TRANSCORTIN AND ALBUMIN

TABLE 6

Summary Statistics for Plasma Transcortin Assay Results (mg/dL)

Treatment	N	Mean	SD	Median	Min	Max
Day 1						
MK-0966	12	2.35	0.20	2.35		
Placebo	12	2.45	0.20	2.50		
Day 10						
MK-0966	12	2.29	0.28	2.20		
Placebo	12	2.36	0.25	2.35		
Day 14						
MK-0966	12	2.30	0.33	2.20		
Placebo	12	2.35	0.28	2.30		
Root MSE = 0.159.						

Data Source: [2.1]

TABLE 7

Summary Statistics for Serum Albumin Assay Results (mg/dL)

Treatment	N	Mean	SD	Median	Min	Max
Day 1						
MK-0966	12	4.48	0.28	4.45		
Placebo	12	4.72	0.19	4.70		
Day 10						
MK-0966	12	4.38	0.19	4.40		
Placebo	12	4.48	0.16	4.50		
Day 14						
MK-0966	12	4.34	0.15	4.40		
Placebo	12	4.43	0.25	4.40		
Root MSE = 0.158.						

Data Source: [2.1]

NDA: 21-042 Volume 1.62-.64

Study Type: Drug-Drug Interaction *Study # P020*

Study Title: 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

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
	OC starting Day1of MC *For MK-966 or Placebo For 14 days*	*10 days*	*2-period crossover*	*Double-blind Randomized Placebo-controlled*	*Snack, lunch 2 & 4 hrs after dose*	*OC dose fasted*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X=18 (complete=18)					

Subject Type			
Males		*Females=18*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
		23-45	*50.35-74.39*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I:OC & MK-0966/II: OC &placebo	*18*		*18*
I:OC& placebo/ II: OC & MK-0966	*18*		*18*

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
I	*MK-966,*	*tablet*	*125 mg* *50 mg*	*MR-3215* *MR-3278*
	placebo	*tablet*	*For 125 mg* *For 50 mg*	*MR-3233* *MR-3283*
II	*ORTHO-NOVUM 1/35 35µg/ml EE, 0.1 mg NET*	*tablet*		*25J514*

Sampling Times

Plasma: EE/NET serum assay: 0, 1, 1.5,2, 3, 4, 6, 8, 10, 12, 16, and 24 hrs post dose (i.e. Day 14) MK-0966 plasma assay: predose on days1, 7 through 15.

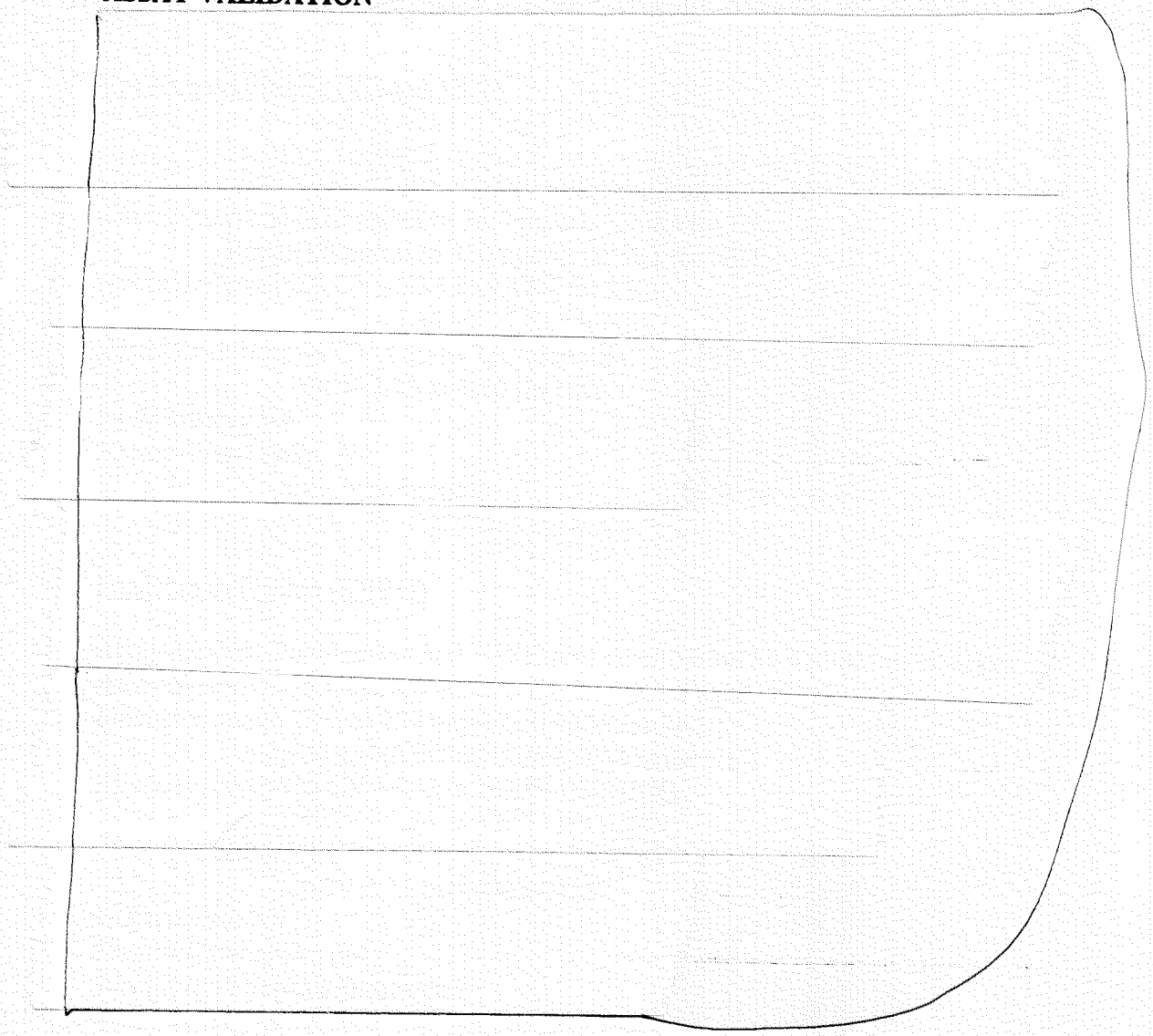
Urine: NA

Allocation Schedule

AN	Period	
	I	II
002, 004, 006, 008, 010, 012, 013, 015, 018	ORTHO-NOVUM™ 1/35 plus MK-0966 175 mg daily	ORTHO-NOVUM™ 1/35 plus matching placebo for MK-0966 daily
001, 003, 103, 005, 105, 007, 009, 011, 014, 016, 017, 117	ORTHO-NOVUM™ 1/35 plus matching placebo for MK-0966 daily	ORTHO-NOVUM™ 1/35 plus MK-0966 175 mg daily

Data Source: [3.6]

ASSAY VALIDATION



Summary Statistics for Sex Hormone Binding Globulin (nmol/L)

Parameter	N	Geometric Mean	Median	Min, Max	Approximate Between-Subject CV (%)[1]	Within-Subject CV	Treatment p-Value
Day 1							
175 mg MK-0966	18	88.7	97.2		38.4	12.4	0.427
Placebo	18	85.7	93.8		33.7		
Day 14							
175 mg MK-0966	18	111.2	118.5		37.5	7.4	0.188
Placebo	18	107.5	113.5		36.7		

[1] RMSE x 100.

Data Source: [2.1]

Summary Statistics for Albumin for Each Treatment by Day (g/dL)

Treatment	Day	N	Mean	Min	Max	Between-Subject STD
MK-0966 175 mg	1	18	4.23			0.23
	14	18	4.23			0.24
Placebo	1	18	4.35			0.15
	14	18	4.27			0.30

Data Source: [2.1]

NDA: 21-042 Volume 1.66-.67

Study Type: Drug-Drug Interaction *Study # P028*

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

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
Digoxin on Day 7	*For MK-966 or Placebo For 11 days*	*14-21 days*	*2-period crossover*	*Double-blind Randomized Placebo-controlled*	*Snack, lunch 3 hrs after dose*	*Digoxin in fasted state*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X=10 (complete=10)					

Subject Type			
Males (N=6)		*Female (N=4)*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
24-44	*76-89*	*33-45*	*58-76*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: Dig & MK-0966/II: Dig &placebo	*5*	*3*	*2*
I: Dig &placebo/ II: Dig & MK-0966	*5*	*3*	*2*

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
I	*MK-966 (3x25 mg)*	*tablet*	*25 mg*	*MR-3285*
	placebo	*tablet*	*For 25 mg*	*MR-3232*
II	*Lanoxim™ (10 mL)*	*Elixir*	*0.05 mg/mL*	*BC-0464A*

Sampling Times

Plasma: Digoxin plasma assay: 0, 30 mins 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 hrs post dose (i.e. starting Day 7and ending day 12). Additional on Day 6, predose of MK-096 and 4 hrs post dose on Day 6.

Urine: For Digoxin and creatinine assay: -1 to 0 hr, 0-6 hr, 6-12 hr, 12-24 hr, 24-36 hr, 36-48 hr, 48-72 hr, 72-96 hr, 96-120 hr (i.e. starting Day 7and ending day 12). Additional sample on Day 6 at 0-6 hrs post MK-0966 post dose to test for interference for MK-0966/metabolites

ASSAY VALIDATION

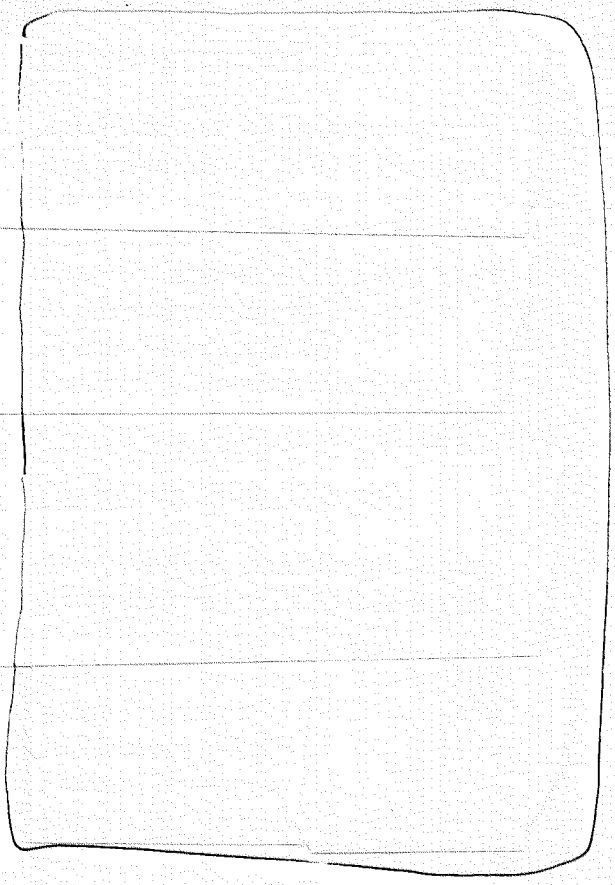


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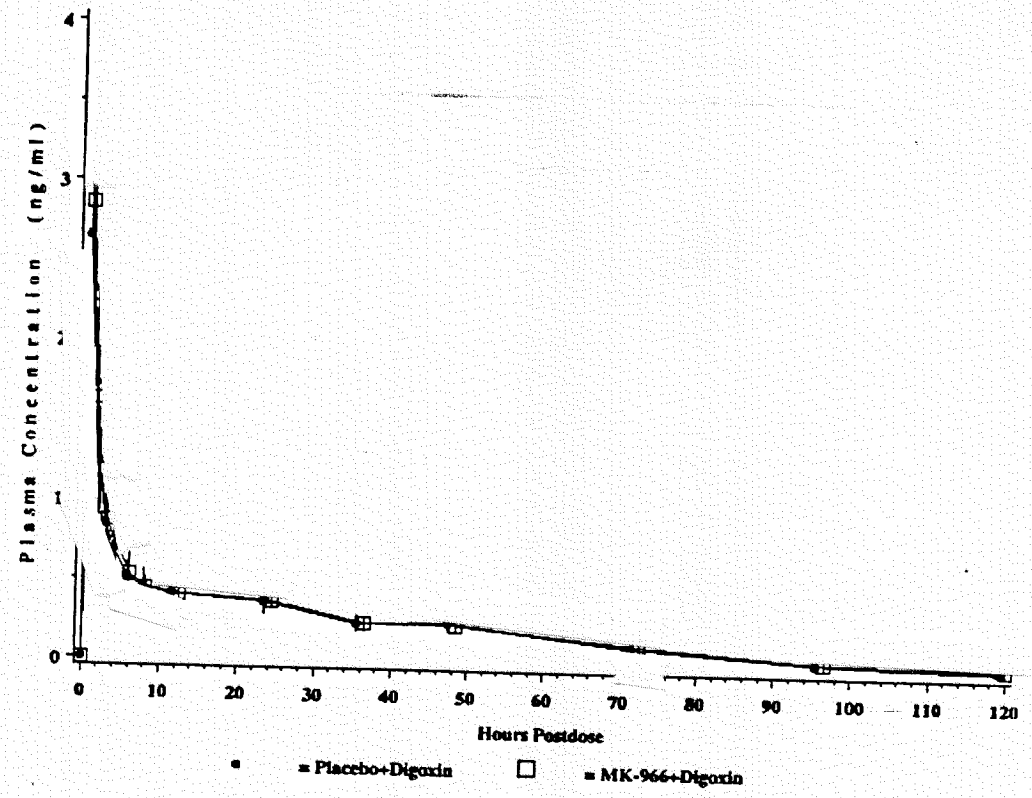
Figure 1:

Plasma Concentrations of Immunoreactive Digoxin Following a Single Dose of Digoxin When Administered With MK-0966 and Placebo
Mean (± SD) (N=10)



NDA: 21-042 Volume 1.71-1.72

Study Type: Drug-Drug Interaction *Study # P039*

Study Title: 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

Study Site	
Clinical Site	*Analytical Site*
Dr. C. Kleinbloesem	*Merck West Point, PA*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
For MK-966 on Day 5	*Cimetidine for 9 days*	*12-14 days*	*2-period crossover (I and II)*	*Open Randomized*	*Snack, lunch 3 hrs after dose*	*8 hrs predose on sampling days*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X=8 (complete=8)					

Subject Type			
Males (N=8)		*Female*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
21-35	*66.8-78.50*		

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: Cimetidine & MK-0966/II: MK-0966 alone	*4*	*4*	
I: MK-0966 alone / II: Cimetidine & MK-0966	*4*	*4*	

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
	MK-966 (3x25 mg)	*tablet*	*25 mg*	*MR-3359*
	Cimetidine (800 mg b.i.d)	*tablet*	*400mg*	*200*

Sampling Times

Plasma: MK-0966 plasma assay: 0, 30 mins 1, 1.5, 2, 3, 4,5, 6, 7.5, 12, 16, 18, 20, 22, 23 24, 25, 26, 30, 33, 36, 39, 46, 48, 49, 50, 55, 60, 72, 96 and 120 hrs post dose (i.e. starting Day 5)

Urine: NA

Assay Validation

NDA: 21-042

Volume 1.78-1.79

Study Type: Drug-Drug Interaction

Study # P053

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

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
Warfarin on Day 7	*For MK-966 & placebo from Day 1-12*	*7-10 days*	*2-period crossover (I and II)*	*Double-blind Randomized*	*Juice 2 hrs after dose. Lunch 4 hrs post dose. No grapefruit*	*4 hr predose Days 1, 6, 13 of periods I & II post study evaluation. Overnight Day 7*

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

Subject Type			
Males (N=12)		*Female*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
22-41	*70-90*		

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: Warfarin & MK-0966 /II: Warfarin & placebo	*6*	*6*	
I: warfarin & placebo / II: Warfarin & MK-0966	*6*	*6*	

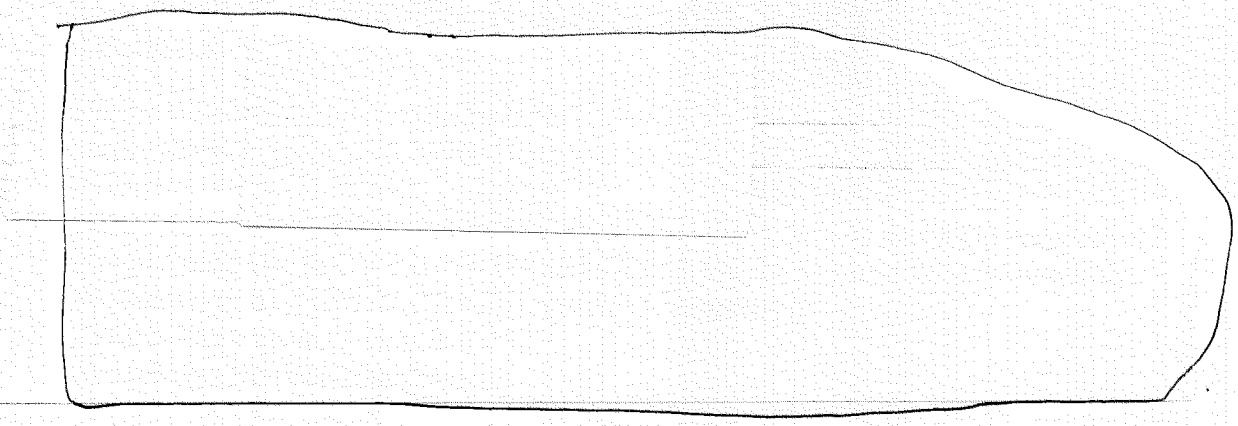
Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
	MK-966 (2x25 mg) placebo	*Tablet tablet*	*25 mg 25 mg*	*MR-3359 MR-3350*
	Warfarin (COUMADIN) (3x10 mg)	*tablet*	*10 mg*	*200*

Sampling Times

Plasma: Warfarin plasma assay: 0, 1, 2, 4,8, 12, 24, 48, 56, 72, 80, 96, 120 and 144 hrs post dose (i.e. starting Day 7)

Urine: NA

ASSAY VALIDATION



NDA: 21-042

Volume 1.87

Study Type: Drug-Drug Interaction

Study # P075

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

Study Site	
Clinical Site	Analytical Site

Single Dose	Multiple dose	Washout Period	Parallel/ crossover	Other Design	Fast/ Fed	No. of fasted hrs.
	For MK-966 & placebo for 21 Days Warfarin for 21 days too		2-period crossover (I and II)	Double-blind Randomized	Juice 2 hrs after dose. Lunch 4 hrs post dose. No grapefruit	4 hr predose Days 1, 6, 13 of periods I & II post study evaluation. Overnight fast Days 21, 22

Subject Category					
Normal	Patients	Young	Elderly	Renal	Hepatic
X=17 (complete=15)					

Subject Type			
Males (N=15)		Female (N=2)	
Age(yr)	Weight(lbs)	Age(yrs)	Weight(lbs)
22-40	136-205	32-42	134-176

Subject Treatment Group			
Group No.	Total No.	Males	Females
I: Warfarin & MK-0966 /II: Warfarin & placebo	9		
I: warfarin & placebo / II: Warfarin & MK-0966	8		

Treatment Group	Dose	Dosage Form	Strength	Lot #
	MK-966 (2x25 mg) placebo	Tablet tablet	25 mg 25 mg	MR-3359 MR-3351
	Warfarin (COUMADIN)	tablet	1 mg 2 mg 2.5 mg	KK357 A LA 034 A KJ 287 A

Sampling Times

Plasma: Warfarin plasma assay: 0, 1, 2, 4,6, 8, 10,12, 14,24 hrs post dose (i.e. Day 21)

Prothrombin time for INR: predose, 4, 8, 12, 16, and 24 hrs post warfarin and MK-0966.placebo dose.

NDA: 21-042 Volume 1.77-1.78

Study Type: Drug-Drug Interaction *Study # P052*

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

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
• *MK-966* • *Liquid magnesium* • *Al hydroxide*		*14 days*	*Balanced crossover*		*Water 2 hrs post dose, on PK days 8 ounce of apple juice*	*Tablets after Overnight fast with 120 ml water, followed by antacid with 120 ml water*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
			X=13 Completed =12		

Subject Type			
Males (N=8)		*Female (N=5)*	
Age(yr)	*Weight(lb)*	*Age(yrs)*	*Weight(lb)*
66-81	*128-228*	*72-78*	*122-150*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
MT-0966 25 mg (tablet)	*12*		
MK-966+Mg Al hydroxide	*12*		
MK-966+ Calcium carbonate	*12*		
MK-0966 1 mg I.V.	*12*		

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
	MK-966 25 mg *MK-966 1mg I.V.*	*Tablet* *Solution.*	*25 mg* *1 mg*	*WP-C711* *HSS001A006*
	Calcium carbonate(Roxane labs, Inc) 10 ml	*suspension*	*25 mEq/5ml*	*NDC 0054-3117-63*
	Maalox (Ciba self mediacation) 20 ml	*suspension*	*26.6 mEq/10 ml*	*NDC 0067-0330-71*

Sampling Times

Plasma: For oral: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 12, 16, 18, 21, 24, 26, 30, 33, 36, 39, 42, 48, 55, 60, 72, 96, and 120 hrs postdose

For I.V. predose, end of infusion, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 12, 16, 18, 21, 24, 26, 30, 33, 36, 39, 42 and 48b hrs following end of infusion

Urine: NA

NDA: 21-042 Volume 1.79-1.80

Study Type: Drug-Drug Interaction *Study # P054*

Study Title: 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.

Study Site	
Clinical Site	*Analytical Site*
6 U.S. Sites	

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
	For MK-966 Placebo, indomethacin Benezapril 12 weeks	*1 week*	*3-period crossover (I,II and III)*	*Double-blind Randomized*		*4 hr prior to lab safety*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X=41 (complete=36) Hypertensive				

Subject Type			
Males (N=27)		*Female (N=14)*	
Age(yr)	*Weight(lbs)*	*Age(yrs)*	*Weight(lbs)*
29-64	*154-276*	*44-65*	*117-242*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: MK-0966 II: Indo III: placebo	*14*		
I: Indo II:placebo III: MK-0966	*14*		
I: placebo II: MK-0966 III: Indo	*14*		
I MK-0966 II:placebo III: Indo	*14*		
I: Indo II: MK-0966 III: placebo	*14*		
I: Placebo II:Indo III: MK-0966	*14*		

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
	MK-966 (25 mg) *Placebo*	*Tablet* *tablet*	*25 mg* *25 mg*	*MR-3359* *MR-3351*
	Indomethacin (INDOCIN SR) *Placebo (75 mg)*	*Capsule* *capsule*	*75 mg* *75 mg*	*MR-3508* *MR-3519*
	Benzapril (LOTENSIN) (10 –40 mg)	*tablet*	*10 mg*	*2T196123* *2B013268*

Sampling Times

Blood pressure: Ambulatory blood pressure measured over 24 hrs,means evaluated 5 times (end of benzapril baseline and end of each 4 week treatment period.

TABLE 1

Summary of Serum Electrolytes

Treatment	Day	N	Mean	SE	Min	Median	Max
Calcium (mg/dL)							
Baseline	BL 1	39	9.38	0.06		9.40	
	BL 3	41	9.33	0.06		9.40	
MK-0966	Day 1	23	9.41	0.10		9.40	
	Day 28	36	9.34	0.06		9.35	
Indocin	Day 1	23	9.45	0.07		9.40	
	Day 28	37	9.37	0.07		9.40	
Placebo	Day 1	26	9.40	0.07		9.45	
	Day 28	38	9.48	0.08		9.50	
Potassium (mEq/L)							
Baseline	BL 1	39	4.20	0.06		4.10	
	BL 3	41	4.27	0.07		4.30	
MK-0966	Day 1	23	4.34	0.10		4.30	
	Day 28	36	4.35	0.09		4.35	
Indocin	Day 1	23	4.37	0.09		4.30	
	Day 28	37	4.32	0.06		4.20	
Placebo	Day 1	26	4.37	0.06		4.35	
	Day 28	38	4.42	0.08		4.40	
Sodium (mEq/L)							
Baseline	BL 1	39	141.1	0.37		141.0	
	BL 3	41	141.0	0.43		141.0	
MK-0966	Day 1	23	140.4	0.58		140.0	
	Day 28	36	139.8	0.44		140.0	
Indocin	Day 1	23	140.7	0.42		140.0	
	Day 28	37	140.0	0.40		140.0	
Placebo	Day 1	26	140.0	0.39		140.0	
	Day 28	38	141.2	0.58		141.0	

NDA: 21-042 Volume 1.82-1.83

Study Type: Drug-Drug Interaction *Study # P063*

Study Title: 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

Study Site	
Clinical Site	*Analytical Site*

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fast/ Fed*	*No. of fasted hrs.*
	MK-966 Placebo, For 10 days Aspirin Day4-10		*parallel*	*Double-blind Randomized*		*No restrictions*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X=24 (complete=(24)					

Subject Type			
Males (N=12)		*Female (N=12)*	
Age(yr)	*Weight(kg)*	*Age(yrs)*	*Weight(kg)*
18-38	*51.8-96.8*	*22-36*	*45.2-103.7*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
Mk-0966	*12*	*7*	*5*
Placebo	*12*	*5*	*7*

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
	MK-966 (10x50 mg)	*Tablet*	*50 mg*	*MR-3370*
	Placebo (10x50 mg)	*tablet*	*50 mg*	*MR-3362*
	Aspirin (7x81 mg)	*tablet*	*81 mg*	

Sampling Times

Plasma: blood samples for TXB2 and platelet aggregation were collected within 72 hours prior to dosing, on Day 1(prior to initiation of MK-0966 or placebo therapy,
On Day 4 (prior to initiation of aspirin therapy)
On Day 10 as a measure of anti-platelet effects (predose and 4 hrs post dose)
Urine: NA