Table XXII

Areas Under the Plasma Concentration *vs.* Time (AUC) Observed Following Administration of Single Oral Doses to Healthy Subjects, μg·h/mL

Allocation Number	10 mg	50 mg	125 mg	250 mg	125 mg Old Formulation
Men:					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
Mean	1.65	11.2	27.7	53.0	25.2
Std. Dev.	0.45	3.8	10.0	17.7	8.9
Women:					
11					
12					
13					
14					
15					
16					
17					
18					
Mean	1.82	11.3	26.9	51.5	—
Std. Dev.	0.25	1.4	4.2	5.4	—

14 pages
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Clinical Pharmacology/Biopharmaceutics Study Summary Sheet

NDA/IND#	SUPPL/AMEND. #	SUBMISSION DATE:	VOLUME:
21042		23 Nov. 98	
Study Type:	Pharmacokinetics/ metabolism	Study 046	
Study Title:	A 2-Period, Double-Blind, Placebo-Controlled, Crossover Study to Investigate the Effect of MK-0966 on the [^{14}C *N*-Methyl] Erythromycin Breath Test (EBT) in Healthy Volunteers		

CLINICAL INVESTIGATOR(s)	SITE(s)	ANALYTICAL INVESTIGATOR	SITE

SINGLE DOSE:	X	MULTIPLE DOSE:	NA	WASHOUT PERIOD:	4 weeks
CROSS-OVER	X	PARALLEL	NA	OTHER DESIGN:	NA

FASTED	X	FOOD STUDY		FDA HIGH FAT BREAKFAST	NA
If fasted, how long (hrs.)?	NA	NA		NA	NA

SUBJECT BREAKDOWN											
Normal	X	Patients	NA	Young	X	Elderly	NA	Renal	NA	Hepatic	NA

	SUBJECT TYPE						GROUP						
Weight	Mean	77.5 Kg	M	Range	57.7	99.6	Group	N=	12	M=	12	F=	NA
Age	Mean	27.9 Yr	M	Range	20	41	Group	N=	NA	M=	12	F=	NA
								N=	NA	M=	12	F=	NA
	SUBJECT TYPE												
Weight	Mean	NA	F	Range	NA	NA	GROUP	N=	NA	M=	NA	F=	NA
Age	Mean	NA	F	Range	NA	NA	Group	N=	NA	M=	NA	F=	NA
								N=	NA	M=	NA	F=	NA

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
MK-0966 25 mg	75	Tablet	25 mg	MR-3359	NA
Placebo MK-0966 25 mg	NA	Tablet	NA	MR-3350	NA

SAMPLING TIMES	
CO_2	On Days -1 and 14, samples of exhaled CO_2 were collected prior to and 20 minutes following the administration of [^{14}C *N*-methyl] erythromycin. Tests were performed at approximately (±1 hour) the same time of day.
Plasma	NA
Urine	NA
Feces	NA

ASSAY METHOD:	
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Pharmacokinetics/metabolism

NDA: 21-042 Volume 1.76-1.77

Study Type: PK/PD Study *Study # P051*

Study Title: A Randomized, Placebo and Active Comparator-Controlled Dose-Ranging Trial of the Effect of a [redacted] Formulation of MK–0966 in the Treatment of Postoperative Dental Pain.

Study Site	
Clinical Site	*Analytical Site*
[redacted]	

Single Dose	*Multiple dose*	*Washout Period*	*Parallel/ crossover*	*Other Design*	*Fasted/ Fed*	*No. of fasted hrs.*
For MK-0966 12.5, 25 and 25 mg Naproxen sodium 500mg			*Parallel*	*Double-blind Randomized Placebo-controlled Active-comparator*	*Fasted*	*Overnight fast prior to surgery, and 2 hours fast following dosing*

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X				

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
I: MK-0966			
12.5 mg	*72*	*27*	*45*
25 mg	*72*	*27*	*45*
50 mg	*72*	*25*	*47*
II: placebo	*48*	*24*	*24*
II: Naproxen	*49*	*18*	*31*
Total	*313*	*121*	*192*

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot*
I	*MK-0966*	*Tablet*	*12.5 mg*	*MR-3358*
II	*MK-0966*	*Tablet*	*25 mg*	*MR-3359*
III	*MK-0966*	*Tablet*	*50 mg*	*MR-3370*
IV	*Placebo W*	*Tablet*		*MR-3349*
	Placebo X	*Tablet*		*MR-3351*
	Placebo Y	*Tablet*		*MR-3362*
V	*Naproxen*	*Tablet*	*500 mg*	*MR-3340*

Sampling Times

Plasma: postsurgery screening, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 hrs postdose for MK-0966.

Pain Intensity rating: postsurgery screening, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24 hrs postdose.

MK-0966 (Protocol #051-00; D.M. #1340)

6

Table 3

Individual Plasma Concentrations (ng/mL) of Selected Subjects Receiving 12.5, 50, or 100 mg Oral Doses of MK-0966 (Notebook 15891, pages 323-333)

I. 12.5 mg

	Allocation Number									
Hour Postdose	6004	6011	6015	6042	6313	6318	6323	6008	6016	6020
0										
0.5										
1										
1.5										
2										
3										
4										
5										
6										
7										
8										

II. 25 mg

	Allocation Number									
Hour Postdose	6001	6002	6007	6022	6026	6032	6316	6017	6320	6325
0										
0.5										
1										
1.5										
2										
3										
4										
5										
6										
7										
8										

nq = non-quantifiable

MK-0966 (Protocol #051-00; D.M. #1340) 7

Table 3
(Continued)

III. 50 mg

Hour Postdose	Allocation Number									
	6003	6005	6010	6024	6025	6312	6023	6314	6315	6317
0										
0.5										
1										
1.5										
2										
3										
4										
5										
6										
7										
8										
Rescue Sample										

nq = non-quantifiable
NA = sample not available

Clinical Pharmacology/Biopharmaceutics Study Summary Sheet

NDA/IND#	SUPPL/AMEND. #	SUBMISSION DATE:	VOLUME:
21042		23 Nov. 98	
Study Type:	Drug Interaction	Study 073	
Study Title:	A Partially Open-Label, 3-Part, Randomized, Crossover Study to Investigate the Influence of Altered CYP3A Activity on MK-0966 Pharmacokinetics and of MK-0966 on CYP3A Activity in Healthy Subjects		

CLINICAL INVESTIGATOR	SITE	ANALYTICAL INVESTIGATOR	SITE
Dr. T. Marbury		Merck	West Point, PA
Dr. S. Zeig			

SINGLE DOSE:	X	MULTIPLE DOSE:	NA	WASHOUT PERIOD:	21 Days
CROSS-OVER	X	PARALLEL	NA	OTHER DESIGN:	NA

FASTED	X	FOOD STUDY		FDA HIGH FAT BREAKFAST	
If fasted, how long (hrs.)?	8 hrs prior to Labs	Part I fasting Part II fed		NA	

SUBJECT BREAKDOWN											
Normal	X	Patients	NA	Young	X	Elderly	NA	Renal	NA	Hepatic	NA

Part I

	SUBJECT TYPE						GROUP		N=	8	M=	4	F=	4
Weight	Mean	157.8 lbs	M	Range	150	168	Group		N=	NA	M=	4	F=	NA
Age	Mean	34 Yr	M	Range	29	39	Group		N=	NA	M=	4	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	4
Weight	Mean	129.8 lbs	F	Range	117	150	Group		N=	NA	M=	NA	F=	4
Age	Mean	28 Yr	F	Range	24	32	Group		N=	NA	M=	NA	F=	4

Part II

	SUBJECT TYPE						GROUP		N=	8	M=	3	F=	5
Weight	Mean	159 lbs	M	Range	150	169	Group		N=	NA	M=	3	F=	NA
Age	Mean	27 Yr	M	Range	21	33	Group		N=	NA	M=	3	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	5
Weight	Mean	137.5 lbs	F	Range	122	155	Group		N=	NA	M=	NA	F=	5
Age	Mean	35 Yr	F	Range	19	41	Group		N=	NA	M=	NA	F=	5

Part III

	SUBJECT TYPE						GROUP		N=	9	M=	8	F=	1
Weight	Mean	191 lbs	M	Range	174	221	Group		N=	NA	M=	8	F=	NA
Age	Mean	33 Yr	M	Range	24	43	Group		N=	NA	M=	8	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	1
Weight	Mean	115 lbs	F	Range	115	115	Group		N=	NA	M=	NA	F=	1
Age	Mean	41Yr	F	Range	41	41	Group		N=	NA	M=	NA	F=	1

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
MK-0966 25 mg	25	Tablet	25 mg	MR-3359	NA
Placebo MK-0966 25 mg	NA	Tablet	NA	MR-3351	NA
Ketoconazole 200 mg	200	Tablet	200 mg	96L638E, 97P0049E	NA
Rifampin	300	Capsule	300 mg	73003975	NA
Midazolam 1 mg	1	I. V. solution		6992	NA

SAMPLING TIMES	
Plasma	Part I: Blood samples for plasma midazolam concentrations were collected predose on Day 1 and at the following time points on Day 11: 0, 0.17, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 32 hours postdose. Part II: Blood samples for plasma MK-0966 concentrations were collected predose on Days 1 through 12 and at the following time points on Day 11: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 12, 15, 18, 21, and 24 hours postdose.
Urine	Amounts of 1-hydroxy-midazolam (1-OH-midazolam, mg) recovered in the urine of subjects administered a single dose of 2 mg midazolam on Day 11 of a 12-day course of placebo or MK-0966, were determined based on urine collected across the time intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 32 hours postdose.
Feces	NA

ASSAY METHOD:	[redacted]
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Drug Interaction

Table XV

Pharmacokinetic Parameters of Midazolam Observed Following Administration of Single 2-mg Oral Doses to Subjects Receiving a Twelve-Day Course of 25-mg MK-0966 or Placebo

A.N.	Placebo				MK-0966			
	AUC (ng•hr/mL)	C_{max} (ng/mL)	T_{max} hr	$t_{½}$ hr	AUC (ng•hr/mL)	C_{max} (ng/mL)	T_{max} hr	$t_{½}$ hr
1								
2								
3								
4								
5								
6								
7								
8								
Mean	31.0	13.70	0.85	1.34	22.0	9.12	1.01	1.25
SD	17.3	7.41	0.23	—	12.7	3.04	0.46	—

Revised 5/13/98

Table XVI

Pharmacokinetic Parameters of MK-0966 at Steady State Observed Following Administration of a Twelve-Day Course of Daily Doses of 25-mg MK-0966 and 400-mg Ketoconazole or 25-mg MK-0966 and Placebo

A.N.	Placebo			Ketoconazole		
	AUC_{24h} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} hr	AUC_{24h} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} hr
9						
10						
11						
12						
13						
14						
15						
16						
Mean	6715	550	2.4	7034	481	3.1
SD	1986	118	1.2	1912	111	1.7

n.a. = Parameters not estimated because subject discontinued from study.

Table XVII

Pharmacokinetic Parameters of MK-0966 at Steady State Observed Following Administration of a Twelve-Day Course of Daily Doses of 25-mg-MK-0966 and 600-mg Rifampin or 25-mg MK-0966 and Placebo

A.N.	Placebo			Rifampin		
	AUC_{24h} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} hr	AUC_{24h} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} hr
109						
18						
19						
20						
21						
22						
23						
24						
Mean	4380	328	2.6	2182	231	2.4
SD	953	138	1.5	538	73	1.1

APPEARS THIS WAY
ON ORIGINAL

NDA/IND#	SUPPL/AMEND. #		SUBMISSION DATE:		VOLUME:	
21042			23 Nov. 98			
Study Type:	Bioavailability/ Pharmacokinetics		Study 076			
Study Title:	A 2-Part, Open, Randomized Study to Determine the Absolute Bioavailability of 12.5- and 25-mg Final Market Image Tablets of MK-0966					

CLINICAL INVESTIGATOR	SITE	ANALYTICAL INVESTIGATOR	SITE
		Merck	West Point, PA

SINGLE DOSE:	NA	MULTIPLE DOSE:	X	WASHOUT PERIOD:	7 Days between Part I and II and 7 days between periods in Part II
CROSS-OVER	X	PARALLEL	NA	OTHER DESIGN:	NA

FASTED	X	FOOD STUDY		FDA HIGH FAT BREAKFAST	
If fasted, how long (hrs.)?	8 hrs prior to Labs	NA		NA	

SUBJECT BREAKDOWN											
Normal	X	Patients	NA	Young	X	Elderly	NA	Renal	NA	Hepatic	NA

	SUBJECT TYPE						GROUP		N=	16	M=	9	F=	7
Weight	Mean	162 lbs	M	Range	141	178	Group		N=	NA	M=	9	F=	NA
Age	Mean	32 Yr	M	Range	28	43	Group		N=	NA	M=	9	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	7
Weight	Mean	141lbs	F	Range	125	156	Group		N=	NA	M=	NA	F=	7
Age	Mean	31 Yr	F	Range	22	43	Group		N=	NA	M=	NA	F=	7

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
[$^{13}C_7$]MK-0966/ I.V. solution	1 (200 mL)	I.V. solution	5 µg/mL	0966 HSS003A002, 0966 HSS003A004	NA
MK-0966/ I.V. solution	1 (200 mL)	I.V. solution	5 µg/mL	0966 HSS001A007	
MK-0966 12.5 mg	12.5	Tablet	12.5 mg	MR-3427	NA
MK-0966 25 mg	25	Tablet	25 mg	MR-3426	NA

SAMPLING TIMES	
Plasma	Part I: Pre infusion start, 0.5 hr into infusion, at end of infusion and at 2-, 2.5-, 3-, 4-, 5-, 6-, 7-, 8.5-, 10-, 13-, 16-, 19-, 22-, 25-, 28-, 31-, 34-, 37-, 40-, 43-, 49-, 56-, 61- and 73 -hour time points following the end of the infusion. Part II: 0 hour pre oral dose, 0.5, 1, 1.5, post oral dose, 2 hr (pre IV dose), 2.5 (end of IV dose), and at 3-, 4-, 5-, 6-, 7-, 8.5-, 10-, 13-, 16-, 19-, 22-, 25-, 28-, 31-, 34-, 37-, 40-, 43-, 49-, 56-, 61-, 73-, 97-, and 121 -hour time points.
Urine	NA
Feces	NA

ASSAY METHOD:	
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Bioavailability/Pharmacokinetics

Table XV

Pharmacokinetic Parameters for MK-0966 Following Administration of a 2-mg Intravenous Dose (Average Ratio of [$^{13}C_7$]MK-0966 to MK-0966 = 1.18, cf. Table VIII)

A.N.	AUC MK-0966 (ng•hr/mL)	AUC [$^{13}C_7$]MK-0966 (ng•hr/mL)	Corrected[a] Ratios	Clearance[b] (mL/min)	V_{dss} L	$t_{1/2}$ MK-0966 h	$t_{1/2}$ [$^{13}C_7$]MK-0966 h
1							
2							
3							
4							
5							
6							
7							
8							
9							
Mean	85	101.1		191	105		
SD	23	25.5		71	23		
Geo. Mean			1.01				
Harm. Mean						6.09	6.28

[a]The AUC ratios were corrected by dividing each ratio of AUCs by the ratio of labeled to unlabeled drug determined for the dosing solution. These ratios are listed individually in Table VIII.
[b]Clearance and V_{dss} were estimated from total concentrations in plasma (MK-0966 + [$^{13}C_7$]MK-0966) since no isotope effect was apparent in the disposition of this drug.

Table XVI

Pharmacokinetic Parameters for MK-0966 Following Administration of a 1-mg Intravenous Dose of [$^{13}C_7$]MK-0966 Two Hours After Administration of a Single Oral Dose of MK-0966, 12.5 mg

A.N.	AUC (ng•hr/mL)	Clearance (mL/min)	V_{dss} L	$t_{½}$ h
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
Mean	127.6	140.7	91	
SD	34.4	41.8	17	
Mean (A.N.s 1-9)	128.1	137.0	91	
SD (A.N.s 1-9)	28.1	37.1	13	
Harmonic. Mean (A.N.s 1-9)				8.43
Harmonic. Mean (A.N.s 1-16)				7.49

n.a. = Not available

Table XVII

Pharmacokinetic Parameters for MK-0966 Following Administration of a 1-mg Intravenous Dose of [$^{13}C_7$]MK-0966 Two Hours After Administration of a Single Oral Dose of MK-0966, 25 mg

A.N.	AUC (ng•hr/mL)	Clearance (mL/min)	V_{dss} L	$t_{½}$ h^{-1}
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
Mean (A.N.s 1-9)	145.6	119	86	
SD (A.N.s 1-9)	27.3	29	13	
Mean (A.N.s 1-16)	144.6	121.4	84	
SD (A.N.s 1-16)	31.3	31.6	12	
Harmonic. Mean (A.N.s 1-9)				9.02
Harmonic. Mean (A.N.s 1-16)				8.24

n.a. = Not available

Table XVIII

Pharmacokinetic Parameters for MK-0966 Estimated Following Administration of Single Oral Doses of 12.5 and 25 mg

A.N.	12.5 mg			25 mg		
	C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
Mean	106.3	3.6	1479	227.6	4.2	3403
SD	21.7	2.8	347	51.5	3.2	745

n.a. = Not available

Table XIX

Estimated Oral Bioavailabilities of 12.5- and 25-mg Tablets of MK-0966

A.N.	12.5 mg Dose	25 mg Dose
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
Mean	0.93	0.94