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Table XI

Maximum Concentrations of L-748,731 Observed in Plasma of Healthy Young Volunteers Following Administration of Single and Multiple Oral Doses, ng/mL

25 mg			100 mg			250 mg			375 mg		
A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose
1			9			17			25		
3			11			18			26		
4			12			19			28		
6			15			21			29		
7			16			22			31		
8						23			32		
Mean	208	391	Mean	1108	1900	Mean	1171	2687	Mean	1367	3187
S.D.	51	92	S.D.	132	546	S.D.	305	482	S.D.	333	372

Table XII

Time of Occurrence of C_{max} of L-748,731 Observed in Plasma of Healthy Young Volunteers Following Administration of Single and Multiple Oral Doses, h.

25 mg			100 mg			250 mg			375 mg		
A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose
1			9			17			25		
3			11			18			26		
4			12			19			28		
6			15			21			29		
7			16			22			31		
8			---			23			32		
Mean	4.0	4.2	Mean	4.1	4.8	Mean	6.3	4.1	Mean	7.4	4.0
S.D.	0.0	0.4	S.D.	0.0	1.8	S.D.	3.6	0.0	S.D.	8.1	0.0

Table XIII

Terminal Half-Lives of L-748,731 Observed in Plasma of Healthy Young Volunteers Following Administration of Single and Multiple Oral Doses, h.

25 mg			100 mg			250 mg			375 mg		
A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose
1			9			17			25		
3			11			18			26		
4			12			19			28		
6			15			21			29		
7			16			22			31		
8			---			23			32		
Harmonic Mean	9.0	9.9	Harmonic Mean	10.1	11.1	Harmonic Mean	17.8	17.5	Harmonic Mean	20.7	16.6

Table XIV

Areas Under the Plasma Concentration Curves (0 - 48 h) of L-748,731 Observed in Plasma of Healthy Young Volunteers Following Administration of Single Oral Doses, ng·h/mL.

A.N.	25 mg	A.N.	100 mg	A.N.	250 mg	A.N.	375 mg
1		9		17		25	
3		11		18		26	
4		12		19		28	
6		15		21		29	
7		16		22		31	
8		---		23		32	
Mean	3899	Mean	20119	Mean	29537	Mean	39225
S.D.	1022	S.D.	5071	S.D.	3666	S.D.	9596

Table XV

Areas Under the Plasma Concentration Curves (24 h) of L-748,731 Observed in Plasma of Healthy Young Volunteers Following Administration of Single Oral Doses, ng·h/mL.

25 mg			100 mg			250 mg			375 mg		
A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose	A.N.	First Dose	Last Dose
1			9			17			25		
3			11			18			26		
4			12			19			28		
6			15			21			29		
7			16			22			31		
8			—			23			32		
Mean	3001	5650	Mean	14686	27158	Mean	18610	41180	Mean	22324	42970
S.D.	699	1832	S.D.	3264	6775	S.D.	2425	7073	S.D.	3896	9732

Table XVI

Accumulation Ratios of L-748,731 Administered as Daily Doses to Healthy Young Subjects

A.N.	25 mg	A.N.	100 mg	A.N.	250 mg	A.N.	375 mg
1		9		17		25	
3		11		18		26	
4		12		19		28	
6		15		21		29	
7		16		22		31	
8		---		23		32	
Geometric Mean	1.85	Geometric Mean	1.83	Geometric Mean	2.20	Geometric Mean	1.91

Clinical Pharmacology/Biopharmaceutics Study Summary Sheet

NDA/IND#	SUPPL/AMEND. #		SUBMISSION DATE:		VOLUME:	
21042			23 Nov. 98			
Study Type:	ADME		Study #	012		
Study Title:	An Open, Oral Single-Dose, 4-Period Study in Healthy Subjects to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of ^{14}C-MK-0966 in Solution					

CLINICAL INVESTIGATOR	SITE	ANALYTICAL INVESTIGATOR	SITE
		Merck	West Point, USA

SINGLE DOSE:	X	MULTIPLE DOSE:	NA	WASHOUT PERIOD:	7-10 days
CROSS-OVER	X	PARALLEL	NA	OTHER DESIGN:	NA

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

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

	SUBJECT TYPE						GROUP		N=	12	M=	12	F=	NA
Weight	Mean	75.9 Kg	M	Range	60.3	91	Group		N=	NA	M=	12	F=	NA
Age	Mean	37.8 Yr	M	Range	22	50	Group		N=	NA	M=	12	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	NA
Weight	Mean	Kg	F	Range			Group		N=	NA	M=	NA	F=	NA
Age	Mean	Yr	F	Range			Group		N=	NA	M=	NA	F=	NA

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
^{14}C-MK-0966	125	Solution	10 mg/mL	MR-3262	NA
MK-0966	125	Solution	10 mg/mL	MR-3261	NA
MK-0966 125	125	Tablet	125 mg	MR-3215	NA

SAMPLING TIMES	
Plasma	Part 1 (Period 1): Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 20, 22, 23, 24, 25, 26, 30, 36, 42, 46, 48, 50, 60, 72, 96, and 120 hours postdose. Part 2 (Periods 2, 3, and 4): Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 20, 22, 23, 24, 25, 26, 30, 36, 42, 46, 48, 50, 60, 72, 96, and 120 hours postdose.
Urine	for subjects receiving 14C-MK-0966 -2 to 0 (predose), 0 to 2, 2 to 4, 4 to 6, 6 to 9, 9 to 12, 12 to 16, 16 to 24, 24 to 36, 36 to 48, 48 to 72, 72 to 96, and 96 to 120 hours, postdose
Feces	Each INDIVIDUAL fecal collection obtained during the 168-hour period was packaged individually

ASSAY METHOD:	
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Absorption, Digestion, Metabolism and Excretion

Table XIII

Maximum Concentrations in Plasma (ng or ng-eq./mL) Observed Following Administration of Single 125-mg Oral Doses

	Solution			Tablet	
	MK-966		Radioactivity	MK-966	
A.N.	1st Dose	2nd Dose	1st Dose	1st Dose	2nd Dose
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	851		1139	930	
Std. Dev.	221		350	195	

n.a. = not applicable
Notebook/Page: 14171/353-400; 15219/3-28; 39899/69

Revised 12/19/97
Revised 3/13/98

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Table XIV

Time of Occurrence of C_{max} (h) Observed Following Administration of Single 125-mg Oral Doses

	Solution			Tablet	
	MK-0966		Radioactivity	MK-0966	
A.N.	1st Dose	2nd Dose	1st Dose	1st Dose	2nd Dose
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	8.8		6.6	8.6	
Std. Dev.	2.6		5.9	4.0	

n.a. = not applicable
Notebook/Page: 14171/353-400; 15219/3-28; 39899/69

Revised 12/19/97
Revised 3/13/98

Table XV

Areas Under the Plasma Concentration *vs.* Time Curve Following Administration of Single 125-mg Oral Doses of MK-966, µg•h/mL or µg-eq•h/mL

	Solution			Tablet	
	MK-0966		Radioactivity	MK-0966	
A.N.	1st Dose	2nd dose	1st Dose	1st Dose	2nd Dose
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	22.8		35.3	21.8	
Std. Dev.	4.6		4.7	5.2	

n.a. = not applicable

Revised 12/19/97
Revised 3/13/98

Table XVI

Effective Half-life of MK-966 Observed Following Administration of Single Oral Doses of 125 mg in Solution in PEG-400 or as a Compressed Tablet Formulation, hr

	Solution		Tablet	
A.N.	1st Dose	2nd Dose	1st Dose	2nd Dose
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Harmonic Mean	12.5		11.2	

Revised 3/13/98

Clinical Pharmacology/Biopharmaceutics Study Summary Sheet

NDA/IND#	SUPPL/AMEND. #		SUBMISSION DATE:		VOLUME:	
21042			23 Nov. 98			
Study Type:	Metabolism		Study #	018		
Study Title:	An Open Study to Investigate the Biliary Excretion of MK-0966 and its Metabolites Following Single Oral Doses of ^{14}C-MK-0966 in Patients Having a Surgically Implanted T-Tube or L-Tube					

CLINICAL INVESTIGATOR	SITE	ANALYTICAL INVESTIGATOR	SITE
		Merck	West Point, PA

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

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

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

	SUBJECT TYPE						GROUP		N=	4	M=	NA	F=	4
Weight	Mean	Kg	M	Range	NA		Group		N=	NA	M=	NA	F=	NA
Age	Mean	Yr	M	Range	NA		Group		N=	NA	M=	NA	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	4
Weight	Mean	75.3 Kg	F	Range	62	84	Group		N=	NA	M=	NA	F=	4
Age	Mean	57 Yr	F	Range	53	61	Group		N=	NA	M=	NA	F=	4

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
MK-0966 ^{14}C	125	Tablet	125 mg	MR-3341	NA
CardioGreen(indocyanine)	25	Solution	25 mg	MR-3356	NA
Aqueous solvent	NA	NA	NA	MR-3356	NA

SAMPLING TIMES	
Plasma	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 30, 36, 45, 48, 60, 72, 96, and 120 hours postdose
Bile	-2→0, 0→2, 2→4, 4→6, 6→9, 9→12, 12→16, 16→20, 20→24, 24→30, 30→36, 36→48, 48→60, 60→72, 72→84, 84→96, 96→108, 108→120 hours
Urine	-2-0, 0-2, 2-4, 4-6, 6-9, 9-12, 12-16, 16-24, 24-36, 36-48, 48-72, 72-96, 96-120
Feces	All collections up to 120 hours postdose

ASSAY METHOD:	
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Safety and Pharmacokinetics/ Metabolism

Table XVI

Overall Recoveries (as % of Dose) of MK-0966, L-755,190 and Radioactivity in Urine, Feces and Bile of Cholecystectomized Patients Following Administration of a Single Oral Dose, 142 mg (100 μCi)

A.N.	Radioactivity				MK-0966	L-755,190
	Urine	Feces	Bile	Total	Bile	Bile
1						
2						
3						
4						
Mean	29%	50%	1.8%	81%	0.013%	0.020%
SD	8%	25%	1.3%	19%	0.010%	0.015%

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Table XVIII

Pharmacokinetic Parameters Estimated from MK-0966 and Radioactivity Concentrations in Plasma of Cholecystectomized Patients Given a Single Oral Dose of [^{14}C]MK-0966 (142 mg, 100 μCi)

	AUC, ng•hr/mL			C_{max}, ng/mL		T_{max}, hr	
A.N.	MK-0966	Radioactivity	Ratio	MK-0966	Radioactivity	MK-0966	Radioactivity
1							
2							
3							
4							
Mean	5825	18473	0.317	188	425	8.0	10.0
SD	2093	8115	0.260	50	117	4.6	5.2

Clinical Pharmacology/Biopharmaceutics Study Summary Sheet

NDA/IND#	SUPPL/AMEND. #		SUBMISSION DATE:		VOLUME:	
21042						
Study Type:	Pharmacokinetic		Study #	021		
Study Title:	Part I: An Open, 5-Period Study of MK-0966 to Assess Dose-Proportionality and Compare Different Formulation Profiles in Healthy Male Volunteers. Part II: An Open, 4-Period Study of MK-0966 to Assess Dose-Proportionality Profiles in Healthy Female Volunteers at Similar Doses.					

CLINICAL INVESTIGATOR	SITE	ANALYTICAL INVESTIGATOR	SITE
[redacted]		Merck	West Point, Pa

SINGLE DOSE:	NA	MULTIPLE DOSE:	X	WASHOUT PERIOD:	7-10 days
CROSS-OVER	X	PARALLEL	NA	OTHER DESIGN:	NA

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

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

Part I

	SUBJECT TYPE						GROUP		N=	10	M=	10	F=	NA
Weight	Mean	76.5 Kg	M	Range	59.1	90.8	Group		N=	NA	M=	10	F=	NA
Age	Mean	30 Yr	M	Range	23	37	Group		N=	NA	M=	10	F=	NA
	SUBJECT TYPE						GROUP		N=	NA	M=	NA	F=	NA
Weight	Mean	Kg	F	Range			Group		N=	NA	M=	NA	F=	NA
Age	Mean	Yr	F	Range			Group		N=	NA	M=	NA	F=	NA

Part II

	SUBJECT TYPE						GROUP		N=	8	M=	NA	F=	8
Weight	Mean	Kg	M	Range			Group		N=	NA	M=	NA	F=	NA
Age	Mean	Yr	M	Range			Group		N=	NA	M=	NA	F=	NA
	SUBJECT TYPE						GROUP		N=	8	M=	NA	F=	8
Weight	Mean	69.2 Kg	F	Range	60.3	87.0	Group		N=	NA	M=	NA	F=	8
Age	Mean	37 Yr	F	Range	26	45	Group		N=	NA	M=	NA	F=	8

PART I

TREATMENT GROUP	DOSE(mg)	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
MK-0966	125	Tablet	125mg	MR-3215	NA
MK-0966	10	Tablet	10 mg	MR-3292	NA
MK-0966	50	Tablet	50 mg	MR-3286	NA
MK-0966	125	Tablet	125 mg	MR-3281	NA

PART II

TREATMENT GROUP	DOSE	DOSAGE FORM	STRENGTH	LOT#	LOT SIZE
MK-0966	10	Tablet	10 mg	MR-3292	NA
MK-0966	50	Tablet	50 mg	MR-3286	NA
MK-0966	125	Tablet	125 mg	MR-3281	NA

PART I & PART II

SAMPLING TIMES	
Plasma	Predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 12, 16, 18, 20, 22, 23, 24, 25, 26, 30, 33, 36, 39, 42, 46, 47, 48, 49, 50, 55, 60, 72, 96, and 120 hours postdose
Urine	-2 to 0 (predose), 0 to 2, 2 to 4, 4 to 6, 6 to 9, 9 to 12, 12 to 16, 16 to 24, 24 to 36, 36 to 48, 48 to 72, 72 to 96, and 96 to 120 hours, postdose
Feces	NA

ASSAY METHOD:	
Assay Sensitivity	
Assay Accuracy	

LABELING CLAIMS FROM STUDY	Safety and Pharmacokinetics

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Table XX

Maximum Values of Plasma Concentration (C_{max}) Observed in Plasma Following Administration of Single Oral Doses to Healthy Subjects, ng/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	122	527	1216	2074	1032
Std. Dev.	34	98	460	462	376
Women:					
11					
12					
13					
14					
15					
16					
17					
18					
Mean	125	549	1170	1737	—
Std. Dev.	26	89	331	372	—

Table XXI

Time of Occurrence of C_{max} (t_{max}) Observed in Plasma Following Administration of Single Oral Doses to Healthy Subjects, h

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	3.0	4.1	5.0	8.0	6.3
Std. Dev.	1.9	1.6	5.0	5.9	6.4
Women:					
11					
12					
13					
14					
15					
16					
17					
18					
Mean	3.5	4.8	3.8	4.1	—
Std. Dev.	2.6	5.6	2.6	2.4	—