pre-dose baseline to 4 hours post-dose on Day 10 after concomitant administration of low-dose aspirin and MK-0966,was not significantly different from the percent inhibition in ex vivo generated serum TXB_2 at 4 hours post-dose on Day 10 observed after aspirin alone (p=0.970, Table below). The mean difference of aspirin with MK-0966 to aspirin alone was 0.02%. Thus, the expected effect of aspirin at Day 10, 4 hours, was not altered by the presence of MK-0966. Percent inhibition of TXB_2 on Day 4, pre-dose (0 hours), for the MK-0966 and placebo treatments was 6.79 and -4.94%, respectively.

Day	Time (Hours)	Treatment	N	Mean†	Between-Treatment p-Value	Mean Difference† (MK - Placebo) (%)	90% CI About Mean Difference† (%)
4	0	MK-0966 Placebo	12 12	6.79 -4.94	0.159	11.73	(-2.92, 24.39)
Pooled approximate between-subject CV is 19.9%.¶							
Day	Time (Hours)	Treatment	N	Mean†	Between-Treatment p-Value	Mean Difference† (MK + Aspirin) - Aspirin (%)	90% CI About Mean Difference† (%)
10	0	MK-0966 + aspirin‡ Aspirin	12 12	97.22 96.99	0.724	0.22	(-1.09, 1.12)
Pooled approximate between-subject CV is 52.87%.¶							
10	4	MK-0966 + aspirin‡ Aspirin	12 12	98.37 98.36	0.970	0.02	(-1.14, 0.70)
Pooled approximate between-subject CV is 73.53%.¶							

† Back-transformed from the log scale.
‡ Note that concomitant therapy with aspirin began on Day 4.
¶ Note that this coefficient of variation (CV) was calculated using the log scale Root Mean Square Error (RMSE) * 100.

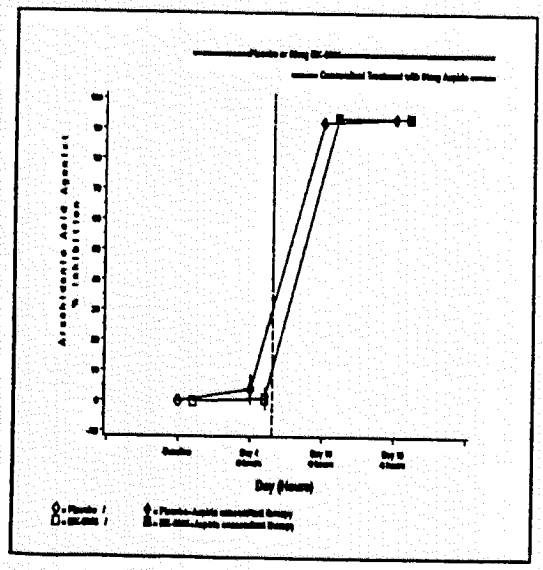
Data Source: [2.1]

Neither treatment was significantly different from zero (p 0 . 133). Therefore, MK-0966 had no effect on TXB_2.

Platelet Aggregation

1) Primary Platelet Aggregation—Arachidonic Acid

The MK-0966 treatment did not interfere with aspirin's inhibition of platelet aggregation. the percent inhibition from baseline platelet aggregation using arachidonic acid as an agonist is shown in the figure. On Day 10 predose and 4 hours postdose, both aspirin with MK-0966 or aspirin alone inhibited approximately 93% of the platelet aggregation seen at baseline. The mean difference of aspirin with MK-0966 to aspirin alone on Day 10, 4 hours was 0.19%, with 90% CIs of (-1.10%, 1.48%) (see Table below). Thus, the expected effect of aspirin on platelet aggregation at Day 10, 4 hours, was not altered by the presence of MK-0966.



Platelet aggregation in the presence of MK-0966 alone was not significantly different from placebo on Day 4, predose (0 hours) (p=0.346). Thus, as judged from this biochemical parameter, MK-0966 has no effect on the platelet aggregation for subjects using 1 mM of arachidonic acid as agonist.

Day	Time (Hours)	Treatment	N	Mean	Between-Treatment p-Value	Mean Difference (MK - Placebo) (%)	90% CI About Mean Difference (%)
4	0	MK-0966 Placebo	12 12	0.83 4.05	0.346	-3.21	(-9.21, 2.78)
Pooled between-subject SD is 8.17%.‡							
Day	Time (Hours)	Treatment	N	Mean	Between-Treatment p-Value	Mean Difference (MK + Aspirin) - Aspirin (%)	90% CI About Mean Difference (%)
10	0	MK-0966 + aspirin† Aspirin	12 12	93.78 92.13	0.138	1.66	(-0.28, 3.59)
Pooled between-subject SD is 2.64%.‡							
10	4	MK-0966 + aspirin† Aspirin	12 12	93.73 93.54	0.793	0.19	(-1.10, 1.48)
Pooled between-subject SD is 1.76%.‡							

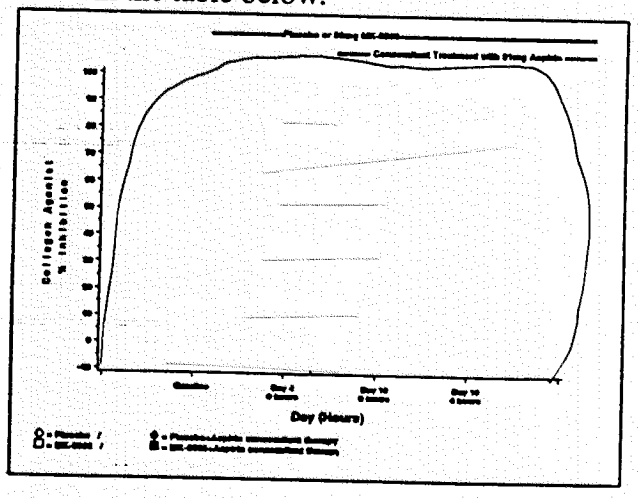
† Note that concomitant therapy with aspirin began on Day 4.
‡ Note that this is the RMSE from the ANOVA model.

Data Source: [2.2]

2) ***Secondary Platelet Aggregation—Collagen***

Within and between-group comparison results for platelet aggregation using collagen were generally consistent with those when using 1 mM of arachidonic acid as agonist. The percent inhibition of platelet aggregation using 1µg/ml of collagen as agonist is shown in the figure and the results are summarized in the table below.

The mean difference of aspirin with MK-0966 to aspirin alone on Day 10, 4 hours postdose, was -4.0%, with a 90% CI of (-9.14%, 1.14%). Thus, the expected effect of aspirin on normal platelet aggregation at Day 10, 4 hours postdose was not altered by the presence of MK-0966.



Platelet aggregation in the presence of MK-0966 alone was not significantly different from placebo on Day 4, predose (0 hours) (p=0.184). Thus, MK-0966 had no effect on TXB_2 platelet aggregation as judged using collagen as the agonist. For other details see Appendix II page 25-26.

Day	Time (Hours)	Treatment	N	Mean[†]	Between-Treatment p-Value	Mean Difference (MK - Placebo) (%)	90% CI About Mean Difference (%)
4	0	MK-0966	12	2.79	0.184	-10.87	(-25.10, 3.36)
		Placebo	12	13.66			
Pooled between-subject SD is 19.41%.[‡]							
Day	Time (Hours)	Treatment	N	Mean	Between-Treatment p-Value	Mean Difference (MK + Asp)-Asp (%)	90% CI About Mean Difference (%)
10	0	MK-0966 + aspirin[†]	12	78.31	0.854	-1.30	(-13.81, 11.21)
		Aspirin	12	79.61			
Pooled between-subject SD is 17.06.[‡]							
10	4	MK-0966 + aspirin[†]	12	86.84	0.176	-4.00	(-9.14, 1.14)
		Aspirin	12	90.84			
Pooled between-subject SD is 7.01%.[‡]							
[†] Note that concomitant therapy with aspirin began on Day 4.							
[‡] Note that this is the RMSE from the ANOVA model.							

Data Source: [2.2]

Conclusions

- Low dose aspirin (81 mg), as expected, caused significant inhibition of both ex vivo serum-generated TXB2 (>98%) and ex vivo platelet aggregation (>93%).
- MK-0966 mg once daily (3 days dosing would approximate steady state trough concentrations) has no effect on the anti-platelet effects of low dose aspirin.
- MK-0966 50 mg daily alone does not significantly inhibit ex vivo serum generated TXB_2 and platelet aggregation compared to placebo.

Overall Summary of Drug Interaction studies

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 $AUC_{(0-24)}$ increased by 40% and 20%, respectively. The renal clearance of methotrexate conversely decreased by 38% and 11%, 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-099 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.

/S/ 5/4/99

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CC: NDA 21-042
HFD-550/Div File
HFD-550/CSO/Cook
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

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NDA 21-042

APPENDIX II

(DRUG INTERACTION STUDIES)

NDA: 21-042 Volume 1.58-1.59

Study Type: Drug-Drug Interaction *Study # P011*

Study Title: A double-blind parallel study to investigate the effect of 250 mg MK-0966 on oral methotrexate (MTX) pharmacokinetics in rheumatoid arthritis patients.

Study Site	
Clinical Site	*Analytical Site*
[redacted]	[redacted]

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fasted/ Fed*	*No. of fasted hrs.*
For MTX On Day –1 & Day 10	*For MK-966 For 10 days*		*Parallel*	*Double-blind Randomized Placebo-controlled*	*Light breakfast 2 h after dose, lunch 4 hrs after*	*Overnight fast prior to Day 1 and day 10 dose.* *No restrictions for Day1-9*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X=20 (complete=15)				

Subject Type			
Males=3		*Females=17*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
34-52 yrs	*74-91*	*38-74 yrs*	*56-112*

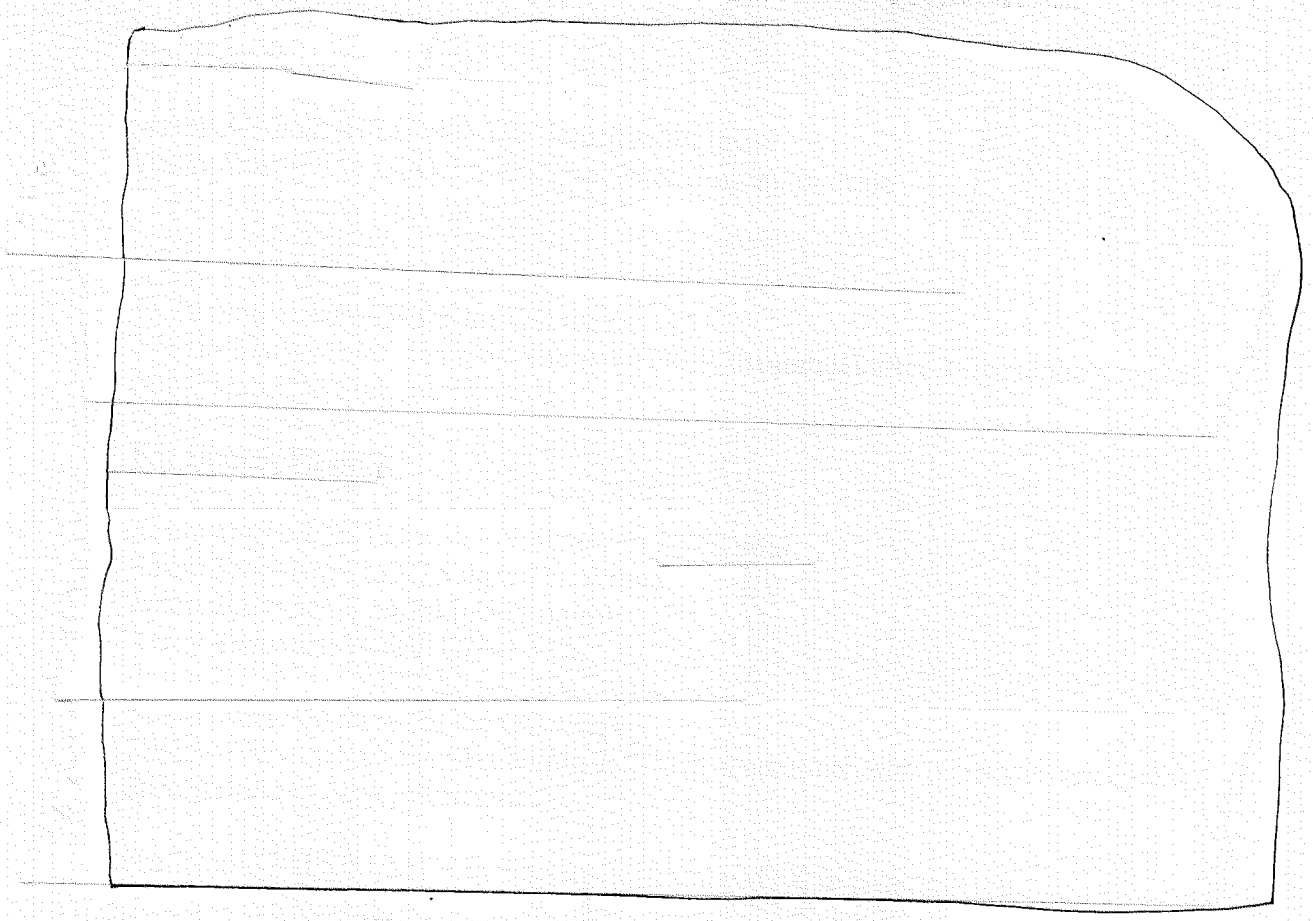
Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: MK-0966 and MTX	*12*	*1*	*11*
II: placebo and MTX	*5*	*2*	*3*

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
I	*MK-966*	*tablet*	*250 mg*	*MR-3217*
II	*placebo*	*tablet*		*MR-3238*
	MTX 7.5, 12 and 15 mg	*tablet*	*7.5,12 or 15 mg*	*397-336*

Sampling Times

Plasma: predose, 0, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24hrs postdose for MTX.
The percent unbound MTX blood samples at 1,1.5 and 2 hrs after MTX dose.
Urine: -2-0, 0-2, 2-4, 4-6, 6-12, and 12-24 hrs postdose relative to MTX dose

ASSAY VALIDATION



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NDA: 21-042 Volume 1.67-1.69

Study Type: Drug-Drug Interaction *Study # P030*

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

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fasted/ Fed*	*No. of fasted hrs.*
For MTX On Day –1 & Day 10	*For MK-966 For 10 days*		*Parallel*	*Double-blind Randomized Placebo-controlled*	*Light breakfast 2 h after dose, lunch 4 hrs after*	*Overnight fast prior to Day 1 and day 10 dose.* *No restrictions for Day1-9*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X=21 (complete=21)				

Subject Type			
Males=5		*Females=16*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
52-72 yrs		*32-69 yrs*	

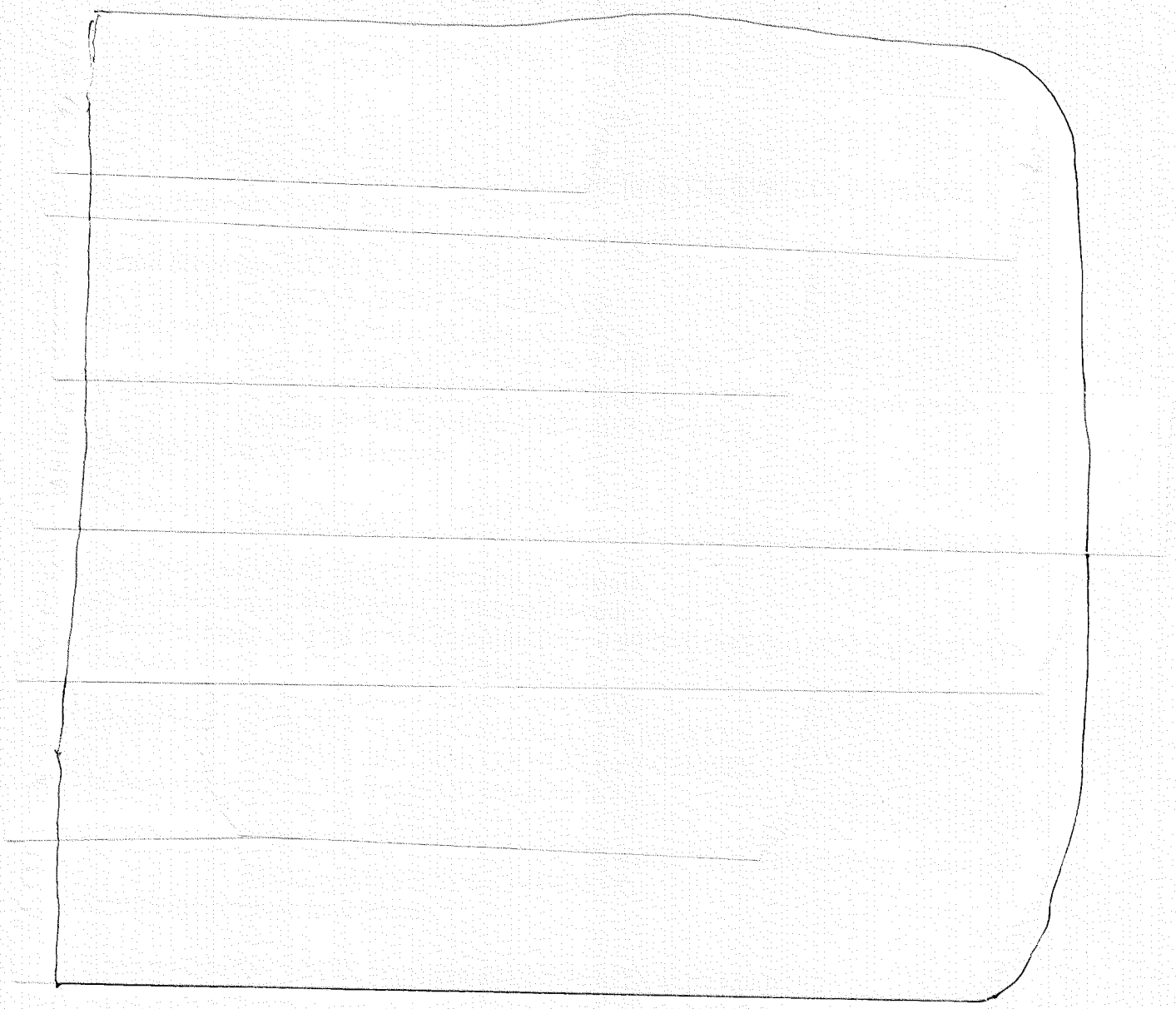
Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: MK-0966 and MTX	*16*		
II: Placebo and MTX	*5*		

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
I	*MK-966, (3x25mg)*	*tablet*	*25 mg*	*MR-3285*
II	*placebo*	*tablet*		*MR-3232*
	MTX 7.5, 12 and 15 mg	*Tablet (Lederle)* *Tablet(Roxane)*	*7.5,12 or 15 mg*	*384-350* *952-235*

Sampling Times

Plasma: predose, 0, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24hrs postdose for MTX.
The percent unbound MTX blood samples at 1,1.5 aand 2 hrs after MTX dose.
Urine: -2-0, 0-2, 2-4, 4-6, 6-12, and 12-24 hrs postdose relative to MTX dose

ASSAY VALIDATION



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NDA: 21-042

Volume 1.60-1.61

Study Type: Drug-Drug Interaction

Study # P014

Study Title: 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

Study Site	
Clinical Site	*Analytical Site*
[redacted]	[redacted]

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
Prednisolone (IV) & prednisone(oral) On Day 10 & Day 14	*For MK-966 For 14 days*	*14 days*	*2-period crossover*	*Double-blind Randomized Placebo-controlled*		*8 hrs fast on PK days* *No restrictions for Day1-9*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X=12 (complete=21)					

Subject Type			
Males=12		*Females*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
23-45	*63.96-114.53*		

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: MK-09666+I.V.on Day 10,oral on Day 14 *I: placebo+ I.V.on Day 10,oral on Day 14**	*6* *6*		
II: Placebo +oral .on Day 10, I.V. on Day 14 *II: MK-09666+oral on Day 10,I.V. on Day 14**	*6* *6*		

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
I	*MK-966,*	*tablet*	*250 mg*	*MR-3217*
II	*placebo*	*tablet*		*MR-3238*
	Prednisolone (MSDJapan) 1.5ml=30mg	*2-ml vials*	*20 mg/ml*	*J882L*
	Predisone (Upjohn) (3x10)mg	*tablet*	*10 mg*	*273KT*

** see page 6 for further details of sequences*

Sampling Times

Plasma: For IV route for evaluation of prednisolone/prednisone: 0, 10, 20, 30 mins, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, and 24 hrs.
For oral route for evaluation of prednisolone/prednisone: 0, 30 mins, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, and 24 hrs
Urine: NA

Treatment Schedule

Period	Sequence	ANs	MK-0966 or Placebo	Steroid Route	Study Day
1	A	3, 6, 9	MK-0966	I.V. Oral	10 14
	B	4, 8, 10	Placebo	I.V. Oral	10 14
	C	1, 7, 11	MK-0966	Oral I.V.	10 14
	D	2, 5, 12	Placebo	Oral I.V.	10 14

At Least 14 Days Between Periods

Period	Sequence	ANs	MK-0966 or Placebo	Steroid Route	Study Day
2	A	3, 6, 9	Placebo	I.V. Oral	10 14
	B	4, 8, 10	MK-0966	I.V. Oral	10 14
	C	1, 7, 11	Placebo	Oral I.V.	10 14
	D	2, 5, 12	MK-0966	Oral I.V.	10 14

Data Source: [3.2] and [3.6]

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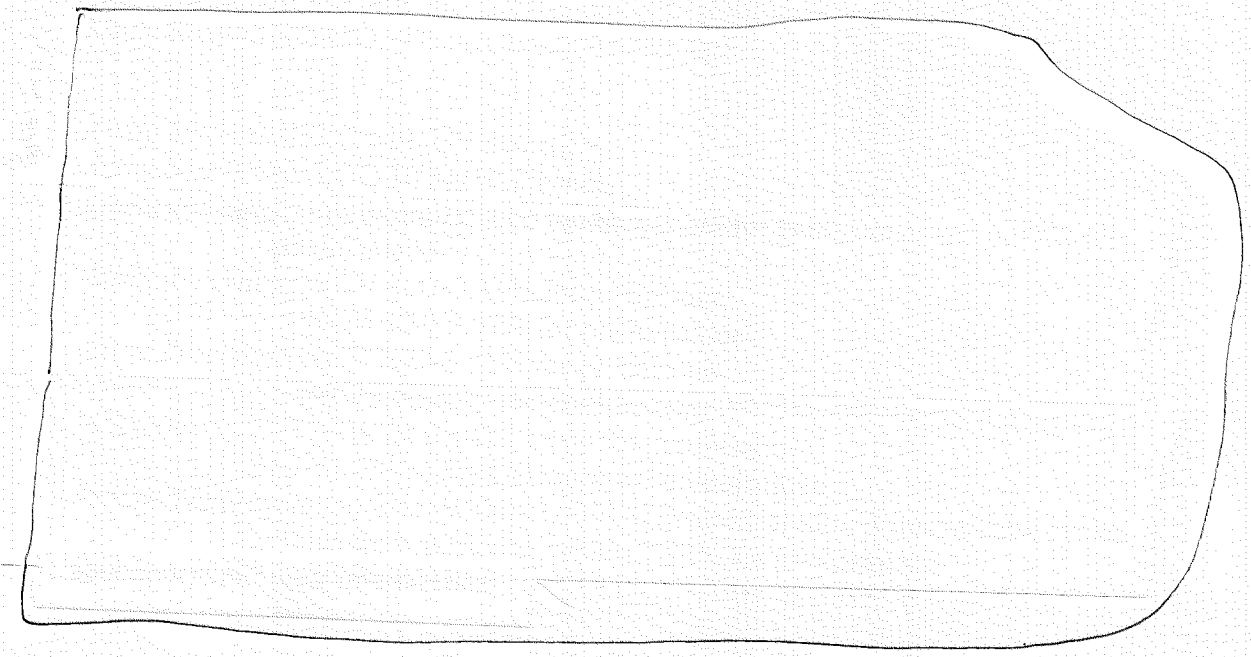

PREDNISOLONE DATA

FIGURE 1

Mean (±SD) Profile for Prednisolone Plasma Concentration Following I.V. Prednisolone

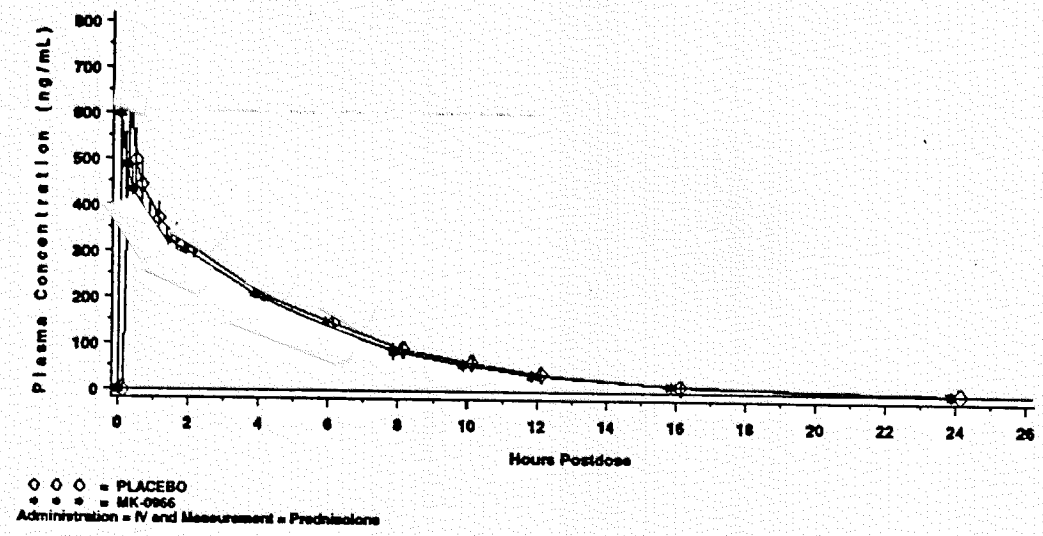

FIGURE 2

Mean (±SD) Profile for Prednisolone Plasma Concentration Following Oral Prednisone

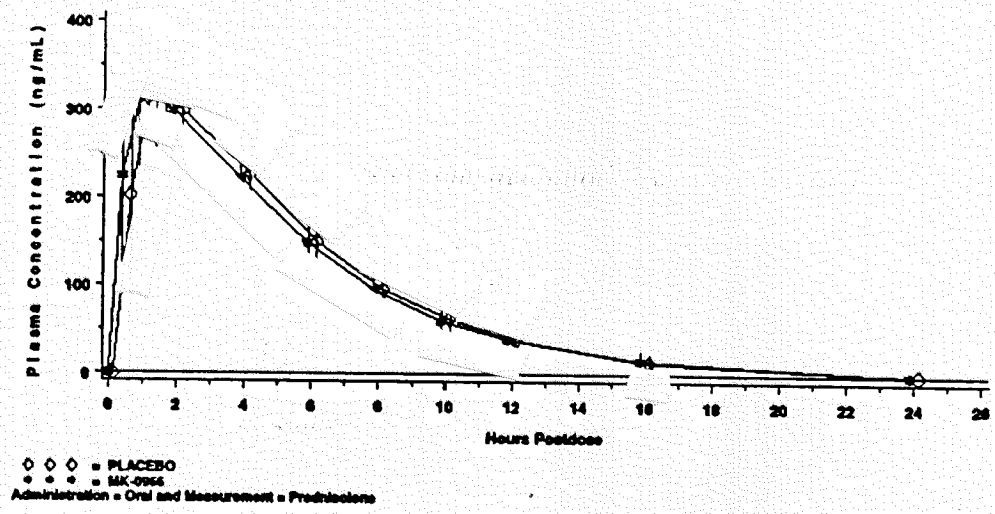

TABLE 1

Prednisolone Summary Statistics for $AUC_{(0-\infty)}$ and C_{max}

Variable/ Administration	Treatment	N	Mean†	Between-Subject CV(%)‡	Median†	Min†	Max†	p-Value
$AUC_{(0-\infty)}$ (ng•hr/mL)								
I.V.	MK-0966	12	2279.6	13.20	2328.0			0.246
	Placebo	12	2339.9	13.66	2332.4			
Oral	MK-0966	12	1971.2	19.00	1972.0			0.909
	Placebo	12	1982.1	17.90	2041.7			
C_{max} (ng/mL)								
Oral	MK-0966	12	336.8	16.18	336.0			0.842
	Placebo	12	340.7	14.66	337.3			

† Back-transformed from log scale.
‡ Between-subject SD on the log-scale x 100.

TABLE 2

Prednisolone Summary Statistics for T_{max}

Variable/ Administration	Treatment	N	Median	Min	Max	p-Value
T_{max} (hr)						
Oral	MK-0966	12	1.3			0.590
	Placebo	12	1.0			

TABLE 3

Prednisolone Summary Statistics for $t_{½}$ and Clearance

Variable/ Administration	Treatment	N	Mean†	SD‡	Median†	Min†	Max†	p-Value
$t_{½}$ (hr)								
I.V.	MK-0966	12	3.4	0.42	3.4			0.704
	Placebo	12	3.4	0.49	3.4			
Clearance (mL/min)								
I.V.	MK-0966	12	221.1	29.78	214.8			0.253
	Placebo	12	215.5	29.13	214.6			

† For $t_{½}$, back-transformed to the original scale from the inverse transformation.
‡ For $t_{½}$, SD is computed by using jackknife method.

PREDNISONE

FIGURE 3

Mean (±SD) Profile for Prednisone Plasma Concentration Following I.V. Prednisolone

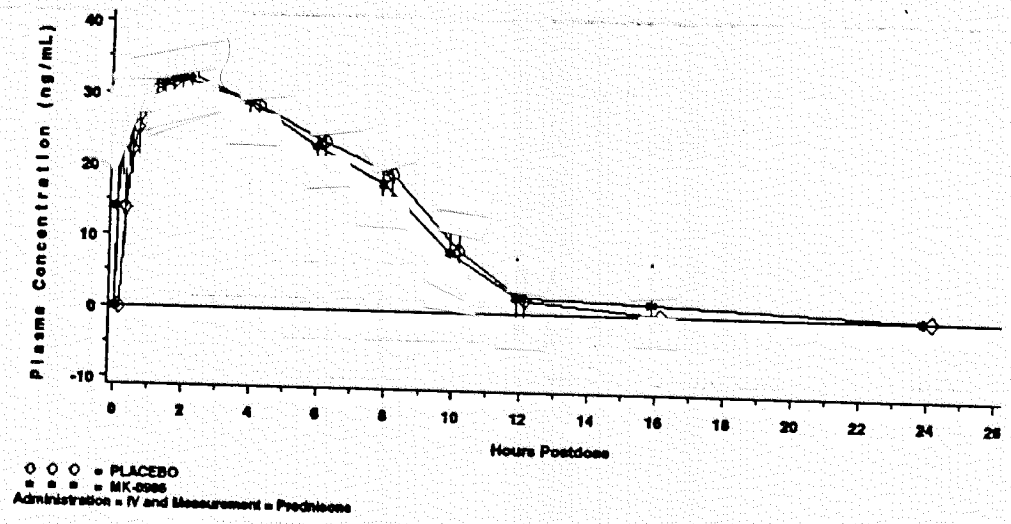

FIGURE 4

Mean (±SD) Profile for Prednisone Plasma Concentration Following Oral Prednisone

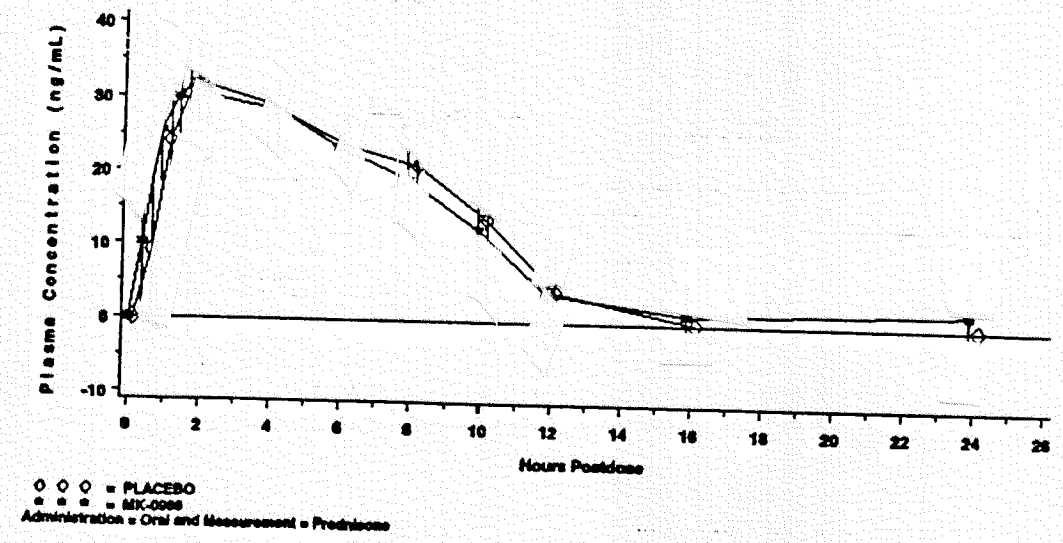

TABLE 4

Prednisone Summary Statistics for AUC and C_{max}

Variable/ Administration	Treatment	N	Mean†	Between-Subject CV(%)‡	Median†	Min†	Max†	p-Value
$AUC_{(0-\infty)}$ (ng•hr/mL)								
I.V.	MK-0966	12	310.9	16.91	304.5			0.531
	Placebo	12	302.8	14.97	296.0			.
Oral	MK-0966	12	322.1	24.77	296.0			0.407
	Placebo	12	297.8	21.20	319.4			.
C_{max} (ng/mL)								
Oral	MK-0966	12	33.2	9.48	33.8			0.987
	Placebo	12	33.2	13.85	32.1			.

† Back-transformed from log scale.
‡ Between-subject SD on the log-scale x 100.

Data Source: [2.1]

TABLE 5

Prednisone Summary Statistics for T_{max}

Variable/ Administration	Treatment	N	Median	Min	Max	p-Value
T_{max} (hr)						
Oral	MK-0966	12	2.0			0.590
	Placebo	12	2.0			.

Data Source: [2.1]