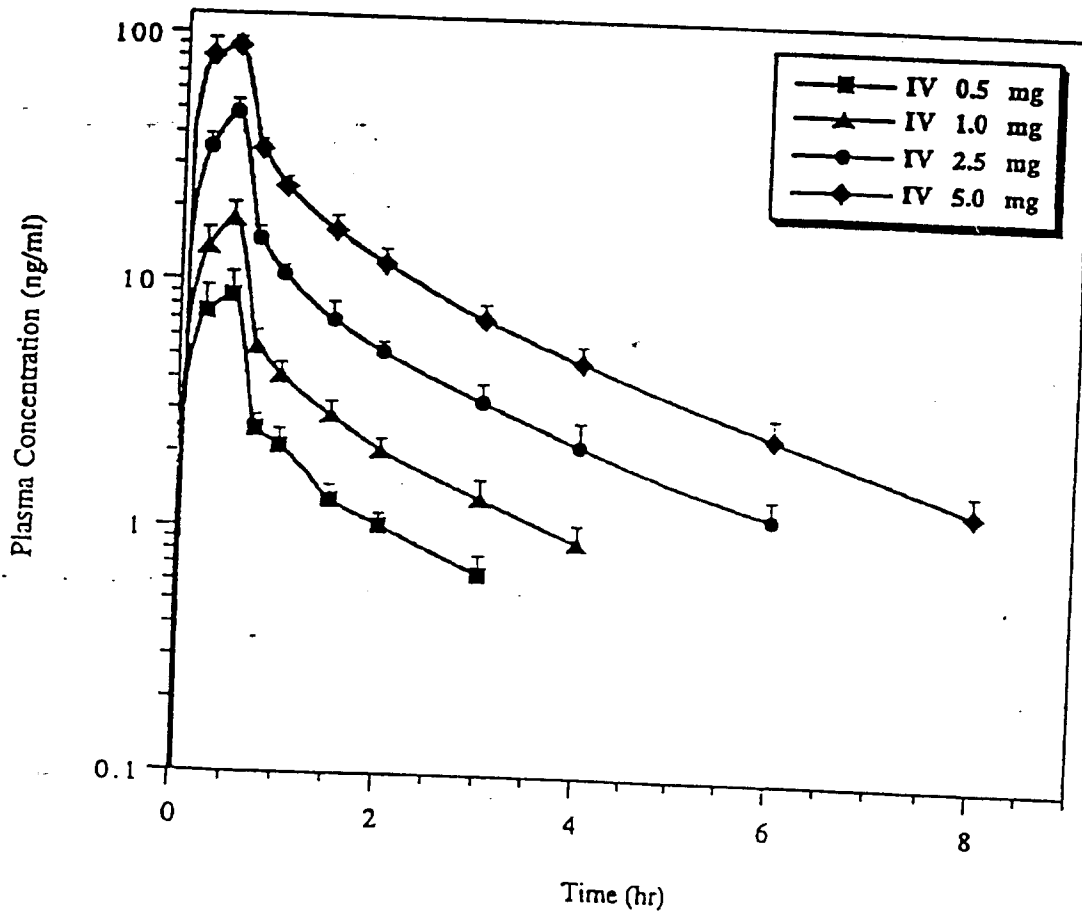


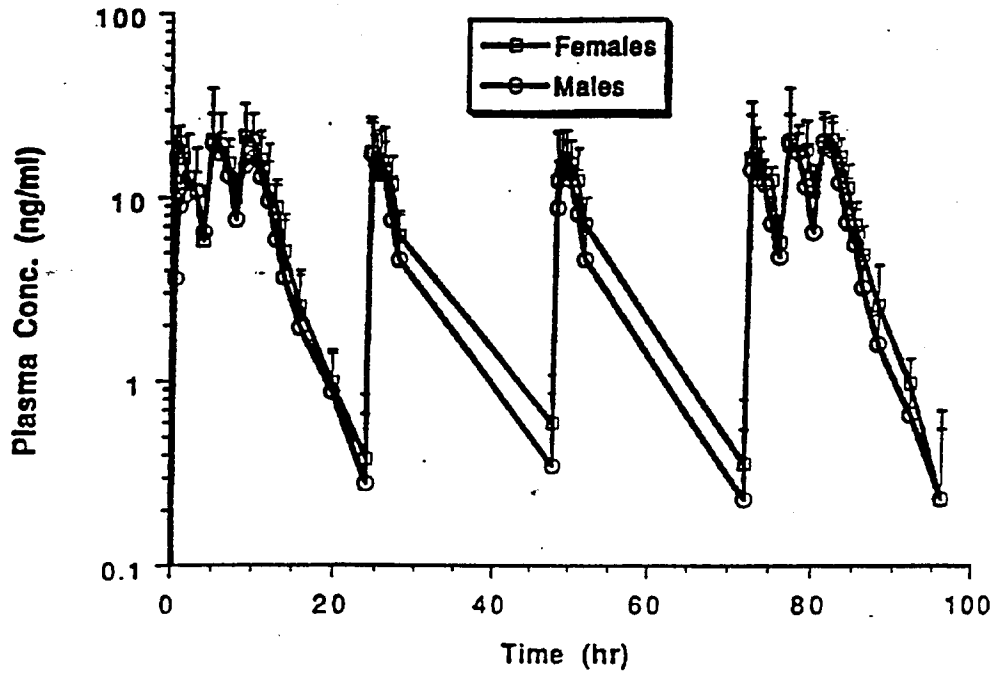
Figure 7. Mean Plasma Concentration Versus Time Profiles Following Intravenous Administration of MK-0462 0.5 mg to 5.0 mg



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Figure 8.

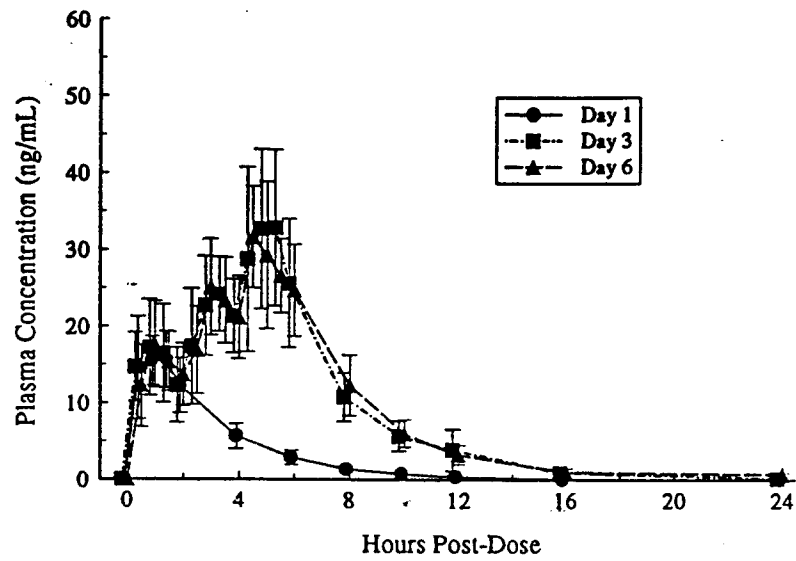
Figure 8 Mean (\pm S.D.) Plasma Concentration-time Profiles of MK-462 in Healthy Males (N = 5) and Healthy Females (N = 4) Receiving Three 10-mg Doses of MK-462 (q4h) per Day for Four Consecutive Days



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Figure 9.

Mean (\pm SD, N=8) Plasma Concentration-Time Profiles of Rizatriptan in Males on Days 1, 3, and 6



Mean (\pm SD, N=8) Plasma Concentration-Time Profiles of Rizatriptan in Females on Days 1, 3, and 6

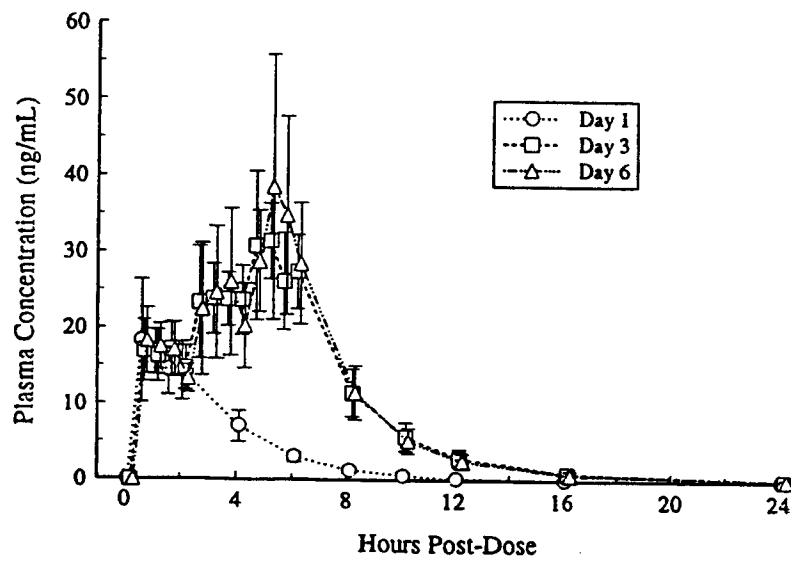
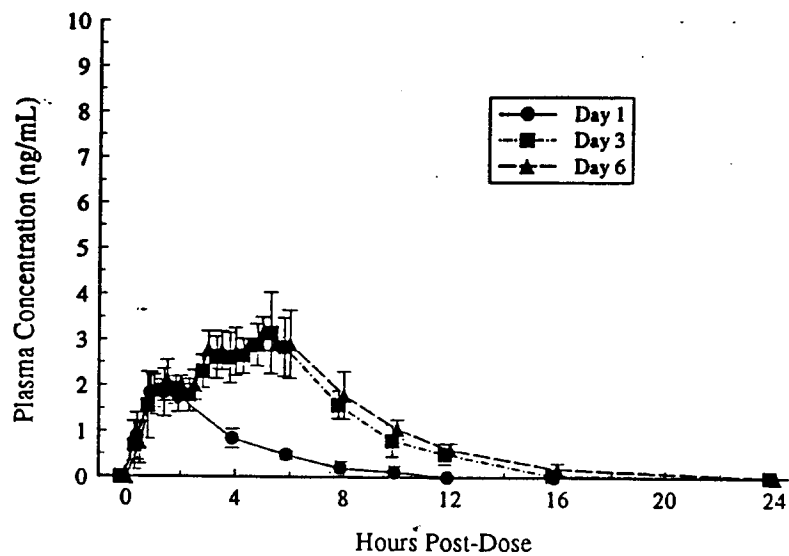


Figure 10.

Mean (\pm SD, N=8) Plasma Concentration-Time Profiles of L-706,248 in Males on Days 1, 3, and 6



Mean (\pm SD, N=8) Plasma Concentration-Time Profiles of L-706,248 in Females on Days 1, 3, and 6

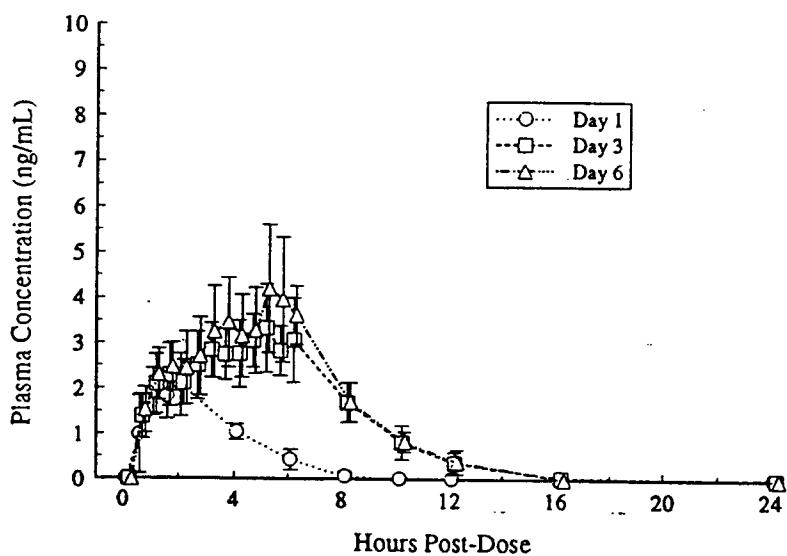
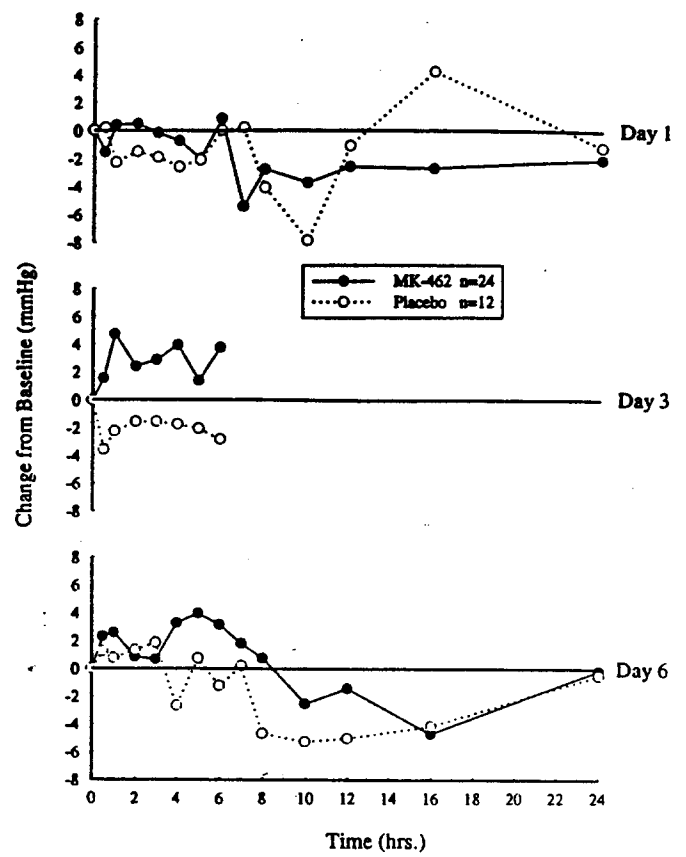
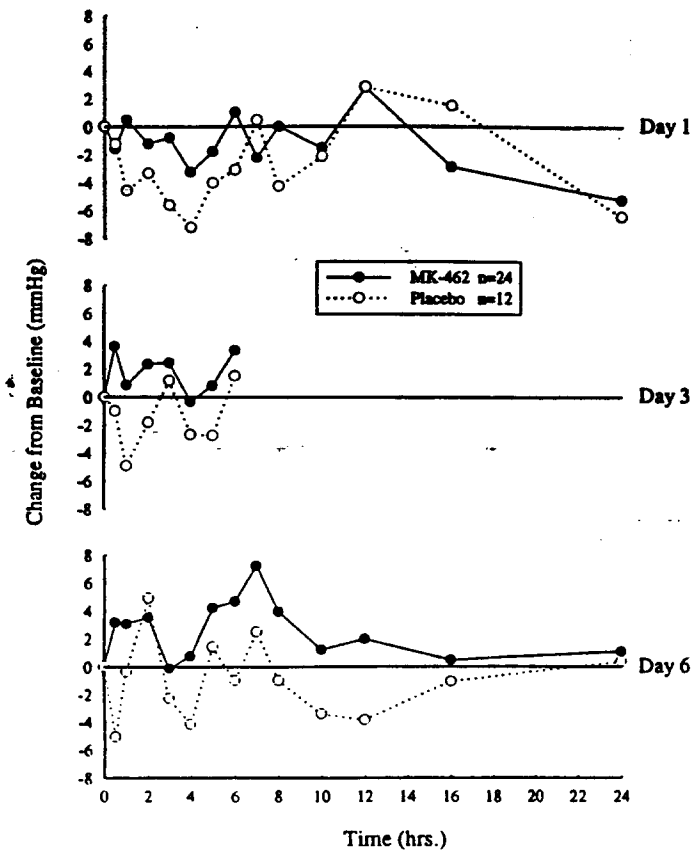


Figure 11.

Systolic Blood Pressure Mean Change From Baseline on Days 1, 3, and 6

Diastolic Blood Pressure Mean Change From Baseline on Days 1, 3, and 6



Heart Rate Mean Change From Baseline

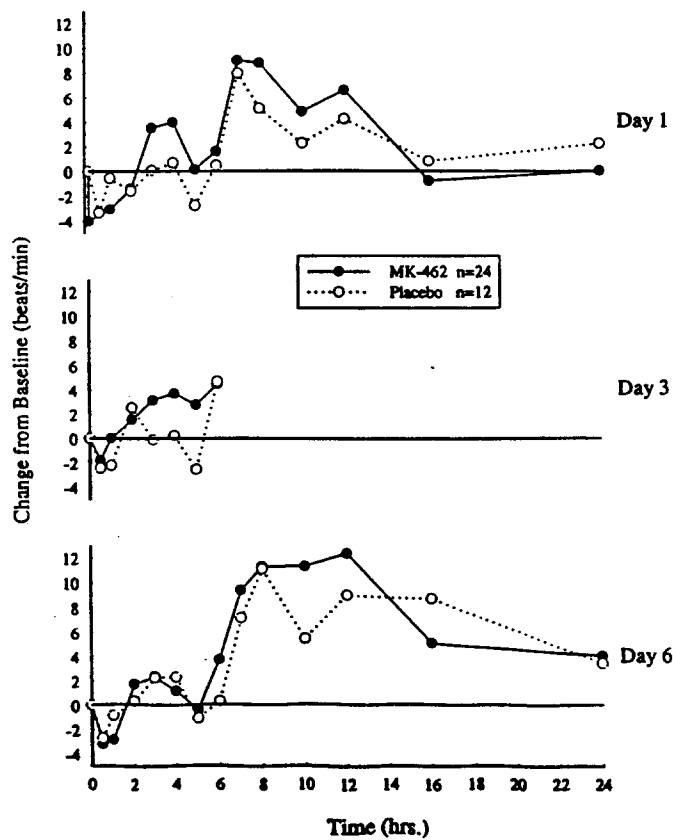


Figure 12.

Mean (\pm S. D., N= 12) Plasma Concentration - Time Profiles of MK-0462 in Healthy Males Receiving Single Oral Doses of 10 mg of MK-0462

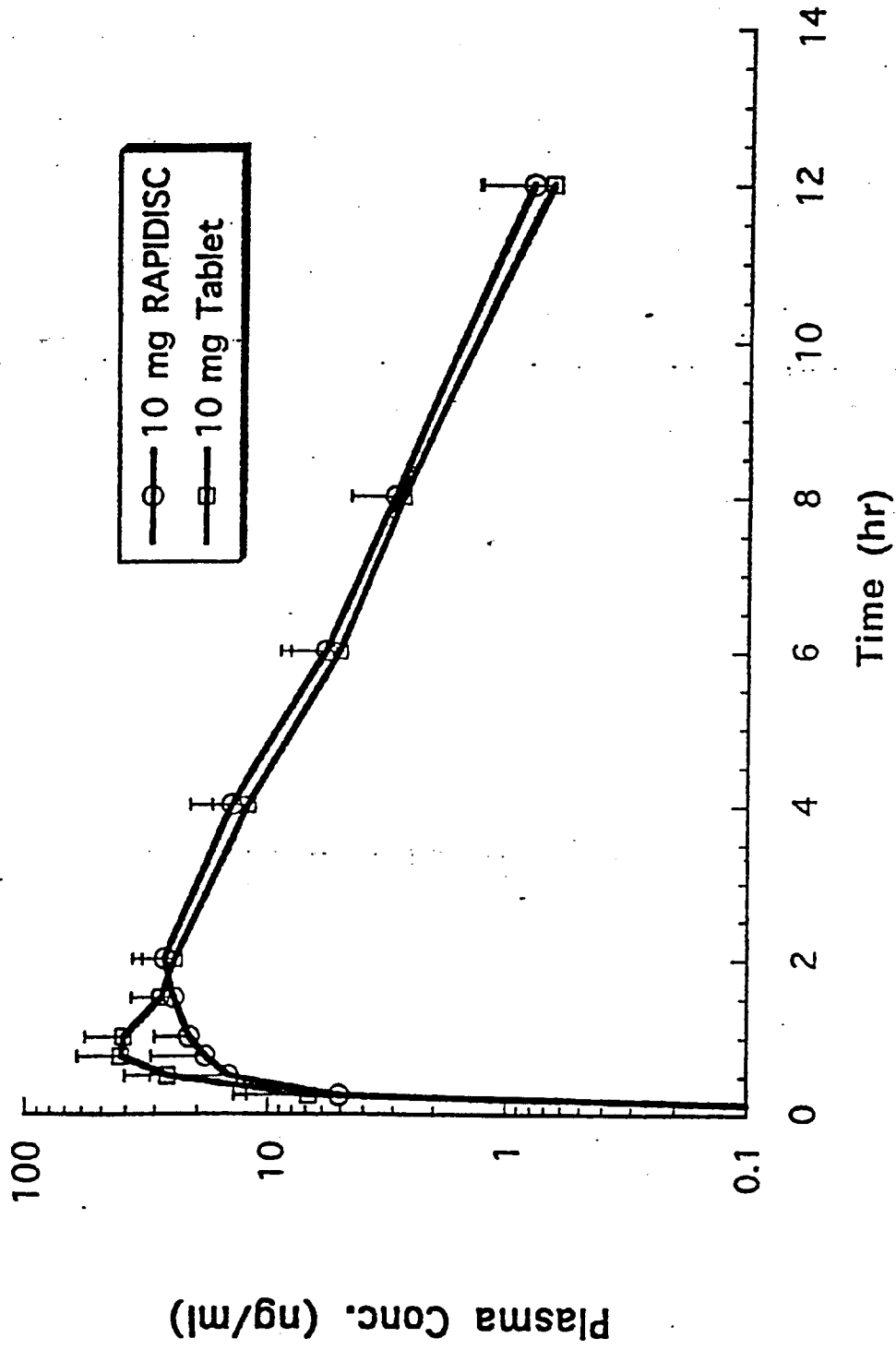
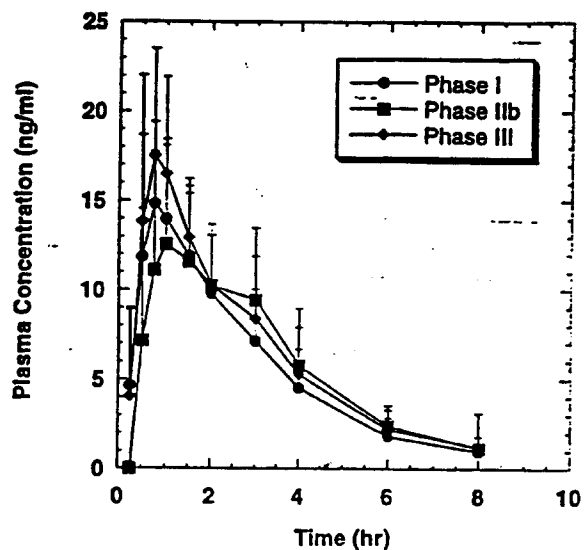
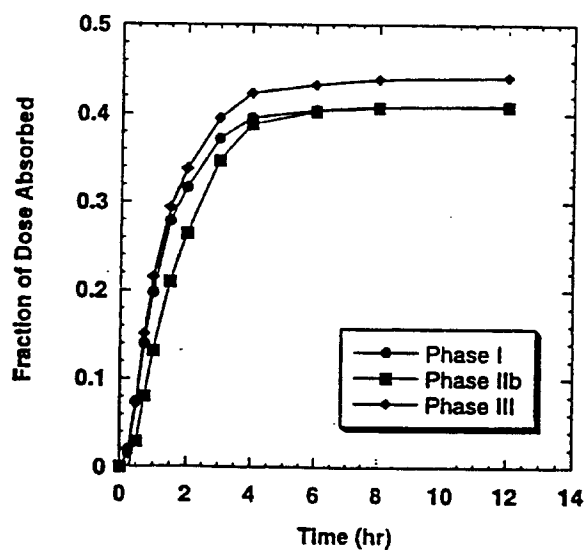


Figure 13.

Mean (\pm S.D., N = 18) Plasma Concentration-Time Profiles of a Single 10-mg Dose of MK-0462 in Formulations of Either Two 5-mg Tablets Used in the Initial Phase I Study, One 10-mg Tablet (Encapsulated) Used in the Phase IIb Dose-Finding Study, or One 10-mg Final Market Composition Tablet Used in Phase III Studies



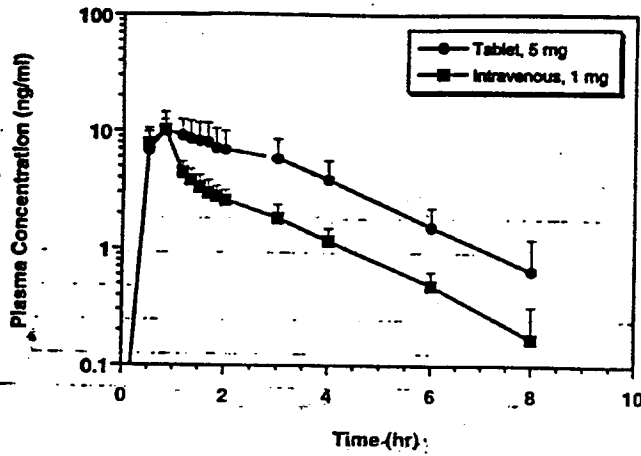
Mean (N = 18) cumulative absorption-time profiles of a Single 10-mg Dose of MK-0462 in Formulations of Either Two 5-mg Tablets Used in the Initial Phase I Study, One 10-mg Tablet (Encapsulated) Used in the Phase IIb Dose-Finding Study, or One 10-mg Final Market Composition Tablet Used in Phase III Studies



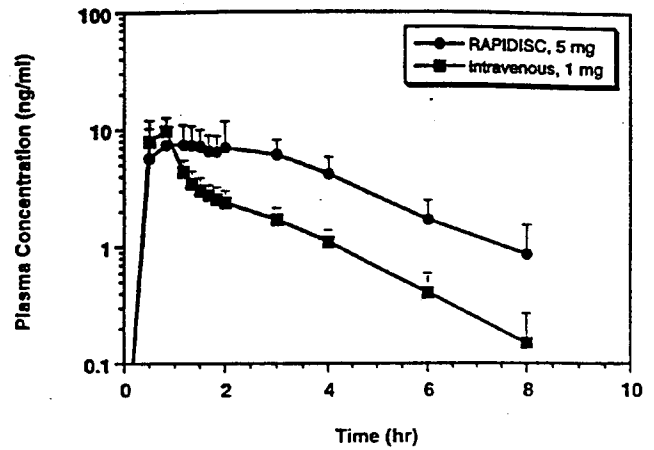
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Figure 14.

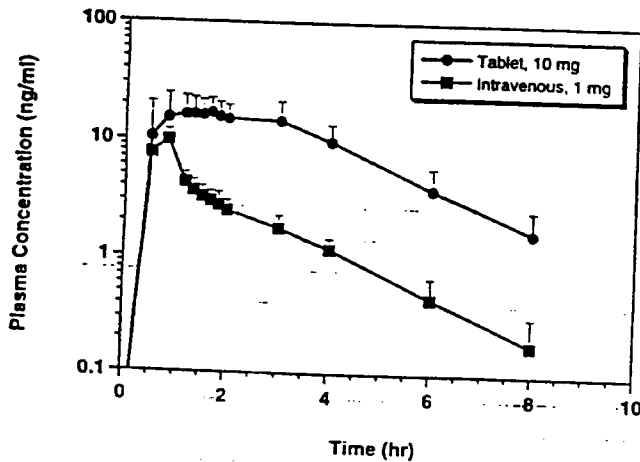
Mean (\pm S.D., N = 12) Plasma Profiles for MK-0462 Following Oral Administration of 5-mg MK-0462 FMC Tablet and Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 to Healthy Female Subjects



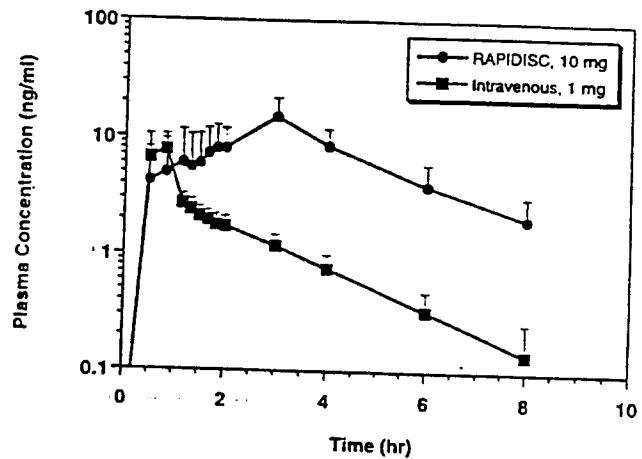
Mean (\pm S.D., N = 12) Plasma Profiles for MK-0462 Following Oral Administration of 5-mg MK-0462 FMC RAPIDISC™ and Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 to Healthy Female Subjects



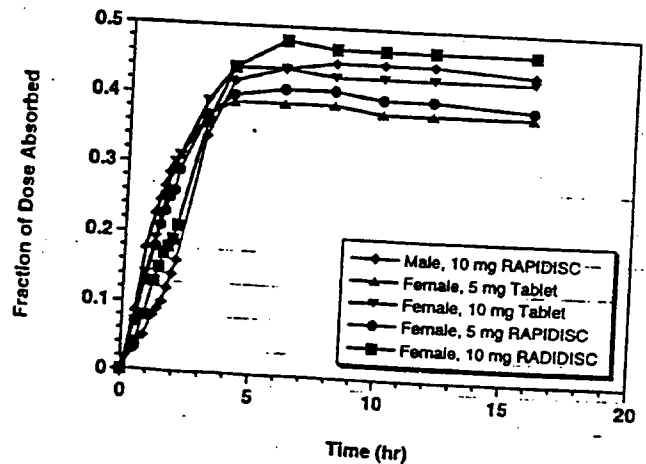
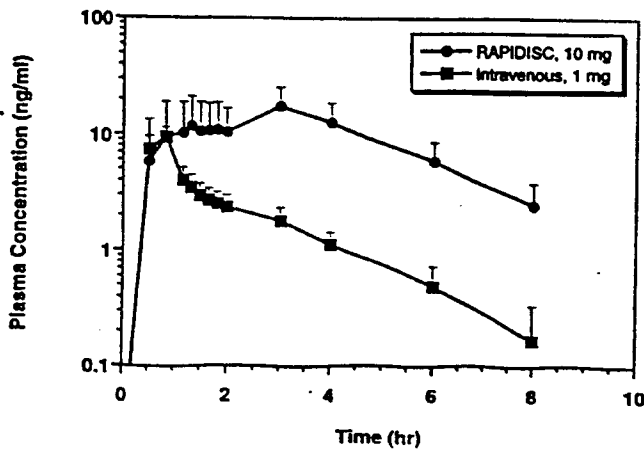
Mean (\pm S.D., N = 12) Plasma Profiles for MK-0462 Following Oral Administration of 10-mg MK-0462 FMC Tablet and Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 to Healthy Female Subjects



Mean (\pm S.D., N = 12) Plasma Profiles for MK-0462 Following Oral Administration of 10-mg MK-0462 FMC RAPIDISC™ and Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 to Healthy Male Subjects



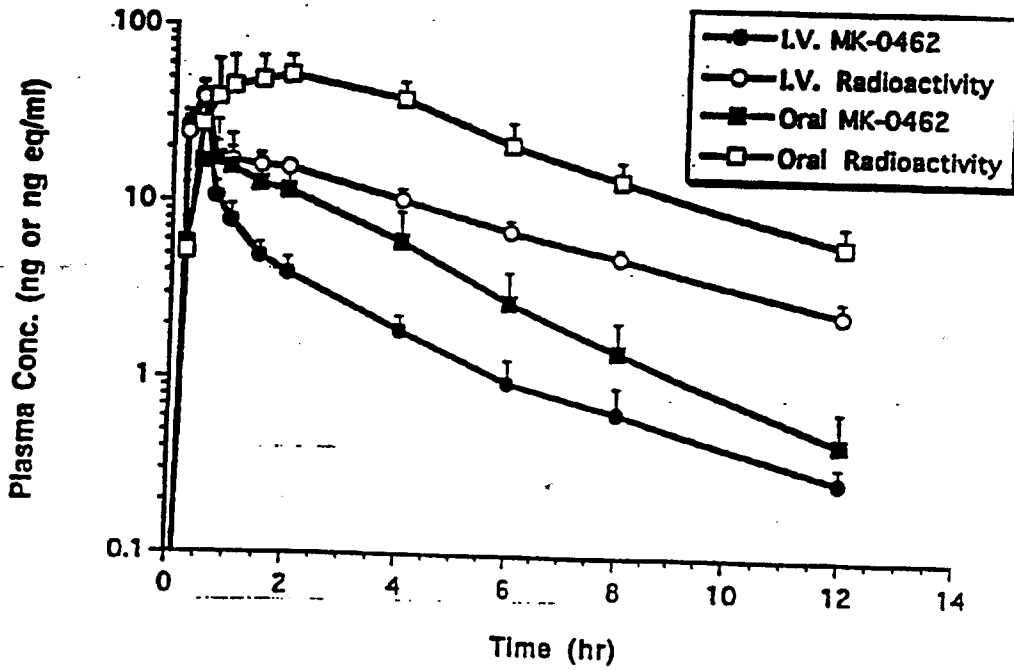
Mean (\pm S.D., N = 12) Plasma Profiles for MK-0462 Following Oral Administration of 10-mg MK-0462 FMC RAPIDISC™ and Simultaneous Intravenous Infusion of 1-mg Stable-Labeled MK-0462 to Healthy Female Subjects



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Figure 15

Mean (\pm S.D., N = 6) 0-12 Hour Plasma Concentration-Time Profiles of MK-0462 and 14 C-Radioactivity after Separate I.V. (3 mg, \sim 75 μ Ci) and Oral (10 mg, \sim 75 μ Ci) Administration of 14 C-MK-0462



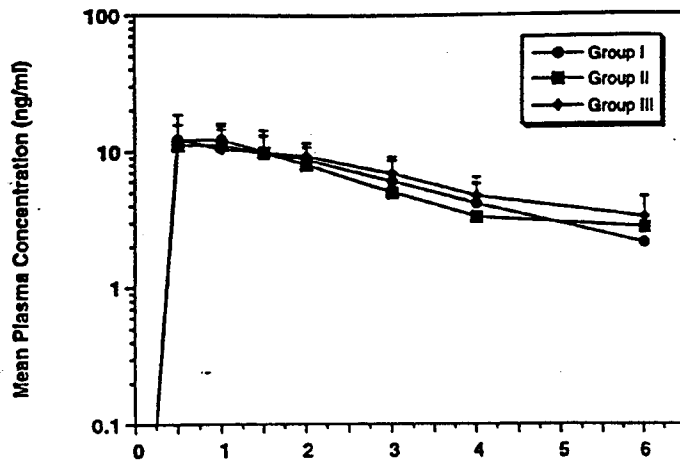
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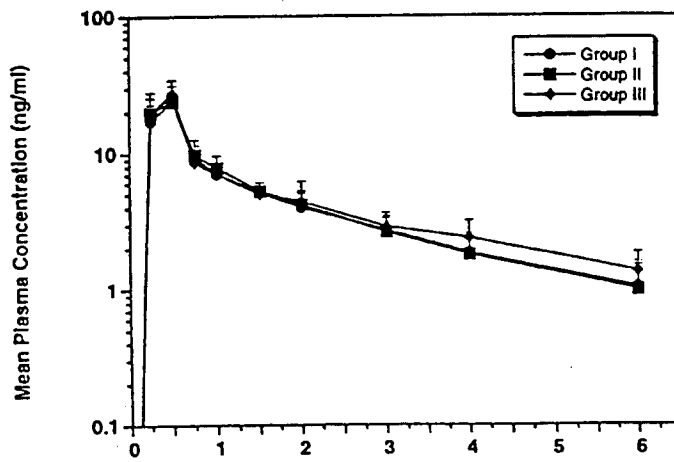
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INFORMATION**

Figure 21. Mean (\pm S.D., N = 7, 5, or 6) Plasma Concentration-Time Profiles of MK-0462 in Renal Insufficiency Patients Following the Administration of a 5-mg Oral Dose of MK-0462 (Solution)



Mean (\pm S.D., N = 7, 5, or 6) Plasma Concentration-Time Profiles of MK-0462 in Renal Insufficiency Patients Following the Administration of a 2-mg Intravenous MK-0462 Infusion Over 30 Minutes



Mean (N = 7, 5, or 6) Cumulative Absorption-Time Profiles of a 5-mg Oral Dose of MK-0462 (Solution) in Patients from Group I, Group II, and Group III of Renal Insufficiency

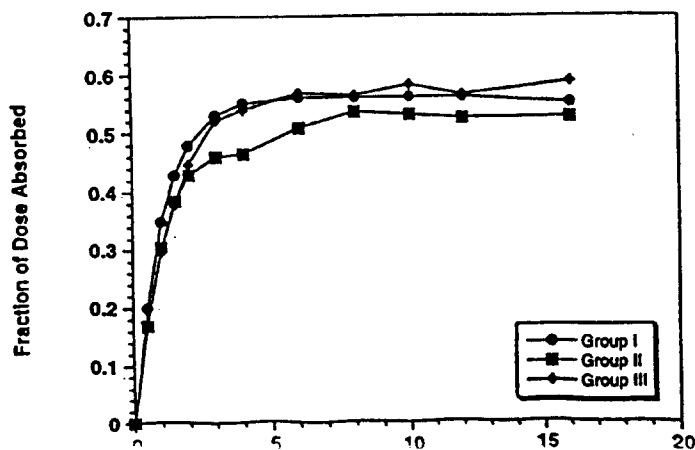
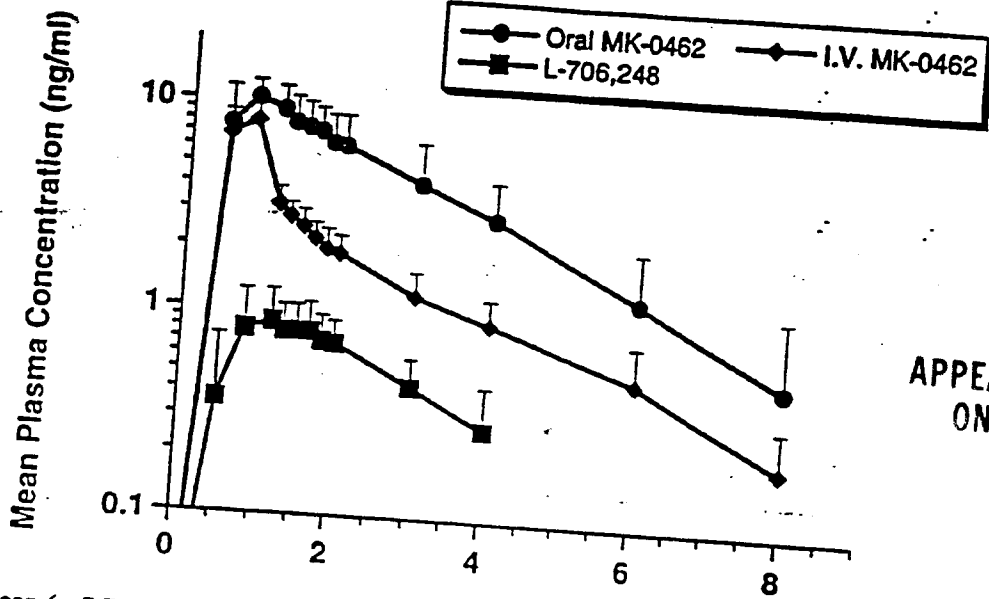


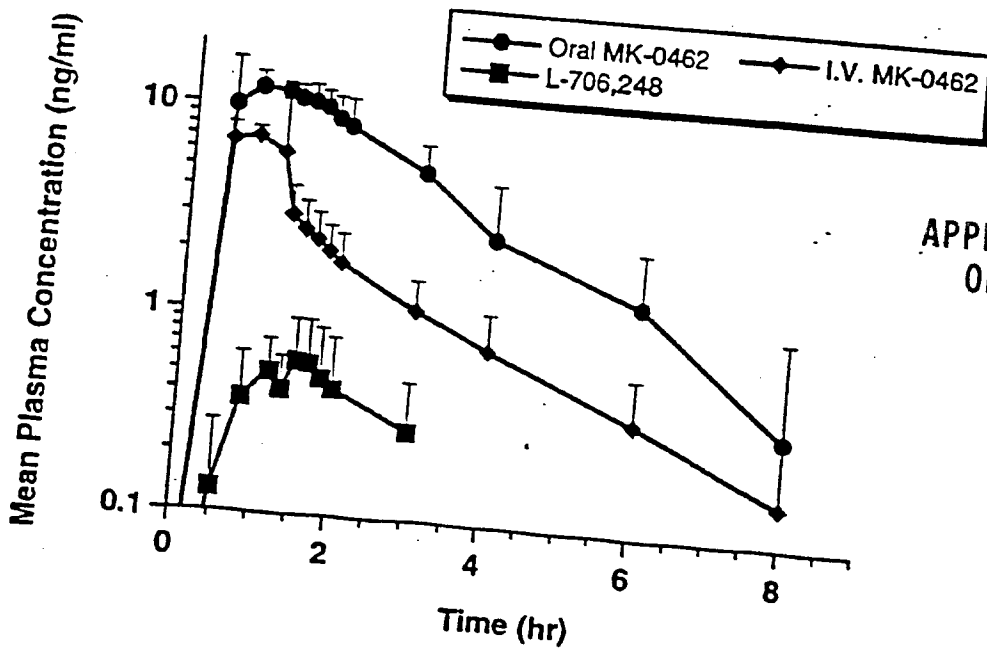
Figure 22.

Mean (\pm S.D., N = 7) Plasma Concentration Profiles for oral MK-0462 and L-706,248, and I.V. MK-0462 in Patients with Mild Hepatic Insufficiency Receiving Orally a 5-mg MK-0462 Tablet and a Simultaneous I.V. Infusion of 1.0-mg Stable-Labeled MK-0462 Over 50 Minutes (Part 2)



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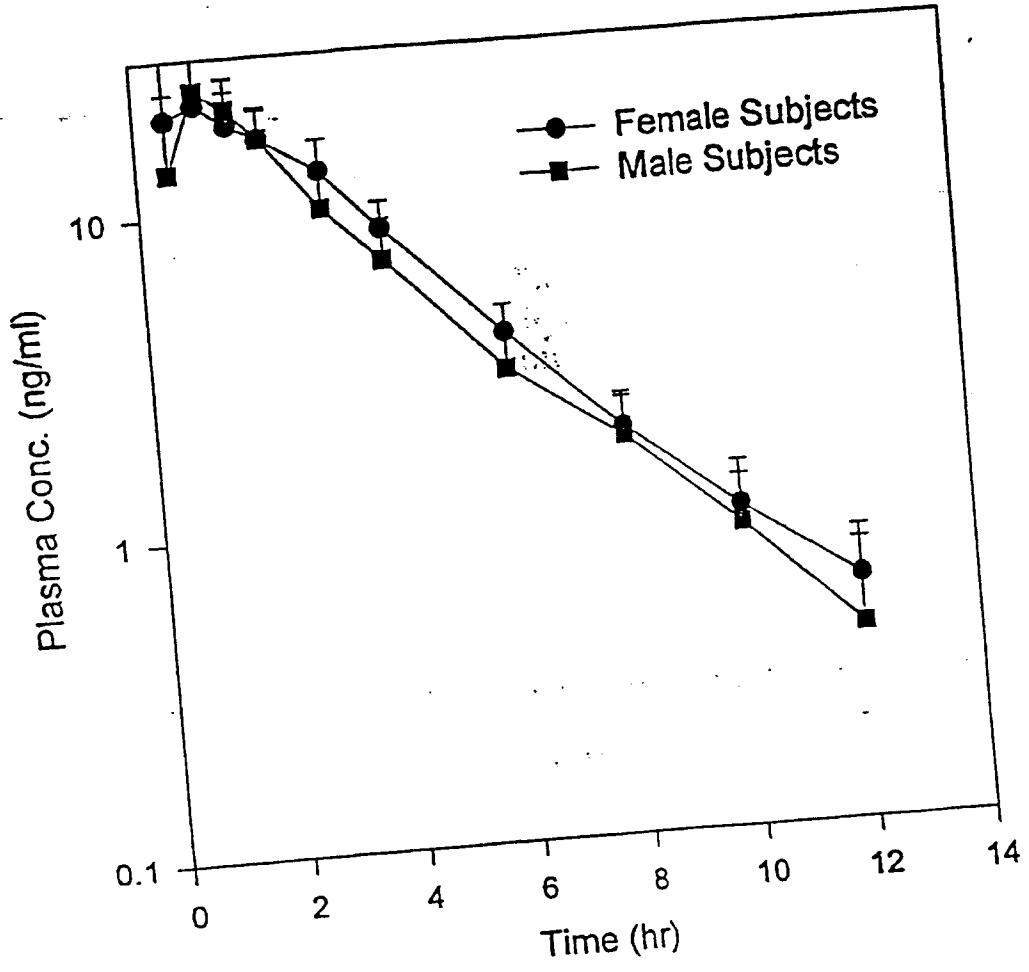
Mean (\pm S.D., N = 3) Plasma Concentration Profiles for oral MK-0462 and L-706,248, and I.V. MK-0462 in Patients with Moderate Hepatic Insufficiency Receiving Orally a 5-mg MK-0462 Tablet and a Simultaneous I.V. Infusion of 1.0-mg Stable-Labeled MK-0462 Over 50 Minutes (Part 2)



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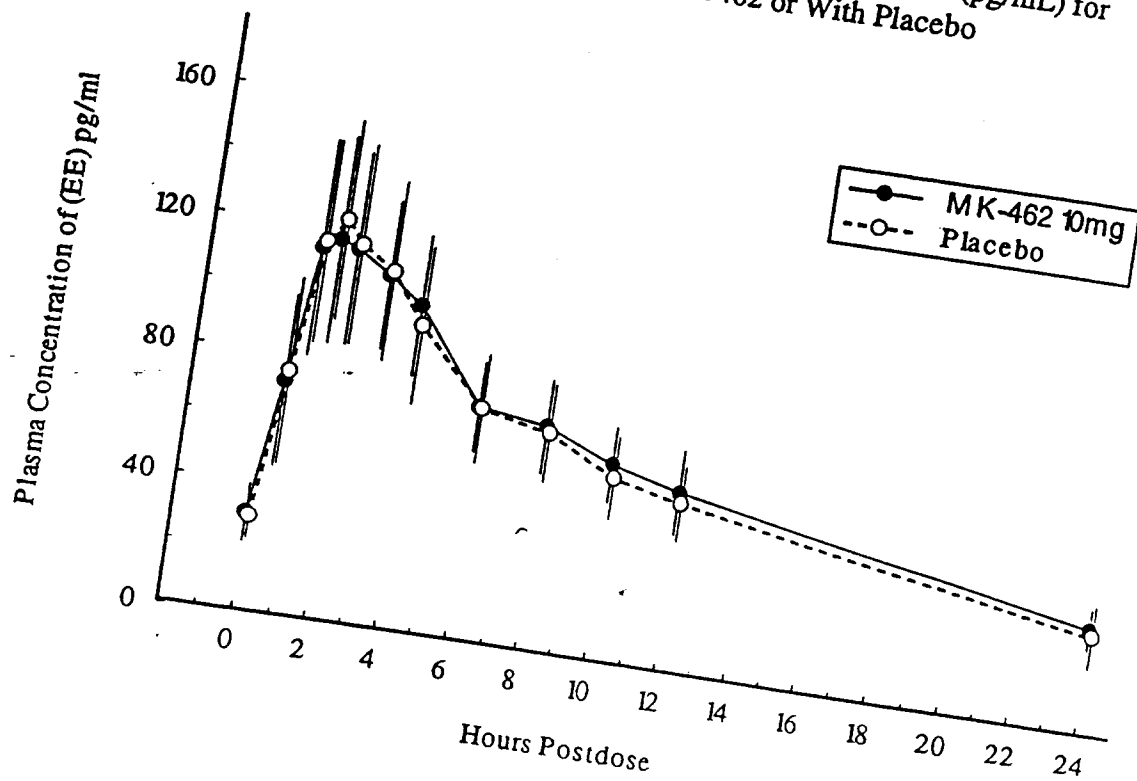
Figure 23,

Mean (\pm S.D., N=8) Plasma Concentration-Time Profiles of MK-0462 in Healthy Male and Female Elderly Subjects Receiving a Single Dose of 10-mg Tablet



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Figure 24. Mean (\pm SD) Ethinyl Estradiol (EE) Plasma Concentrations (pg/mL) for ORTHO-NOVUM With MK-0462 or With Placebo



Mean (\pm SD) Norethindrone (NET) Plasma Concentrations (pg/mL) for ORTHO-NOVUM With MK-0462 or With Placebo

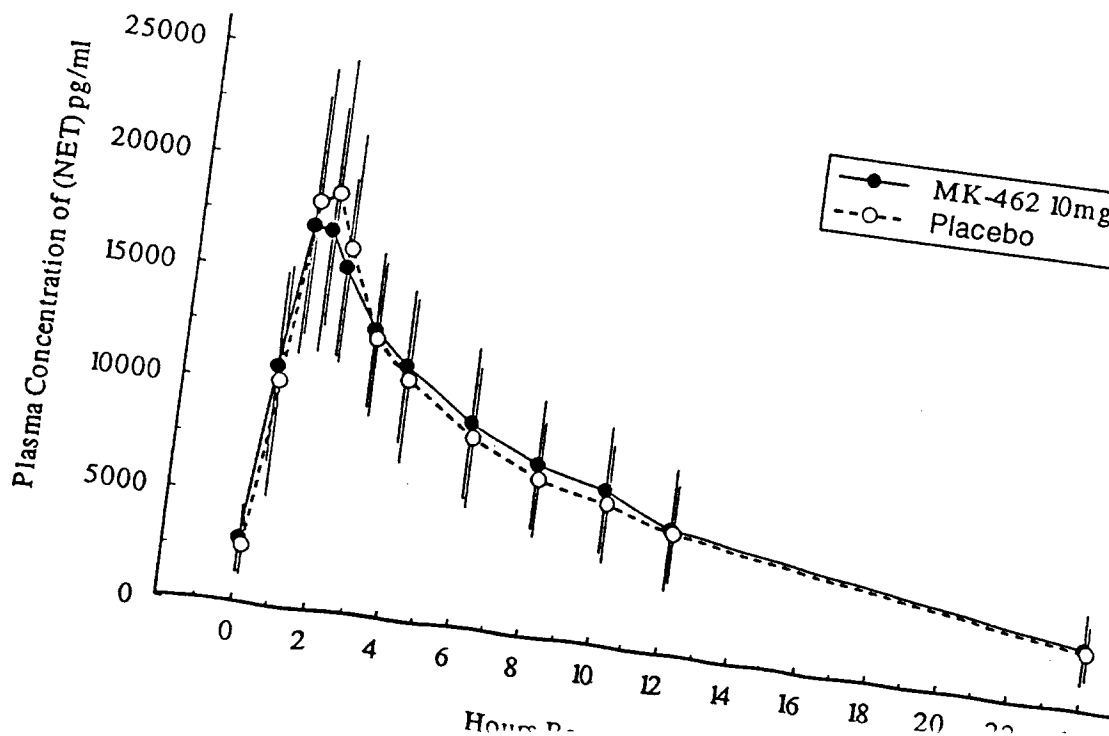
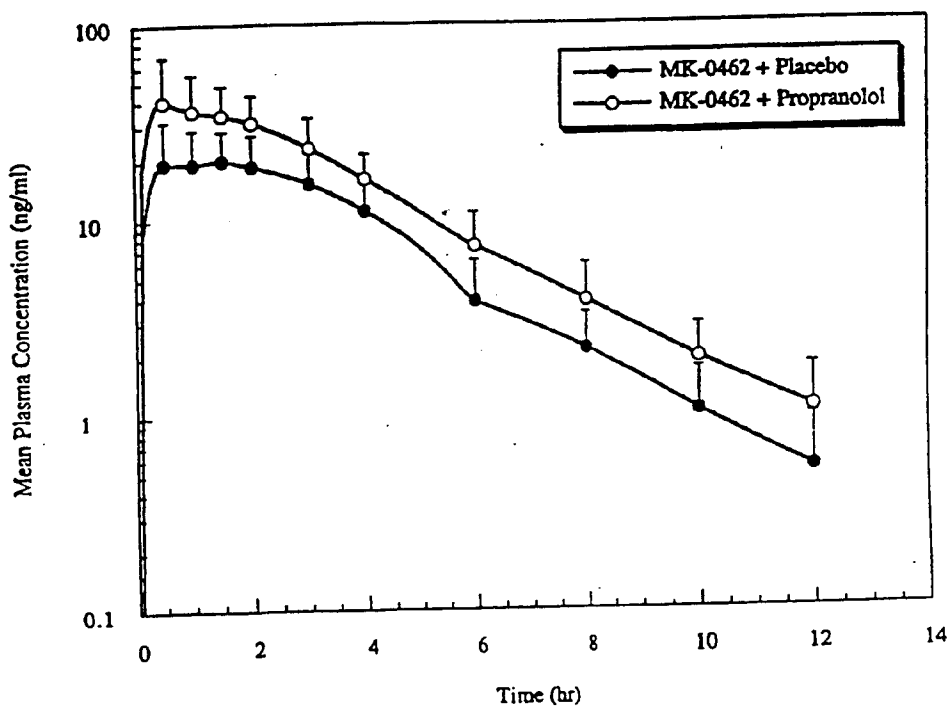


Figure 25.

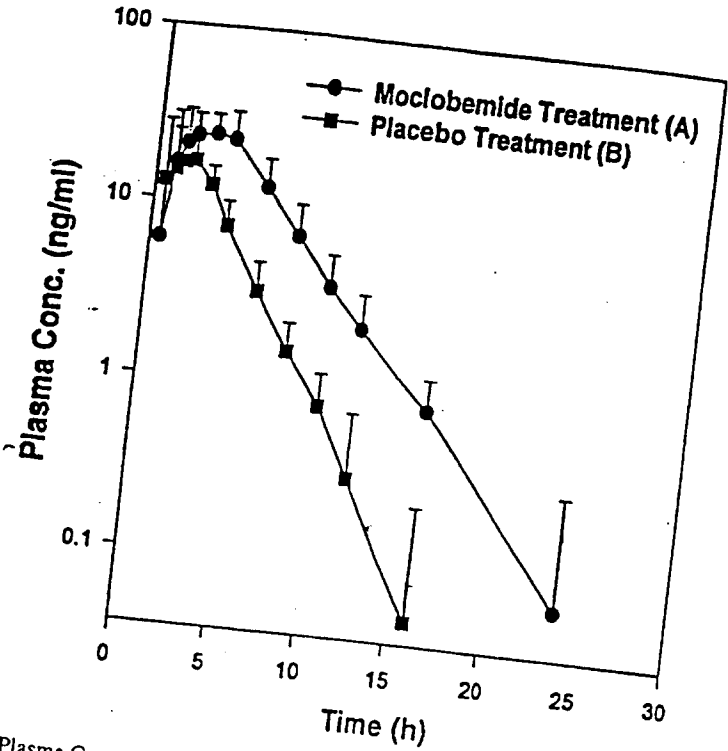
Mean (\pm S.D., N=11) Plasma Concentration-Time Profiles of MK-462 on Day 7 in Healthy Subjects Receiving Orally 10 mg of MK-0462 on Days 7 and 8 with and without Propranolol (120 mg q12h for 7.5 Days)



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Figure 26.

Mean Plasma Concentration-Time Profiles of Rizatriptan in Young Healthy Subjects Receiving Single 10-mg Doses of Rizatriptan Following Four Days of Dosing with Moclobemide (150 mg) or Placebo (N=12)



Mean Plasma Concentration-Time Profiles of L-706,248 in Young Healthy Subjects Receiving Single 10-mg Doses of Rizatriptan Following Four Days of Dosing With Moclobemide (150 mg) or Placebo (N=12)

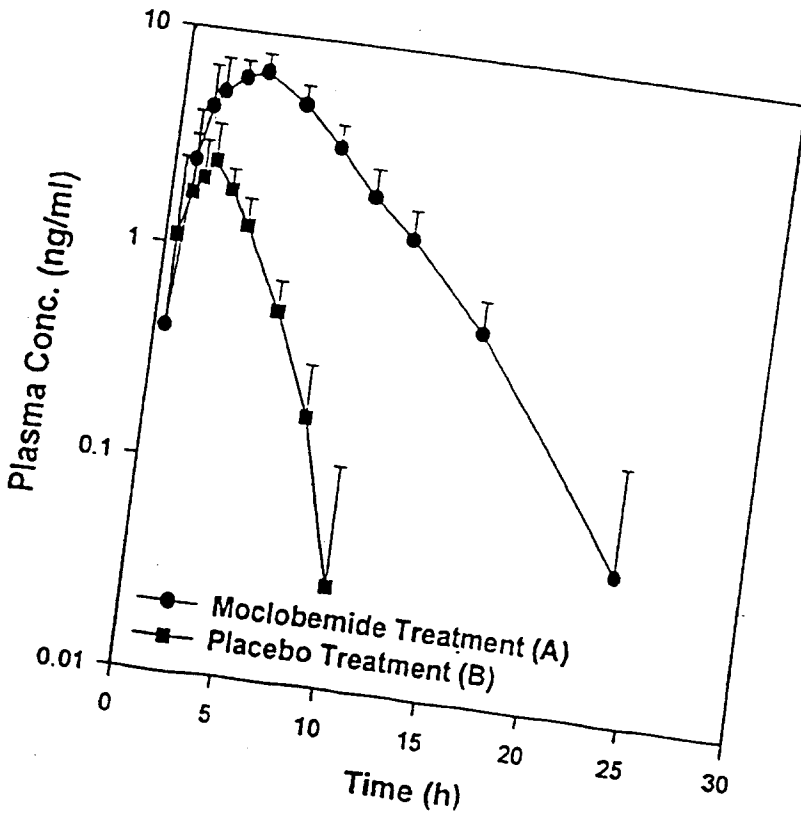
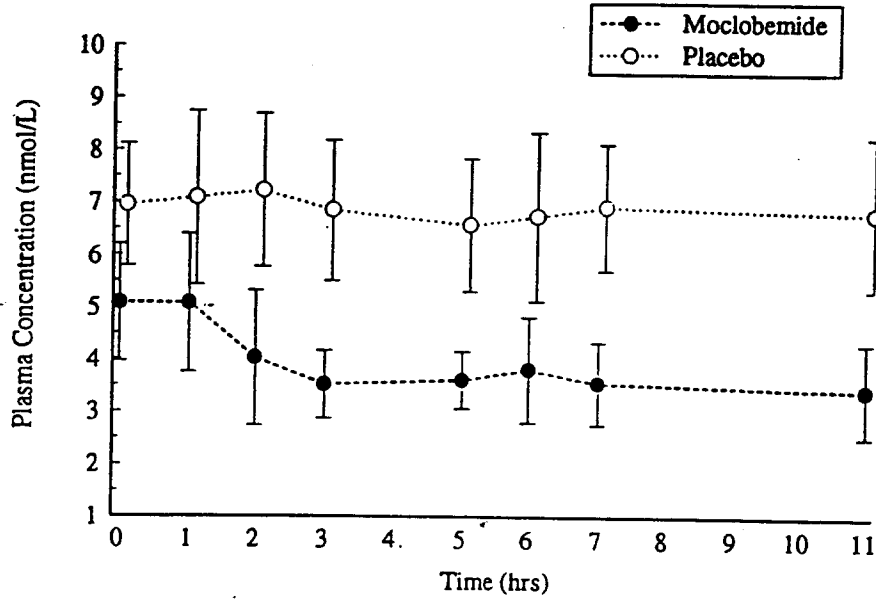


Figure 27.

Mean Plasma Concentration-Time Profiles of DHPG in Young Healthy Subjects Receiving Moclobemide (150 mg) or Placebo on Day 4 (N=12)



Mean Change from Baseline for DHPG Plasma Concentrations in Young Healthy Subjects Receiving Moclobemide (150 mg) or Placebo (N=12)

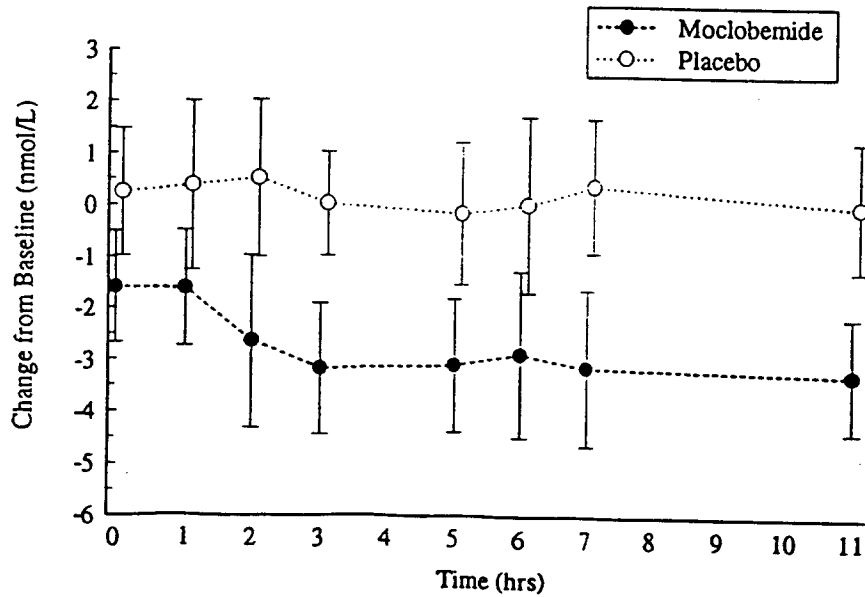
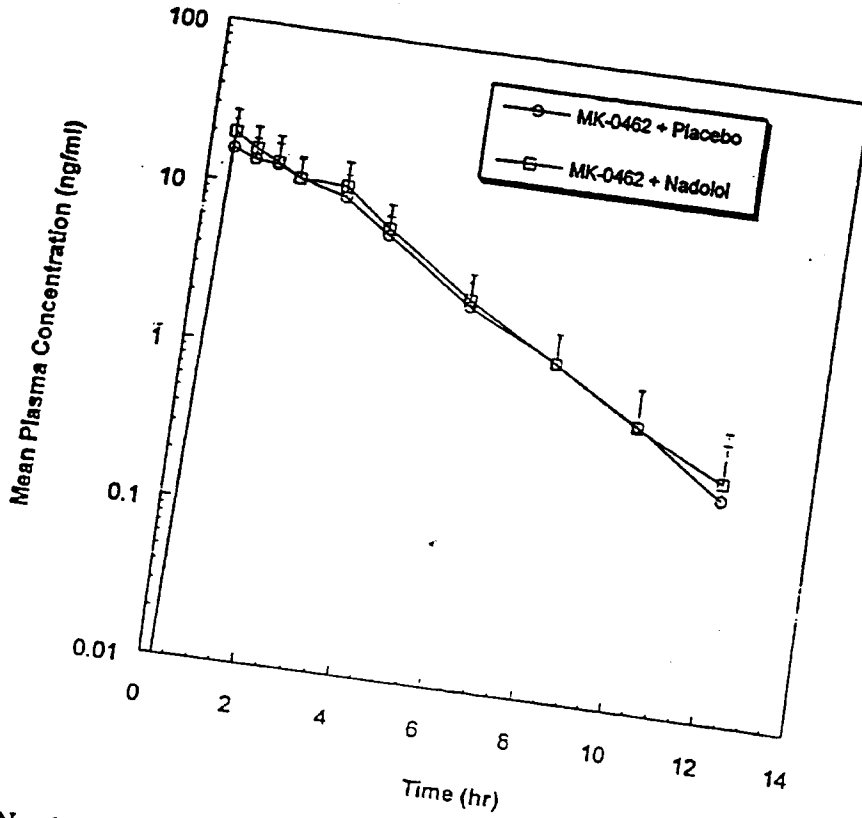
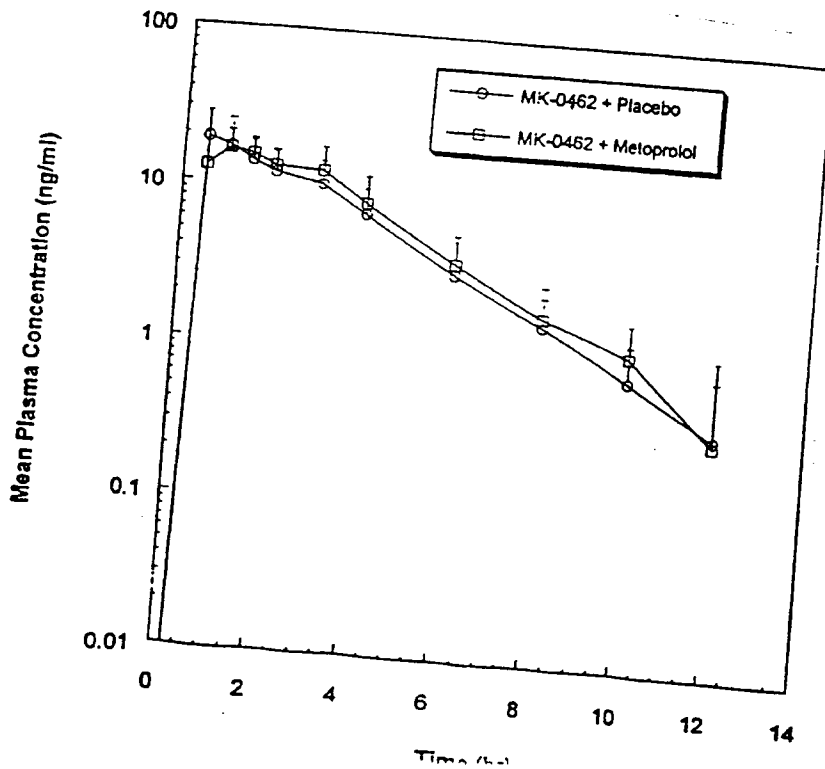


Figure 28.

Mean (\pm S.D., N = 12) Plasma Concentration-Time Profiles of MK-0462 on Day 7 in Healthy Subjects Receiving Orally 80 mg of Nadolol or Placebo q12h for 7 Days and a Single 10-mg Dose of MK-0462 on Day 7

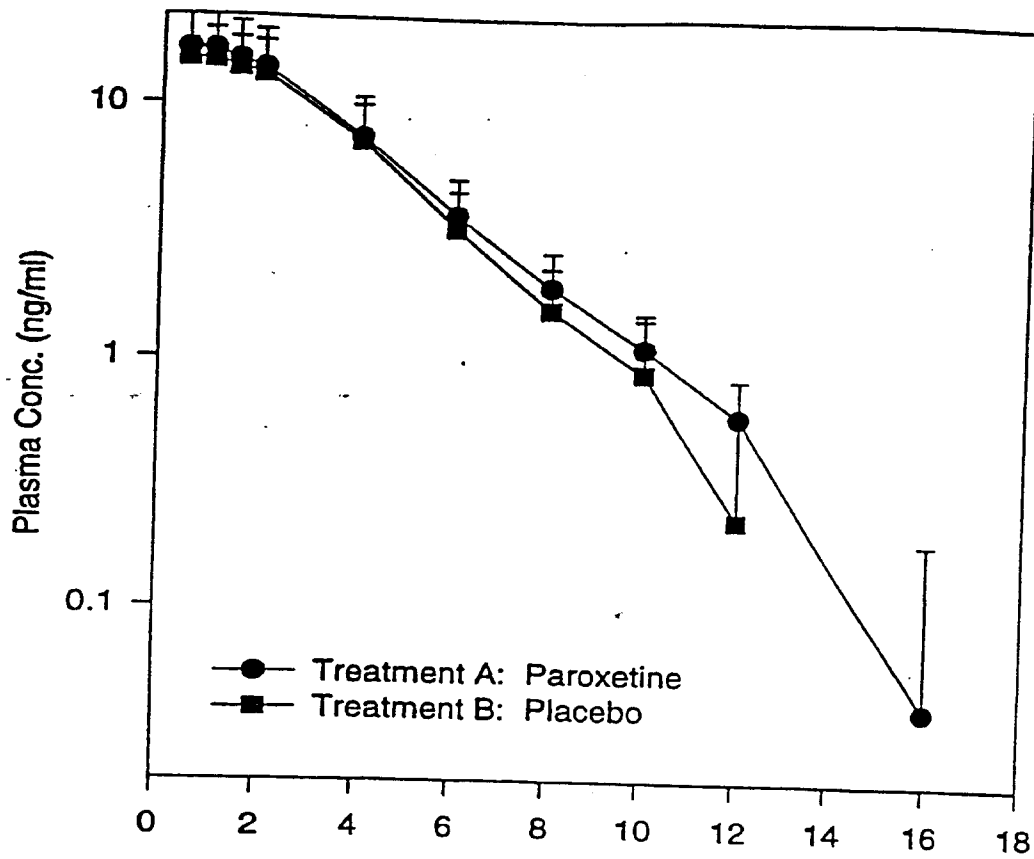


Mean (\pm S.D., N = 12) Plasma Concentration-Time Profiles of MK-0462 on Day 7 in Healthy Subjects Receiving Orally 100 mg of Metoprolol or Placebo q12h for 7 Days and a Single 10-mg Dose of MK-0462 on Day 7



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Figure 29.
 Mean (\pm S.D., N=12) Plasma Concentration-Time Profiles of MK-0462 in Healthy Subjects
 Receiving Paroxetine and MK-0462 or Placebo and MK-0462



Mean (\pm S.D., N=12) Plasma Concentration-Time Profiles of N-Desmethyl Metabolite in Healthy
 Subjects Receiving Paroxetine and MK-0462 or Placebo and MK-0462

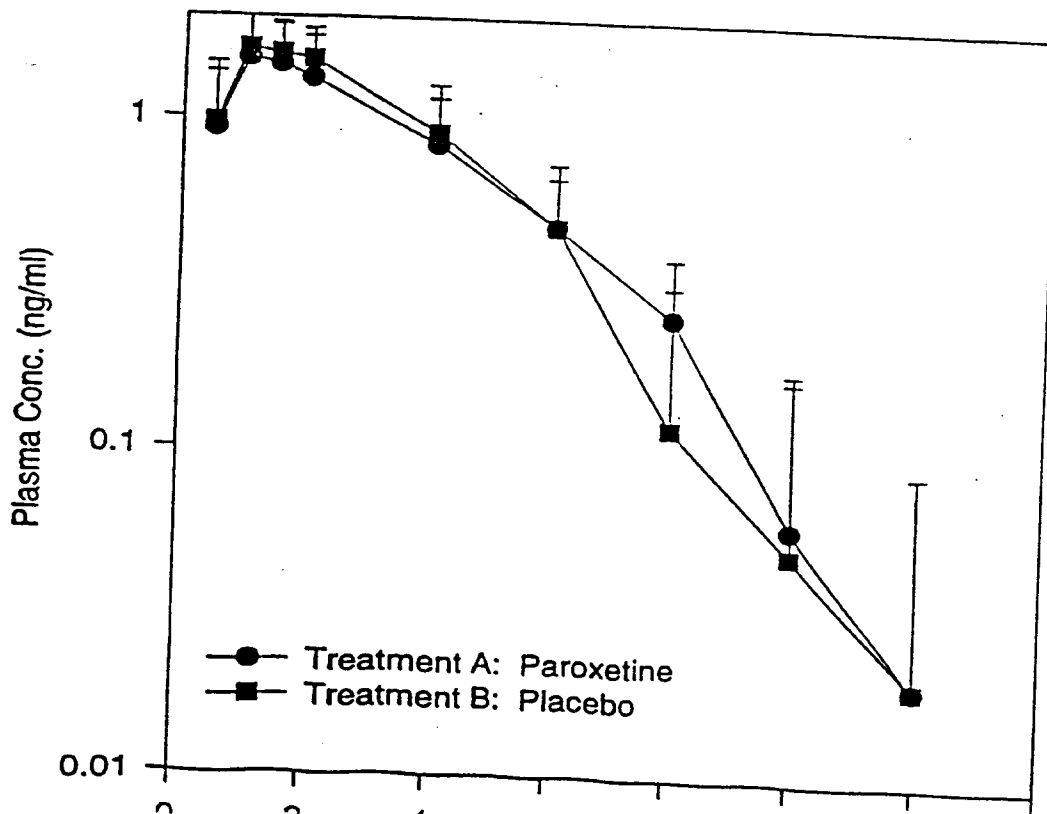
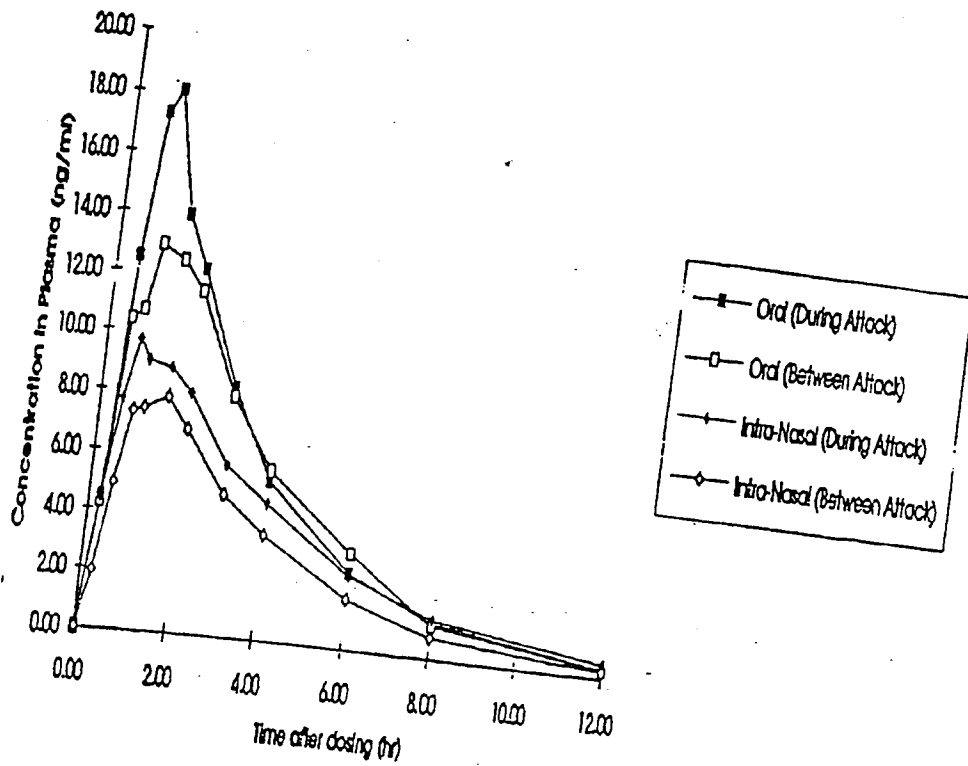


Figure 30.

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Mean Plasma Concentration Profile of MK-0462 After a 5-mg Dose



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Table f. Individual and Mean $AUC_{0-\infty}$, $t_{1/2}$, C_{max} and T_{max} for L-705,126 in Healthy Volunteers Receiving a Single Oral Dose of 5, 10, 20, 40, 60 or 80 mg of L-705,126

Dose (mg)	Subj. No.	$AUC_{0-\infty}$ (ng·hr/ml)	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)
5	009				
	010				
	011				
	012				
	014				
	015				
Mean ± S.D.		17.4 ± 3.6	1.36 ^a	7.82 ± 2.92	1.2 ± 1.0

Dose (mg)	Subj. No.	$AUC_{0-\infty}$ (ng·hr/ml)	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)
10	001				
	002				
	003				
	005				
	107				
	008				
	Mean ± S.D.		49.6 ± 11.7	2.02 ^a	19.8 ± 6.6

Dose (mg)	Subj. No.	$AUC_{0-\infty}$ (ng·hr/ml)	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)
20	009				
	010				
	012				
	013				
	014				
	016				
	Mean ± S.D.		101 ± 12	1.88 ^a	39.4 ± 15.7

Dose (mg)	Subj. No.	$AUC_{0-\infty}$ (ng·hr/ml)	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)
40	001				
	002				
	004				
	005				
	006				
	107				
Mean ± S.D.		265 ± 95	2.24 ^a	90.8 ± 47.0	1.5 ± 1.2

Dose (mg)	Subj. No.	$AUC_{0-\infty}$ (ng·hr/ml)	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)
60	013				
	014				
	015				
	016				
Mean ± S.D.		394 ± 28	2.06 ^a	89.6 ± 16.3	2.1 ± 1.6

Dose (mg)	Subj. No.	$AUC_{0-\infty}$ (ng·hr/ml)	$t_{1/2}$ (hr)	C_{max} (ng/ml)	T_{max} (hr)
80	011				

Table 3a Summary of Individual and Mean (\pm S.D., n = 16) Pharmacokinetic Parameters of Sumatriptan in Healthy Volunteers Receiving a Single Oral Dose of 100 mg of Sumatriptan

Subject Number	AUC _{0-∞} (ng·hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)
001				
002				
003				
004				
005				
006				
107				
008				
009				
010				
011				
012				
013				
014				
015				
016				
Mean	186	47.4	2.5	2.33*
S.D.	35	14.7	1.0	--
Median	--	--	3	--
Range	--	--	1-4	--

*Harmonic mean.

Table 9.

Individual and Mean Renal Clearance of L-705,126 in Healthy Volunteers Receiving A Single Oral Dose of 5, 10, 20, 40, 60 or 80 mg of L-705,126

Dose (mg)	Subj. No.	CL _r (ml/min)
5	009	
	010	
	011	
	012	
	014	
	015	
Mean ± S.D.		386 ± 40

Dose (mg)	Subj. No.	CL _r (ml/min)
10	001	
	002	
	003	
	005	
	107	
	008	
Mean ± S.D.		414 ± 86

Dose (mg)	Subj. No.	CL _r (ml/min)
20	009	
	010	
	012	
	013	
	014	
	016	
Mean ± S.D.		363 ± 58

Dose (mg)	Subj. No.	CL _r (ml/min)
40	001	
	002	
	004	
	005	
	006	
	107	
Mean ± S.D.		453 ± 98

Dose (mg)	Subj. No.	CL _r (ml/min)
60	013	
	014	
	015	
	016	
Mean ± S.D.		332 ± 77

Dose (mg)	Subj. No.	CL _r (ml/min)
80	011	371

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 Table 3 Unadjusted Area Under the Plasma Concentration-time Curve (AUC) for MK-462 Following I.V. Doses of MK-462

Subj. No.	AUC (ng-hr/ml)				
	10 µg/kg	20 µg/kg	40 µg/kg	60 µg/kg	90 µg/kg
1					
3					
4					
105					
7					
8					
10					
Mean ± SD	10.2 + 1.9	19.5 ± 4.6	35.2 ± 7.9	58.0 ± 15.0	138.4 ± 20.1

4
 Table 4 Pharmacokinetic Parameters for MK-462 Following Separate I.V. Infusion at 10-90 µg/kg

Dose (µg/kg)	Subj. No.	CL (ml/min)	V _{ss} (l)	t _{1/2} (hr)	MRT (hr)
10	1	1234			
	3	1726			
	4	1162			
	105	1078			
	7	1279			
	Mean S.D.	1296 252	154 34	1.9 0.5	2.0 0.6
20	1	1020			
	3	1319			
	4	1341			
	105	1327			
	7	1455			
	8	1546			
Mean S.D.	1335 178	117 27	1.7 0.4	1.5 0.5	
40	1	1162			
	3	1958			
	4	1567			
	105	1198			
	7	1780			
	8	1307			
Mean S.D.	1495 327	157 41	1.8 0.3	1.8 0.2	
60	1	1034			
	3	1617			
	4	1197			
	105	1135			
	7	1729			
	8	1468			
Mean S.D.	1363 282	134 26	1.0 0.3	1.6 0.1	
90	3	836.7			
	4	754.7			
	105	650.1			
	7	974.4			
	8	687.2			
	10	940.9			
Mean S.D.	807.3 133.1	91.6 27.4	2.5 0.7	1.9 0.5	

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Table 5

Geometric Mean AUCs and Geometric Mean Ratio AUCs for Intravenous Doses of MK-0462 10 µg/kg to 90 µg/kg

Dose (µg/kg)	Dose-Adjusted Geometric Mean AUC (ng·hr/mL)	Geometric Mean Ratio AUC (90% Confidence Interval)				
		10 µg/kg	20 µg/kg	40 µg/kg	60 µg/kg	90 µg/kg
10	12.58	—	—	—	—	—
20	12.17	0.97 (.85, 1.10)	—	—	—	—
40	11.00	—	0.90 (0.80, 1.02)	—	—	—
60	12.03	—	—	1.09 (0.97, 1.23)	—	—
90	21.70	—	—	—	1.80 (1.59, 2.04)	—

Table 6

Table 6 Individual and Mean Values of Pharmacokinetic Parameters of MK-462 in Subjects Receiving a 40-mg Tablet of MK-462 Without Breakfast

Subject No.	AUC (ng·hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)
1				
2				
3				
4				
105				
6				
7				
8				
9				
10				
11				
12				
Mean	330	76.8	1.6	1.8 ^a 1.9
S.D.	54	32.4	1.2	0.3

Table 7

Table 7 Individual and Mean Values of Pharmacokinetic Parameters of MK-462 in Subjects Receiving a 40-mg Tablet of MK-462 With Breakfast

Subject No.	AUC (ng·hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)
1				
2				
3				
4				
105				
6				
7				
8				
9				
10				
11				
12				
Mean	397	72.3	2.9	1.9 ^a 2.0
				0.6

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Table 8

Individual and Mean (\pm S.D., N = 12) Values of AUC (ng·hr/ml) of MK-462 in Healthy Males Receiving Orally 2.5-15 mg and Intravenously 4 mg of MK-462

Subject #	AUC _{2.5po} ^a	AUC _{5po}	AUC _{10po}	AUC _{15po}	AUC _{iv}
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	16.0	32.8	72.0	127	67.8
S.D.	7.0	8.9	22.2	45	15.7

Table 9

Individual and Mean (\pm S.D., N = 12) Values of AUC (ng·hr/ml) of MK-462 in Healthy Females Receiving Orally 2.5-15 mg and Intravenously 4 mg of MK-462

Subject #	AUC _{2.5po} ^a	AUC _{5po}	AUC _{10po}	AUC _{15po}	AUC _{iv}
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
Mean	18.7	41.7	96.7	161	84.0
S.D.	5.1	11.6	28.0	42	17.3

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^a Subscript for AUC denotes mg of dose administered and the route of administration.

Table 10

Individual and Mean (\pm S.D., N = 12) C_{max} of MK-462 in Healthy Males

Subject #	C_{max} (ng/ml)			
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	6.2	12.7	28.6	44.8
S.D.	2.8	4.8	13.5	17.8

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Table 11.

Individual and Mean (\pm S.D., N = 12) C_{max} of MK-462 in Healthy Females

Subject #	C_{max} (ng/ml)			
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
Mean	6.1	13.2	32.1	54.0
S.D.	1.9	3.7	11.9	18.7

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Table 12/

Individual and Mean (\pm S.D., N = 12) T_{max} of MK-462 in Healthy Males

Subject #	T_{max} (hr)			
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	0.77	0.73	0.66	0.88
S.D.	0.50	0.31	0.23	0.42

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Table 13

Individual and Mean (\pm S.D., N = 12) T_{max} of MK-462 in Healthy Females

Subject #	T_{max} (hr)			
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
Mean	0.81	0.94	0.73	0.96
S.D.	0.28	0.41	0.20	0.55

Table 14

Individual and Mean (\pm S.D., N = 12) Values of Apparent $t_{1/2}$ and $t_{1/2}$, respectively, of MK-462 in Healthy Males Receiving Orally 2.5-15 mg and Intravenously 4 mg of MK-462

Subject #	Apparent $t_{1/2}$ (hr)				$t_{1/2}$ (hr)
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.	4 mg i.v.
1	3.4				
2	5.1				
3	4.2				
4	1.3				
5	1.7				
6	1.2				
7	2.9				
8	1.7				
9	1.7				
10	2.2				
11	2.6				
12	2.5				
Harmonic Mean	2.1	2.2	2.4	2.4	2.9

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Table 15

Individual and Mean (\pm S.D., N = 12) Values of Apparent $t_{1/2}$ of MK-462 in Healthy Females Receiving Orally 2.5-15 mg and Intravenously 4 mg of MK-462

Subject #	Apparent $t_{1/2}$ (hr)				
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.	4 mg i.v.
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
Harmonic Mean	2.2	2.4	2.6	2.4	2.4

Table 16

Individual and Mean (\pm S.D., N = 12) Values of Pharmacokinetic Parameters of MK-462 in Healthy Males

Subject #	CL (ml/min)	V _d (l)	MRT (hr)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	1042	141	2.3
S.D.	281	31	0.5

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Table 17.

Individual and Mean (\pm S.D., N = 12) Values of Apparent Pharmacokinetic Parameters of MK-462 in Healthy Females

Subject #	CL (ml/min)	V _d (l)	MRT (hr)
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Mean	821	102	2.1
S.D.	148	29	0.5

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Table 18

Individual and Mean (\pm S.D., N = 12) Values of Percentage of Dose Excreted in Urine as MK-462 (U_e) Following Intravenous or Oral Administration to Healthy Males

Subject #	U_e (% Dose)				
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.	4 mg i.v.
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	7.6	13.0	11.9	13.2	23.4
S.D.	2.4	4.7	6.4	4.7	7.5

Table 19

Individual and Mean (\pm S.D., N = 12) Values of Percentage of Dose Excreted in Urine as MK-462 (U_e) Following Intravenous or Oral Administration to Healthy Females

Subject #	U_e (% Dose)				
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.	4 mg i.v.
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
Mean	7.9	12.1	13.5	13.8	20.8
S.D.	2.0	3.5	6.9	3.2	2.9

- * Value was not included in the calculation of mean and S.D. because of unusually low urinary excretion of MK-462.
- * Value was not included in the calculation of mean and S.D. because no urine volume was recovered for 12-24 hr urine.

Table 20

Individual and Mean Values of Renal Clearance of MK-462 in Healthy Males

Subject #	CL _r (ml/min)				
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o. ^b	4 mg i.v.
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	225	340	295	271	225
S.D.	85	122	121	43	35

Table 21

Individual and Mean Values of Apparent Renal Clearance of MK-462 in Healthy Females

Subject #	Apparent CL _r (ml/min)				
	2.5 mg p.o.	5 mg p.o.	10 mg p.o.	15 mg p.o.	4 mg i.v.
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
Mean	179	244	242	223	174
S.D.	27	54	135	59	28

^a Value was not included in the calculation of mean and S.D. because of unusually low urinary excretion of MK-462.

^b Value was not included in the calculation of mean and S.D. because no urine volume was recorded for 12-24 hr urine.

Table 22 Summary Statistics for Dose-Adjusted (to 2.5 mg) AUC_{0-∞} (ng•hr/mL)

Treatment	N	Geometric Mean	Median	Between-Subject SD	Within-Subject CV	p-Values				
						Overall	2.5 vs	5 vs	10 vs	15 vs
Males										
2.5 mg	12	14.3	16.7	9.1	0.172	0.001		0.174	0.017	<0.001
5.0 mg	12	15.8	16.3	5.0					0.265	0.003
10.0 mg	12	17.1	18.7	6.5						0.043
15.0 mg	12	19.8	20.2	8.9						
Females										
2.5 mg	12	18.0	18.2	5.8	0.110	<0.001		0.018	<0.001	<0.001
5.0 mg	12	20.2	20.0	5.9					0.004	0.000
10.0 mg	12	23.2	24.2	7.6						0.015
15.0 mg	12	26.1	26.2	7.0						

Table 22a ~~Table 22a~~ 90% Confidence Intervals for Dose-Adjusted (to 2.5 mg) AUC_{0-∞} (ng•hr/mL) Geometric Mean Ratio in Relation to 2.5-mg Treatment

Treatment	N	Geometric Mean	Geometric Mean Ratio	90% CI for Geometric Mean Ratio	Within-Subject SD
Males					
2.5 mg	12	14.3	.	(. . .)	2.92
5.0 mg	12	15.8	1.10	(0.98, 1.24)	.
10.0 mg	12	17.1	1.19	(1.06, 1.34)	.
15.0 mg	12	19.8	1.38	(1.23, 1.56)	.
Females					
2.5 mg	12	18.0	.	(. . .)	2.41
5.0 mg	12	20.2	1.12	(1.04, 1.21)	.
10.0 mg	12	23.2	1.29	(1.19, 1.39)	.
15.0 mg	12	26.1	1.45	(1.34, 1.56)	.

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Table 22b ~~Table 22b~~ Summary Statistics for Dose-Adjusted (to 2.5 mg) AUC_{0-∞} (ng•hr/mL) Male Versus Female Comparison

Treatment	N	Male ^a	Female ^a	Pooled Between-Subject SD ^b	Between-Sex p-Value	Overall-Sex p-Value
2.5 mg	12	14.3	18.0	7.8	0.201	0.060
5.0 mg	12	15.8	20.2	5.5	0.050	.
10.0 mg	12	17.1	23.2	7.1	0.032	.
15.0 mg	12	19.8	26.1	8.3	0.058	.

^a Geometric mean
^b Back-transformed standard deviation from log transformation

Table 22c ~~Table 22b~~ Summary Statistics for Dose-Adjusted (to 2.5 mg) C_{max} (ng/mL)

Treatment	N	Geometric Mean	Median	Between-Subject SD	Within-Subject CV (%)	p-Values				
						Over-all	2.5 vs	5 vs	10 vs	15 vs
Males										
2.5 mg	12	5.7	5.7	2.9	24.3	0.192		0.658	0.185	0.050
5.0 mg	12	6.0	5.9	2.4						
10.0 mg	12	6.5	6.3	3.3						
15.0 mg	12	7.0	7.5	3.0						
Females										
2.5 mg	12	5.8	5.8	2.0	19.2	<0.001		0.269	0.002	<0.001
5.0 mg	12	6.3	6.2	1.9						
10.0 mg	12	7.5	7.1	3.1						
15.0 mg	12	8.5	8.5	3.2						

Table ~~22a~~ 22a.

90% Confidence Intervals for Dose-Adjusted (to 2.5 mg) C_{max} (ng/mL) Geometric Mean Ratio in Relation to 2.5-mg Treatment

Treatment	N	Geometric Mean	Geometric Mean Ratio	90% CI for Geometric Mean Ratio	Within-Subject SD
Males					
2.5 mg	12	5.7		(. . .)	1.59
5.0 mg	12	6.0	1.05	(0.88, 1.24)	
10.0 mg	12	6.5	1.14	(0.97, 1.35)	
15.0 mg	12	7.0	1.22	(1.03, 1.45)	
Females					
2.5 mg	12	5.8		(. . .)	1.38
5.0 mg	12	6.3	1.09	(0.96, 1.25)	
10.0 mg	12	7.5	1.30	(1.14, 1.48)	
15.0 mg	12	8.5	1.47	(1.29, 1.68)	

Table ~~22e~~ 22e.

Summary Statistics for T_{max} (Hours)

Treatment	N	Median	Mean	Between-Subject SD	p-Values				
					Over All	2.5 vs	5 vs	10 vs	15 vs
Males									
2.5 mg	12	0.50	0.77	0.51	0.172		0.675	0.930	0.061
5.0 mg	12	0.63	0.73	0.31					
10.0 mg	12	0.50	0.66	0.23					
15.0 mg	12	0.88	0.88	0.42					
Females									
2.5 mg	12	0.75	0.81	0.28	0.526		0.406	0.513	0.980
5.0 mg	12	0.75	0.94	0.41					
10.0 mg	12	0.75	0.73	0.20					
15.0 mg	12	0.75	0.96	0.55					

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Table ~~22f~~^{22f} Summary Statistics for Terminal Half-Life (Hours)

Treatment	N	Harmonic Mean	Median	Jack-knife SD	p-Values				
					Over-all	2.5 vs	5 vs	10 vs	15 vs
Males									
2.5 mg	12	2.11	2.34	0.92	0.531		0.609	0.209	0.230
5.0 mg	12	2.21	2.24	0.61			0.450	0.485	
10.0 mg	12	2.36	2.65	0.97				0.954	
15.0 mg	12	2.35	2.70	0.75					
Females									
2.5 mg	12	2.22	2.20	0.72	0.376		0.357	0.089	0.242
5.0 mg	12	2.40	2.25	0.66			0.420	0.797	
10.0 mg	12	2.57	2.50	0.35				0.581	
15.0 mg	12	2.45	2.50	0.27					

Table ~~22g~~^{22g} Summary Statistics for Percent of Oral Dose Excreted in the Urine

Treatment	N	Median	Mean	Between-Subject SD	p-Values				
					Over-all	2.5 vs	5 vs	10 vs	15 vs
Males									
2.5 mg	12	7.43	7.61	2.44	0.018		0.002	0.073	0.022
5.0 mg	12	11.75	12.97	4.73				0.160	0.384
10.0 mg	12	9.65	11.06	6.80					0.584
15.0 mg	12	12.03	11.84	5.45					
Females									
2.5 mg	12	7.76	7.87	1.98	<0.001		0.002	<0.001	<0.001
5.0 mg	12	12.09	11.57	3.78				0.359	0.044
10.0 mg	12	12.65	13.47	6.89					0.251
15.0 mg	12	14.55	13.82	3.21					

Table ~~22h~~^{22h} Summary Statistics for Renal Clearance of MK-0462 (mL/min)

Treatment	N	Median	Mean	Between-Subject SD	p-Value				
					Over-all	2.5 vs	5 vs	10 vs	15 vs
Males									
2.5 mg	12	193.80	224.80	85.05	0.110		0.016	0.237	0.321
5.0 mg	12	311.35	339.77	121.51				0.192	0.136
10.0 mg	12	259.95	272.44	138.49					0.847
15.0 mg	12	270.15	241.91	81.57					

Table ~~22i~~²²ⁱ Summary Statistics for Systemic Clearance (mL/min)

Gender	N	Geometric Mean	Median	Between-Subject SD	Pooled-Subject SD	Between-Sex p-Value
Cl (mL/min)						
Males	12	1010.8	965.1	264.6	209.1	0.022
Females	12	807.8	829.9	159.8		

Table 23

Individual and Mean (\pm S.D., N=8) Values of AUC (ng \cdot hr/ml) for MK-0462 in Healthy Females Receiving Intravenous Doses of 0.5 - 5.0 mg

Subject #	AUC (ng \cdot hr/ml)			
	AUC _{0.5} ^a	AUC _{1.0}	AUC _{2.5}	AUC _{5.0}
001				
002				
003				
004				
005				
106				
107				
008				
Mean	9.0	18.7	49.1	105
S.D.	1.1	2.1	5.7	8.0

^a Subscript for AUC denotes mg of IV dose administered

Table 24

Individual and Mean (\pm S.D., N=8) Values of Plasma Clearance (CL) for MK-0462 in Healthy Females Receiving Intravenous Doses of 0.5 - 5.0 mg

Subject #	CL (ml/min)			
	0.5 mg	1.0 mg	2.5 mg	5.0 mg
001				
002				
003				
004				
005				
106				
107				
008				
Mean	940.7	899.9	858.9	796.6
S.D.	132.9	94.7	101.4	62.0

Table 25. Individual and Mean (\pm S.D., N=8) Values of Plasma Terminal Half-Life ($t_{1/2}$) for of MK-0462 in Healthy Females Receiving Intravenous Doses of 0.5 - 5.0 mg

Subject #	$t_{1/2}$ (hr)			
	0.5 mg	1.0 mg	2.5 mg	5.0 mg
001				
002				
003				
004				
005				
106				
107				
008				
Mean ^a	1.5	1.9	2.2	2.1
^a Harmonic mean				

Table 26. Individual and Mean (\pm S.D., N=8) Values of V_z for MK-0462 in Healthy Females Receiving Intravenous Doses of 0.5 - 5.0 mg

Subject #	V_z (l)			
	0.5 mg	1.0 mg	2.5 mg	5.0 mg
001				
002				
003				
004				
005				
106				
107				
008				
Mean	90.7	106	103	90.7
S.D.	20.0	25.2	11.9	13.0

Table 27. Individual and Mean (\pm S.D., N=8) Values of Renal Clearance (CL_r) of MK-0462 in Healthy Females Receiving Intravenous Doses of 0.5 - 5.0 mg

Subject #	CL_r (ml/min)			
	0.5 mg	1.0 mg	2.5 mg	5.0 mg
001				
002				
003				
004				
005				
106				
107				
008				
Mean	129.6	187.3	239.2	275.4
S.D.	50.5	76.9	76.3	70.9

* Value was not included in the calculation of mean and S.D. because of unusually high urinary excretion of MK-0462

Table 28. Individual and Mean (\pm S.D., N=8) Values of Percentage of Dose Excreted (U_e) in Urine as MK-0462 Following Intravenous Administration to Healthy Females

Subject #	U_e (% Dose)			
	0.5 mg	1.0 mg	2.5 mg	5.0 mg
001				
002				
003				
004				
005				
106				
107				
008				
Mean	14.5	20.4	28.0	34.6
S.D.	5.6	6.6	9.2	8.8

* Value was not included in the calculation of mean and S.D. because of unusually high urinary excretion of MK-0462

Table 29

~~Table 29A~~

Individual and Mean (\pm S.D., N = 5) Values of AUC of MK-462 in Healthy Males Receiving Three 10-mg Doses of MK-462 (q4h) per Day for Four Days

Subj. No.	AUC ₀₋₄ ¹	AUC ₀₋₂₄ ¹	AUC ₀₋₄ ²	AUC ₀₋₄ ³	AUC ₀₋₄ ⁴	AUC ₀₋₂₄ ⁴
1						
7						
108						
9						
10						
Mean	35.0	172	174	45.5	38.7	175
S.D.	20.6	106	106	23.5	17.0	73

~~Table 29B~~

Individual and Mean (\pm S.D., N = 4) Values of AUC of MK-462 in Healthy Females Receiving Three 10-mg Doses of MK-462 (q4h) per Day for Four Days

Subj. No.	AUC ₀₋₄ ¹	AUC ₀₋₂₄ ¹	AUC ₀₋₄ ²	AUC ₀₋₄ ³	AUC ₀₋₄ ⁴	AUC ₀₋₂₄ ⁴
4						
5						
6						
11						
Mean	49.8	211	214	49.7	50.5	215
S.D.	9.3	52	50	12.8	5.0	49

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Table 30

~~Table 30~~

Individual and Mean (\pm S.D., N = 5) Values of Pharmacokinetic Parameters of MK-462 in Healthy Males Receiving Three 10-mg Doses of MK-462 (q4h) per Day for Four Days

Subj. No.	Day 1			Day 4		
	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)
1						
7						
108						
9						
10						
Mean	23.4	6.4	2.3 3.3	25.6	5.1	2.8 ^{3.2}
S.D.	17.2	2.1	0.5	9.2	3.0	-1.0

*Harmonic mean.

~~Table 31~~

Individual and Mean (\pm S.D., N = 4) Values of Pharmacokinetic Parameters of MK-462 in Healthy Females Receiving Three 10-mg Doses of MK-462 (q4h) per Day for Four Days

Subj. No.	Day 1			Day 4		
	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)
4						
5						
6						
11						
Mean	24.4	6.9	3.2 ^{3.7}	30.86	4.8	2.9 ^{3.0}
S.D.	7.2	4.2	-1.0	12.66	2.6	-0.5

*Harmonic mean.

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