Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-042 SUBMISSION DATE: 11/23/98
21-052

PRODUCT: VIOXX™
(Rofecoxib 12.5 and 25 mg tablets)

SPONSOR: Merck Research Labs REVIEWER: Veneeta Tandon, Ph.D.

REVIEW OF THE DRUG INTERACTION SECTION OF VIOXX™ NDA

This review of the NDA covers only the "Drug Interaction" section of the "Clinical Pharmacokinetics Section". The general pharmacokinetic section and the special population section have been reviewed by Dr. Wang and Dr. Lee, respectively, and are provided separately. The final recommendation and the comments will be provided in Dr. Wang's review, which will also include the summary of the entire "Clinical Pharmacokinetics section". Below is an index to facilitate perusal of this review.

INDEX

DRUG INTERACTION STUDIES

Methotrexate

The effect of MK-0966 on the pharmacokinetics of methotrexate was examined in 2 double blind, placebo controlled, parallel group studies using 250 mg and 75 mg MK-0966, respectively. These studies are discussed in this subsection.

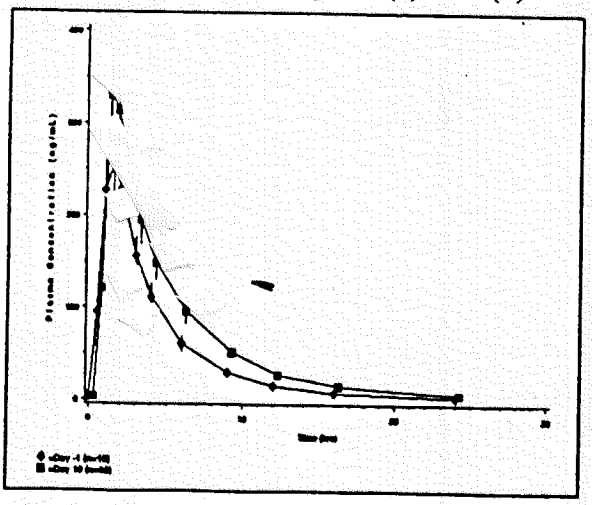
Study #P011: A double blind, parallel study to investigate the effect of 250 mg MK-0966 on oral methotrexate pharmacokinetics in rheumatoid arthritis patients.

Management of rheumatoid arthritis frequently consists of multiple medications administered concomitantly. Methotrexate (MTX) is a commonly used treatment for active rheumatoid arthritis as a once weekly dose and is frequently used in combination with anti-inflammatory medications. Because methotrexate is partially eliminated by renal tubular secretion as an organic anion, it can undergo competitive inhibition at the tubules when co-administered with other organic ions like salicylates. Also, inhibition of renal prostaglandin synthesis by NSAIDs may compromise renal blood flow and subsequently interfere with methotrexate renal clearance. This study examined the impact of a high dose of MK-0966 (250 mg daily) on the plasma concentrations and renal clearance of methotrexate in a parallel, placebo-controlled trial. Patients that had been treated with weekly oral dose methotrexate at a stable dose of 7.5 to 15 mg for at least 2 months could be enrolled. NSAIDS were prohibited during and 1 month prior to Day-1, acetaminophen, dextropropoxyphene, and codiene/hydrocodone were allowed. Other inclusion and exclusion criteria have also been reviewed. Methotrexate was administered at baseline (Day –1) and on Day 10. 12 patients were given MK-966 from Day1-10 and 5 patients were given placebo. Other details of study design have been summarized on page 1of the Appendix II. The assay validation review for this study is provided on page 2 of the Appendix II.

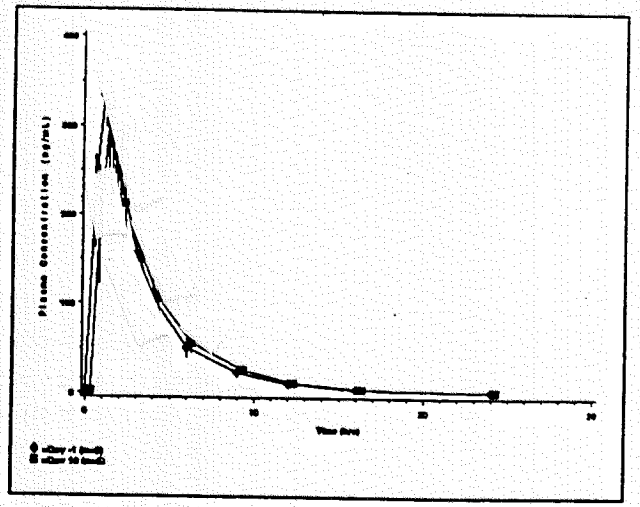
Results

Methotrexate AUC(0-24 hr)

After 10 days of MK-0966 dosing, the mean methotrexate plasma concentrations increased at all time points versus the plasma profile obtained prior to MK-0966 (Day -1). Conversely, the methotrexate plasma profile remained fairly consistent and superimposable after 10 days of dosing with placebo plus methotrexate in comparison to Day -1 (Figures (a) and (b) below).



(a) Mean MTX plasma concentration profile for Patients on MK-966+MTX upper curve (day10), lower curve (day-1)



(b) Mean MTX plasma concentration profile for Patients on placebo+MTX vs time upper curve (day10), lower curve (day-1)

The applicant has put forth a hypothesis that no difference in the treatments will be confirmed if the levels of methotrexate prior to MK-966 treatment will be within 30% of the geometric mean ratio (90% CI within 0.77 and 1.30) of the methotrexate after 10 days of MK-966 treatment. Similar comparisons were made with the placebo. This was based on an estimated variance for intra-patient difference.

The methotrexate $AUC_{(0\text{-}24\ hr)}$ GMR (Day 10 versus Day -1) was 0.97 with 90% bounds of (0.77, 1.24) for the placebo treatment. Ten days of dosing with MK-0966 significantly increased the methotrexate plasma $AUC_{(0\text{-}24\ hr)}$ (p=0.004). The methotrexate plasma $AUC_{(0\text{-}24\ hr)}$ GMR (Day 10/Day 1) was 1.40 in the MK-0966 treatment group with 90% CI of (1.19,1.64). 9 out of 10 patients had increased $AUC_{(0\text{-}24\ hr)}$. The summary statistics for all the pharmacokinetic parameters is tabulated below.

	AUC (0-24) (ng.h/ml)					Cmax (ng/ml)				Tmax (h)	
Treat-ment	D	Mean	GMR	p-value	90% CI for GMR	Mean	GMR	p-value	90% CI for GMR	Mean	p-value
Placebo (N=5)	-1 10	1083 1054	0.97	0.821	(.77, 1.24)	307.4 280.77	0.91	0.482	(0.71,1.17)	1.2 1.1	0.374
MK966 (N=10)	-1 10	1066 1492	1.40	**0.004**	(1.19, 1.64)	264.07 323.24	1.22	**0.028**	(1.06,1.41)	1.4 1.2	0.193

	Renal Clearance (ml/min)					Unbound methotrexate			
Treat-ment	D	Mean	GMR	p-value	90% CI for GMR	Mean	Mean Diff (%)	p-value	90% CI for GMR
Placebo (N=5)	-1 10	135.61 127.93	0.94	0.294	(.85,1.05)	52.1 57.0	-4.88	0.378	(-15.39,5.62)
MK966 (N=10)	-1 10	96.69 59.95	0.62	**0.005**	(.0.49,0.79)	53.9 50.4	3.50	0.334	(-2.78,9.77)

GMR=Day10/-1

Methotrexate C_{max} and T_{max}

The C_{max} GMR (post- versus pre-placebo treatment) was 0.91, with a 90% CI of (0.71, 1.17). For the active-treatment group, the methotrexate C_{max} GMR for post-MK-0966 versus that observed prior to MK-0966 administration was 1.22 (p = 0.028) with a 90% CI of (1.06, 1.41). 9 out of 10 patients had an increased C_{max}.

After 10 days of MK-0966 treatment, no significant difference in the methotrexate T_{max} was observed when the two agents were given concurrently on Day 10 (p=0.193); the methotrexate T_{max} values for the placebo patients were also consistent (p>0.200).

Methotrexate Renal Clearance

No significant change in renal clearance of methotrexate occurred after 10 days of dosing with placebo (p>0.200) as supported by the GMR of 0.94 and 90% CI of (0.85, 1.05). For all 10 patients who received MK-0966 for 10 days, the renal clearance of methotrexate decreased on Day 10 as compared to prior to MK-0966 on Day –1, showing a statistical significance of p=0.005. The renal clearance GMR (Day 10 to Day -1) was 0.62, with a corresponding CI of (0.49, 0.79).

Unbound methotrexate in human plasma
The percent unbound methotrexate was not statistically different for the treatment regimen with placebo and that with MK-966.

Conclusions

- After 10 days of MK-0966 treatment, the plasma $AUC_{(0\text{-}24\ hr)}$ and C_{max} of methotrexate was significantly increased approximately 40 and 22%, respectively, relative to
  Day-1.
- The renal clearance of methotrexate conversely decreased by about 38% in the MK-0966 treatment group. This could explain the 40% increased plasma concentration and the likely role of MK-0966 on the renal function.
- The $AUC_{(0\text{-}24\ hr)}$, C_{max}, and renal clearance remained unchanged in the placebo group as indicated by the p-value, however the 90% confidence limits were not between 0.80 and 1.25, suggesting the presence of a change in methotrexate pharmacokinetics.
- Tmax and unbound methotrexate concentrations were not significantly different after MK-0966 or placebo treatment.

Reviewer's Comments

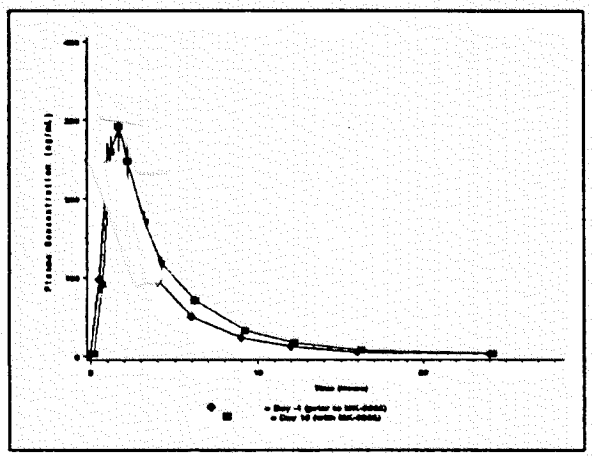
- *7-hydroxymethotrexate concentrations have not been measured in this study.*
- *The usual dose of methotrexate is 7.5-15 mg once a week. In this trial methotrexate has been administered after 10 days to allow enough time for MK-0966 to reach steady state.*
- *The applicant has put forth a hypothesis that no difference in the treatments will be confirmed if the levels of methotrexate prior to MK-966 treatment will be within 30% of the geometric mean ratio of the methotrexate after 10 days of MK-966 treatment. This was based on an estimated variance for intra-patient difference. This criterion is not the most acceptable one, however, this study does indicate that monitoring of MTX toxicity should be done while administering 250 mg MK-0966. At this point one should also note that the dose of MK-0966 used in this study is very high, the recommended dose is 12.5 to 25 mg.*

Study# P030: A double-blind parallel study to investigate the effect of 75 mg MK-0966 on oral methotrexate (MTX) pharmacokinetics in rheumatoid arthritis patients.

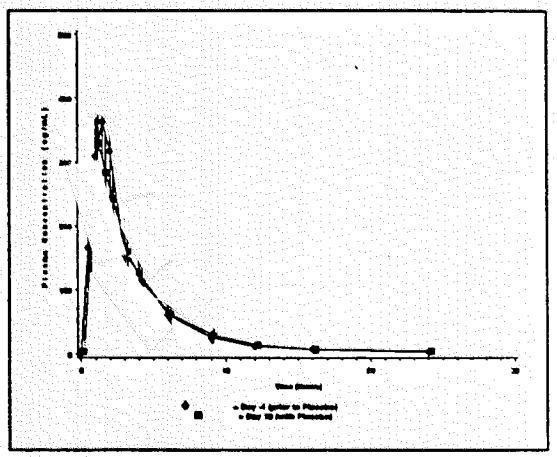
While designing this study it was anticipated that a lower MK-0966 dose (75 mg) would have a smaller effect on methotrexate pharmacokinetics, as compared to the earlier study where the dose of MK-0966 was 250 mg. The study design is similar to Study P011, except that the effect of MK-0966 on 7-hydroxymethotrexate plasma concentration profile was also evaluated. The details of study design and assay validation are provided on pages 3-4 of the Appendix II.

Results

On the tenth day of MK-0966 dosing, the mean methotrexate plasma concentration increased at all time points versus the plasma profile prior to MK-0966 (Day -1). Conversely, the methotrexate plasma profile remained fairly consistent and superimposable on the tenth day of dosing with placebo. Refer to Figures (a) and (b).



(a) Mean MTX plasma concentration for Patients on MK-966 vs time upper curve (day10), lower curve (day-1)



b) Mean MTX plasma concentration for Patients on placebo vs time upper curve (day10), lower curve (day-1)

Methotrexate $AUC_{0\text{-}24\ hr}$

The results indicate that after 10 days of MK-0966 treatment the plasma $AUC_{0\text{-}24\ hr}$ methotrexate were increased approximately 23% relative to prior to MK-0966 (Day -1), with 90% CI of (1.14, 1.34). Methotrexate $AUC_{0\text{-}24\ hr}$ increased after 10 days of MK-0966 in 14 of 16 patients. The methotrexate $AUC_{0\text{-}24\ hr}$ GMR for placebo treatment (Day 10/Day -1) was 0.90, with a 90% CI of (0.73, 1.10).

Methotrexate C_{max} and T_{max}

The results indicate that after 10 days of MK-0966 treatment the plasma C_{max} of methotrexate were increased approximately 11% relative to prior to MK-0966 (Day -1), with 90% CI of (1.00, 1.23). The methotrexate C_{max} GMR was 0.80, with 90% CI of (0.63,1.02), for the placebo treated group.

In both placebo and MK-0966 treatment groups, there was a slight decrease in methotrexate Tmax post 10 days of treatment administration. Methotrexate median Tmax values on Day 10 were the same for both treatment groups.

Free methotrexate and Renal clearance

On Day 10, the mean percent unbound methotrexate after 10 days of MK-0966 treatment was 57.58% and the percent unbound methotrexate prior to MK-0966 administration was 58.32%.

Methotrexate renal clearance after 10 days of dosing with placebo was similar to that prior to placebo. There was an 11% decrease in methotrexate renal clearance after 10 days of dosing with MK-0966. The renal clearance of methotrexate for 13 of the 16 subjects decreased after 10 days of MK-0966. All these results for methotrexate parameters are summarized in the tables below.

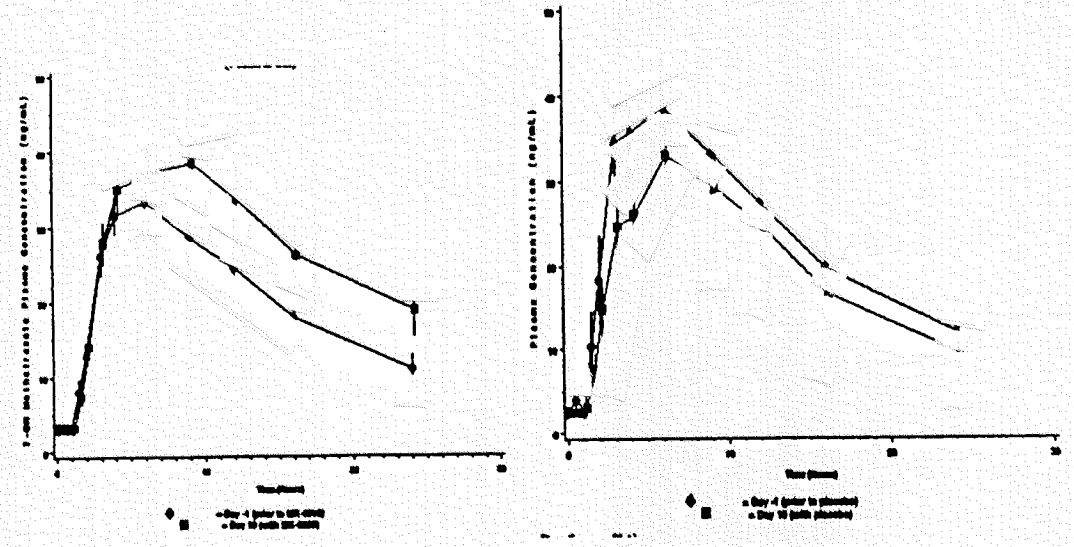
	AUC (0-24) (ng.h/ml)					Cmax (ng/ml)				Tmax (h)	
Treat-ment	D	Mean	GMR	Within Subj. CV	90% CI for GMR	Mean	GMR	Within Subject CV	90% CI for GMR	Mean	Within Subject SE
Placebo (N=5)	-1 10	1097 1076	0.90	15.2%	(.73, 1.10)	377 302	0.80	18.1%	(0.63,1.02)	1.4 1.1	0.21 0.00
MK966 (N=16)	-1 10	985 1215	1.23	12.9%	(1.14, 1.34)	272 302	1.11	17.2%	(1.00,1.23)	1.4 1.3	0.12 0.12

GMR=Day10/Day-1

	Renal Clearance (ml/min)					Unbound methotrexate			
Treat-ment	D	Mean	GMR	Within Subj. CV	90% for GMR	Mean	GMR	p-value	90% CI for GMR
Placebo (N=5)	-1 10	100.65 103.39	1.03	21.5%	(.77,1.37)	48.47 57.44	1.19	0.245	(0.97,1.44)
MK966 (N=16)	-1 10	132.16 117.69	0.89	16.3%	(.80,.99)	58.32 57.58	0.99	0.695	(0.93,1.04)

7-OH methotrexate AUC0-24 hr

On the tenth day of MK-0966 treatment, the mean 7-hydroxy methotrexate (7-OH MTX) plasma concentration increased at all time points versus the plasma profile prior to MK-0966 (Day -1). Conversely, the 7-OH methotrexate plasma concentrations were numerically lower at all time points after 10 days of dosing with placebo. The $AUC_{0\text{-}24\ hr}$ of 7-OH significantly increased to 30%, relative to Day -1. These trends are illustrated in the figures below.



(a) Mean 7-OH MTX plasma concentration for Patients on MK-966 vs time upper curve (day10), lower curve (day-1)

(b) Mean 7-OH MTX plasma concentration for Patients on placebo vs time lower curve (day10), upper curve (day-1)

The GMRs and the 90% CI are shown in the table below.

7-OH methotrexate C_{max} and T_{max}

There was an 18% increase in C_{max} of 7-OH after 10 days of dosing with MK-0966. The 7-OH MTX C_{max} GMR was 1.18, with a 90% CI of (1.04, 1.33). The 7-OH methotrexate C_{max} GMR (Day 10/Day -1) was 0.69, with 90% CI of (0.43,1.13) for the placebo treatment group.

	AUC (0-24) (ng.h/ml)					Cmax (ng/ml)				Tmax (h)	
Treat-ment	D	Mean	GMR	Within Subj. CV	90% CI for GMR	Mean	GMR	Within Subject CV	90% CI for GMR	Mean	Within Subject SE
Placebo (N=5)	-1 10	533 414	0.78	24.6%	(0.56,1.08)	44 31	0.69	36.4%	(0.43,1.13)	4.6 6.2	1.25 0.00
MK966 (N=15)	-1 10	464 602	1.30	20.7%	(1.14, 1.48)	34 39	1.18	18.8%	(1.04,1.33)	5.7 7.1	0.00 1.20

Conclusions

- MK-0966 75 mg once daily increases plasma methotrexate concentration to 23% based on $AUC_{0\text{-}24\ hr}$ and in association with an 11% reduction in renal clearance. The MTX Cmax increases by 11%
- MK-0966 increases the plasma concentration of 7-OH methotrexate (~30%) to an extent comparable to the increase in parent compound. This finding is consistent with the influence of MK-0966 on methotrexate pharmacokinetics being at the level of renal elimination of parent drug rather than on metabolism.

Renal excretion of nonmetabolized methotrexate is the major route of elimination and involves glomerular filtration, tubular secretion, and tubular reabsorption. Drugs excreted in the urine as acidic compounds may compete with the tubular secretion of methotrexate, slow renal clearance, and thereby result in elevated plasma concentrations. Although MK-0966 is not ionic and is not excreted in the urine, it undergoes extensive metabolism primarily via the reduction of the double bond on the middle ring structure, resulting in the formation of the hydroxy acid forms of the dihydro metabolites, which are excreted in urine. In fact, 70% of a dose is recovered from the urine and the dihydro metabolites account for approximately 56% of the urinary recovery. The dihydro metabolites of MK-0966 may compete and interfere with the tubular secretion of methotrexate with the result of decreased renal clearance and increased plasma concentrations of methotrexate. The observed changes in methotrexate renal clearance and plasma AUC in the present study are consistent with such a mechanism. The finding of a comparable influence of MK-0966 on plasma 7-OH methotrexate further suggests that MK-0966 is not influencing metabolism of methotrexate but rather reducing clearance of the parent drug.

Reviewer's Comment

- *Monitoring of methotrexate toxicity and methotrexate plasma concentrations should be considered when there is concurrent administration of 75 mg MK-0966 with methotrexate or dose attenuation may be required. The effects on recommended doses (12.5, 25 and 50 mg) of MK-0966 is unknown, however, the 75 mg dose does approach the clinically recommended dose.*

Prednisolone and Prednisone

Study P014: A double-blind, placebo-controlled, 2-period, crossover study to investigate the effect of oral doses MK-966 250 mg on predinisolone and prednisone pharmacokinetics in healthy male volunteers.

Corticosteroids are frequently added to the treatment of rheumatoid arthritis when other measures fail to control the symptoms, mainly the suppression of inflammation. In order to avoid the side effects due to multiple corticosteroid doses, blood samples were obtained following single doses of I.V. prednisolone and oral prednisone. Prednisone is metabolized in the liver to prednisolone as the active drug. Both conversion of prednisone to prednisolone and then to inactive metabolites are enzymatic reactions, potentially susceptible to drug interactions. Prednisolone is also a known inducer of CYP 3A. This interaction study was carried out because preclinical data suggested that MK-0966 might be a mild inducer of CYP 3A in rat hepatocytes.

The interpretation of the prednisolone and prednisone plasma concentration curves following oral prednisone and MK-0966 is complicated by possible influences on absorption, first-pass metabolism, systemic disposition, conversion of the prodrug (prednisone) to the active moiety (prednisolone), and their subsequent interconversion. The inclusion of the I.V. prednisolone arm permits assessment of drug influences on systemic disposition of prednisolone. Oral prednisone is more commonly administered in the management of arthritis.

Prednisolone circulates in plasma partially bound to plasma proteins, most importantly transcortin, with low affinity interactions with albumin. As the high affinity binding sites may be saturated at high concentrations, nonlinear pharmacokinetics may be observed. To aid in interpreting the data, albumin and transcortin concentrations were determined prior to and following each treatment period.

There were 2 periods during which each subject received oral doses of either a MK-0966 250-mg tablet or matching placebo once daily for 14 days at the clinic. Drug was administered in the morning without regard for food except when safety laboratory tests of blood sampling for pharmacokinetic measurements were performed. On the morning of Days 10 and 14 during both periods, subjects received the usual dose of MK-0966 or placebo followed by either 30 mg prednisolone sodium phosphate (1.5 mL CODELSOL™, MSD, Japan) intravenously in a 20- to 30-second bolus infusion or a single oral dose of 30 mg prednisone (DELTASONE™, Upjohn, Kalamazoo, MI).

Subjects were randomized such that those individuals who received the I.V. steroid on Day 10 received oral on Day 14 in the two periods with a 14 day wash out between periods. Blood samples for prednisolone/prednisone assays were obtained through 24 hours following the doses. Other details of the study design are provided in the Appendix II on page 5-6 along with the assay validation summary on page 6.

Results

Prednisolone

The prednisolone plasma concentration profiles in the presence and absence of MK-0966 following either oral prednisone or I.V. prednisolone are similar (figures 1-2 attached in Appendix II on page 7).

The GMRs (MK-0966 to placebo) for prednisolone $AUC_{(0-\infty)}$ following I.V. and oral steroids, and the prednisolone C_{max} following oral steroids, are shown in the table below.

Variable/ Administration	Treatment	N	Mean†	GMR of MK-0966/ Placebo	90% CI for GMR of MK-0966/ Placebo	Within-Subject CV(%)‡
$AUC_{(0-\infty)}$ (ng•hr/mL)						
I.V.	MK-0966	12	2279.6	0.974	(0.938, 1.012)	5.19
	Placebo	12	2339.9	.	.	.
Oral	MK-0966	12	1971.2	0.995	(0.914, 1.083)	11.46
	Placebo	12	1982.1	.	.	.
C_{max} (ng/mL)						
Oral	MK-0966	12	336.8	0.989	(0.894, 1.094)	13.66
	Placebo	12	340.7	.	.	.

† Back-transformed from log scale, i.e., mean is geometric mean.
‡ Root mean square error (RMSE) on the log-scale x 100.

The 90% CIs were within the bounds of (0.80,1.25), although the applicant has predefined the acceptable bounds as (0.77,1.30). However, even after narrowing the accetability limits, these results show that MK-0966 did not affect the $AUC_{(0-\infty)}$ of prednisolone following I.V. administration of prednisolone nor following oral prednisone. The median T_{max} of prednisolone following oral prednisone plus MK-0966 and oral prednisone plus placebo were 1.3 and 1.0 hours, respectively, with no statistically significant difference ($p>0.200$). The prednisolone $T_{1/2}$ and clearance parameter values following I.V. prednisolone plus MK-0966 and I.V. prednisolone plus placebo showed no statistical difference ($p>0.2000$). The summary statistics are in Table 1-3 in the Appendix II on page 8.

Prednisone

The prednisone plasma concentration profiles also in the presence and absence of MK-0966 following either oral prednisone or I.V. prednisolone are similar (figures 3-4 attached in Appendix II on page 9).

The results show that MK-0966 did not affect the prednisone $AUC_{(0-\infty)}$ following I.V. administration of prednisolone. However, following oral administration of prednisone the 90% CI for $AUC_{(0-\infty)}$ was not within the limit, showing a marginal increase at the upper boundary of the limits. However, the prednisolone form is active moiety and this increase may not be of clinical significance. The GMRs with 90% confidence intervals for prednisone pharmacokinetic parameters are provided in the table below.

Variable/ Adminis-tration	Treatment	N	Mean†	GMR of MK-0966/Placebo	90% CI for GMR of MK-0966/Placebo	Within-Subject CV (%)‡
$AUC_{(0-\infty)}$ (ng•hr/mL)						
I.V.	MK-0966	12	310.9	1.027	(0.953 ,1.106)	10.05
	Placebo	12	302.8	.	.	.
Oral	MK-0966	12	322.1	1.082	(0.918 ,1.275)	22.24
	Placebo	12	297.8	.	.	.
C_{max} (ng/mL)						
Oral	MK-0966	12	33.2	0.999	(0.896 ,1.114)	14.69
	Placebo	12	33.2	.	.	.

† Back-transformed from log scale, i.e., mean is geometric mean.
‡ Root mean square error (RMSE) on the log-scale x 100.

The summary statistics of prednisone AUC, C_{max} and T_{max} are provided in tables 4 and 5 in the Appendix II on page 10. The median prednisone T_{max} following oral prednisone plus MK-0966 and oral prednisone plus placebo were both 2.0 hours, with no statistically significant difference ($p>0.200$). Thus, MK-0966 did not affect the T_{max} of prednisone following oral administration of prednisone.

Transcortin and Albumin

Plasma transcortin and serum albumin concentrations on Days 1, 10, and 14 are summarized in Tables 6 and 7, respectively in the Appendix II on page 11. Mean transcortin concentrations showed no clinically meaningful difference between MK-0966 and placebo groups across the days; similarly consistent results were also observed with mean albumin concentrations.

Clinical safety measures

The mean systolic and diastolic blood pressures in the MK-0966 treated arms showed an increasing trend from Day 1 to Day 14 as compared to placebo. No discernable pattern for the MK-0966 versus placebo treatment was observed for heart rate. An average weight gain during the MK-0966 administration was observed for each of the MK-0966-placebo and placebo-MK-0966 sequences ($p=0.03$). The mean change in body weight was 2.3 lbs.

Conclusions

- Concurrent administration of 250 mg MK-0966 daily with I.V. prednisolone 30 mg does not alter the plasma concentration profile of prednisolone and prednisone.
- Concurrent administration of 250 mg MK-0966 daily with oral prednisone 30 mg does not alter the pharmacokinetics of prednisolone, but did marginally increase the extent of exposure of prednisone (90% CIs of AUC is 0.918,1.275).
- Neither trancortin not albumin concentrations changed throughout the study period.

Reviewer's Comment

- *The applicant has set the acceptable 90% CI limits to be within 0.77 and 1.30. There is a very marginal increase in the prednisone AUC after oral dose of prednisone. However, this is the prodrug and converts to prednisolone. The doses of MK-0966 used in this study are substantially higher than those targeted clinically for any indication. Hence, this increase may not have a clinically important effect on the prednisone or prednisolone pharmacokinetics when administered with MK-0966.*

Oral Contraceptives

Study P020: *A double-blind, 2-period, crossover study to investigate the effect of oral doses MK-966 175 mg on oral contraceptive pharmacokinetics in healthy female volunteers.*

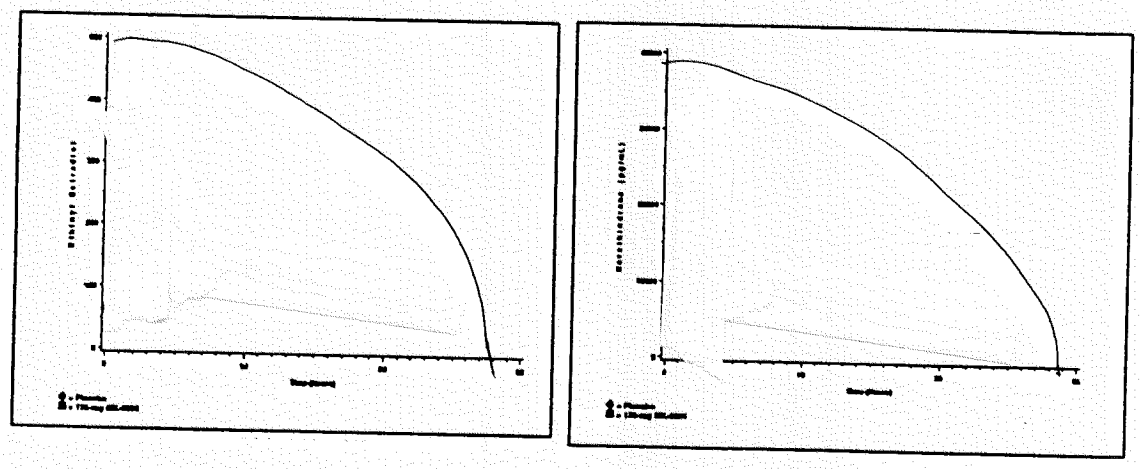
The principal components (ethinyl estradiol [EE] and norethindrone [NET]) of the oral contraceptive tablet (ORTHO-NOVUM 1/35) are partially metabolized by CYP 3A. In vitro studies in rat hepatocyes have demonstrated that CYP 3A was induced in a dose dependent manner after incubation for 48 hours with MK-0966. Hence, it was important to establish an interaction study with oral contraceptives (OC).

Women who had completed at least three cycles of a monophasic OC containing both EE and NET participated in this study. For any individual subject (total N=18), the administration of EE/NET always began on Day 1 of the menstrual cycle. During each study period, subjects received either 175 mg MK-0966 or matching placebo once daily for 14 days starting with Days 1, 2, 3, or 4 of the menstrual cycle to maintain uniformity in dosing within the menstrual cycle and to allow some flexibility in the start of dosing. MK-0966 or placebo was started on the same day of each of two successive menstrual cycles. Study Day 1 was always the first day of MK-0966/placebo in each period regardless of day of EE/NET dose. Subjects who received MK-0966 in Period I received placebo in Period II and vice versa. The area under the curve (AUC) and maximum concentration (C_{max}) for EE and NET were compared for the MK-0966 and placebo periods. For other details and assay validation see page 12-13 of Appendix II.

Results

The plasma concentrations of EE after 175 mg MK-0966 co-administered for 2 weeks with oral contraceptives (OC) were similar to the EE plasma concentrations following OC and placebo, although at all time points the MK-0966 profile showed higher levels as compared to the placebo profile (Figure a). The plasma concentrations of NET after 175 mg MK-0966 co-administered for 2 weeks with OC also showed slightly higher levels at all time points when compared to the NET plasma concentrations following OC and placebo treatment (see Figure b). This is also evident in the AUC for EE and NET given in the table below. Although there is a statistically significant difference in the AUC_{24hr} for NET And EE in the presence of MK-0966 as compared to the placebo (p-value <0.001 and 0.003, respectively), the 90% CI of the geometric mean ratios fall within the acceptable limits of 0.80 to 1.25. However, the upper boundaries of the limits are very close to 1.25.

The mean EE T_{max} values were 1.5 and 1.4 hours for the PBO/OC and MK-0966/OC treatments, respectively, and no significant difference between treatments was evident (p>0.200).



(a) Plasma profile for EE (b) Plasma profile for NET

* upper curve represents MK-0966/OC treatment in both figures.

The geometric mean ratios for the pharmacokinetic parameters for EE for MK-0966 co-administered with OC and placebo co-administered with placebo is shown in the table below.

Number of Subjects	Analyte	Pharma-cokinetic Parameter	Treatment	Geometric Mean	GMR (MK-0966 /Placebo)	(90% CI of GMR)	p-Value
18	Ethinyloestradiol (EE)	$AUC_{24\ hr}$ (pg•hr/mL)	MK-0966	3399.2	1.13	(1.06, 1.19)	0.003
			Placebo	3021.5	–	–	–
		C_{max} (pg/mL)	MK-0966	379.5	1.06	(0.98, 1.16)	0.214
			Placebo	356.4	–	–	–
		Tmax (hr)	MK-0966	1.5†		–	0.219
			Placebo	1.5†		–	–
	Norethindone (NET)	$AUC_{24\ hr}$ (pg•hr/mL)	MK-0966	216.0	1.18	(1.13, 1.24)	<0.001
			Placebo	182.5	–	–	–
		C_{max} (pg/mL)	MK-0966	29.7	1.04	(0.99, 1.09)	0.179
			Placebo	28.6	–	–	–
		T_{max} (hr)	MK-0966	1.0†		–	0.555
			Placebo	1.0†		–	–

† T_{max}=median.
‡ T_{max}=minimum, maximum values.

The contraceptive steroids are highly bound in the circulation and are susceptible to modifications in the binding due alterations in the serum hormone binding globulin and albumin. Serum hormone binding globulin and albumin for treatment Day1 and 14 did not show any significant difference for placebo/OC and MK-0966/OC treatments. The summary statistics for these are provided in the Appendix II on page 14.

Conclusions

- Based on the applicant's study design, concurrent administration of 175 mg MK-0966 once daily for 14 days with oral contraceptive (ORTHO-NOVUM™) did not alter the plasma concentration profile of the OC components EE and NET.

Reviewer's Comment

- *The trial design as such is not very robust. MK-0966 has not been administered to the subjects for the entire menstrual cycle (has been administered for only 14 days).*
- *Direct or indirect measure of the pharmacodynamic property would aid in the interpretation of MK-0966 and OC interaction study.*

Digoxin

***Study P028:** A randomized, 2-period, crossover study to investigate the effect of oral doses MK-966 75 mg on Digoxin pharmacokinetics in normal volunteers*

Digoxin is frequently prescribed in the treatment of arrhythmias and heart failure. Its therapeutic efficacy is associated with its ability to slow the ventricular rate and increase cardiac output. The consequences of decreased or increased digoxin concentrations in patients on digoxin therapy can be substantial given that digoxin has a narrow therapeutic window and the serious clinical conditions for which it is employed. Digoxin is