not followed long enough to allow reliable determination of the relative bioavailability of MK-0966.