of rizatriptan. The absolute bioavailability of rizatriptan, 10 mg, is approximately 45%, though absorption is nearly complete , indicating a substantial first-pass metabolism.

***In vitro* Metabolism Studies**

In contrast to the *in vivo* studies, *in vitro* metabolism of rizatriptan in rat liver, lung and kidney microsomes, and dog and human liver microsomes was limited; only the N-oxide and/or indoleacetic acid (IAA) metabolites were detected in significant quantities:

		Metabolites				
Species	**Prep**	UK-1	6-hydroxy	N^{10}-oxide	IAA	Total
Rat	Liver, control	0.5	-	1.4	-	1.9
	" , PB	2.4	-	1.9	1.1	5.4
	" , 3-MC	0.9	-	1.2	1.1	3.2
	Lung	-	-	8.8	0.8	9.6
	Kidney	-	-	18.3	0.6	18.9
Dog	Liver	-	1.7	12.7	0.9	15.3
Human (n=3)	Liver	-	-	-	7.6	7.6

An *in vitro* study with human liver slices confirmed the results demonstrating that the IAA was the only identifiable human *in vitro* metabolite of rizatriptan (Figure 16). However, N-desmethyl rizatriptan was not detected *in vitro*, although it was found to be of the parent *in vivo*.

In vitro studies were conducted to determine the enzymes responsible for rizatriptan metabolism in humans. In a study with liver S9 fractions, the oxidative deamination of rizatriptan to rizatriptan-IAA was determined to be catalyzed by MAO-A based on the ability of clorgyline to inhibit the reaction (MAO-B inhibitors were effective only at high concentrations; Figure 15). The reaction was independent of NADPH, and blocked by SKF525A and ketoconazole only at high concentrations, indicating a small or negligible role for the P_{450} system in this pathway. The indole ethyl alcohol metabolite of rizatriptan was also identified as a oxidative deamination product; its formation was favored (relative to the IAA) in the presence of NADPH.

A subsequent study on the deamination of rizatriptan and its N-mono- and di-desmethyl metabolites determined that the process favored the less substituted amines. Thus, the inability to detect the N-monodesmethyl metabolite in *in vitro* studies may have been due to its rapid deamination.

The inhibitory activity of rizatriptan versus several P450 isozymes (1A2, 2C9, 2C19, 2D6, 2E1, 3A4/5) was also evaluated *in vitro*. The results are summarized in the following table. The only effect of rizatriptan was WEAK competitive inhibition of 2D6

Metabolic Interactions

Because of the importance of MAO-A in the biotransformation of rizatriptan, clinical studies addressed the potential interaction of rizatriptan with MAO inhibitors. To summarize briefly, the MAO-A inhibitor moclobemide (150 mg, t.i.d.) did not alter the qualitative profile of rizatriptan metabolism, but markedly decreased the formation of the IAA metabolite and increased the exposure to rizatriptan (2.2-fold) and the N-monodesmethyl metabolite (5-fold). These studies suggest that an important drug interaction may exist between rizatriptan and inhibitors of MAO, particularly of the MAO-A isozyme.

The potential influence of β-blockers on the oxidative deamination of rizatriptan was evaluated *in vitro*. Propranolol appeared to have significant inhibitory effects (Figures 19 and 20), whereas the remaining compounds tested had only slight (metoprolol) or negligible effects (nadolol, atenolol, timolol).

Pharmacodynamics of Metabolites.

The radioligand binding activity of several rizatriptan metabolites at human 5-HT receptor subtypes was determined. There were no unique 5-HT binding activities of any of the metabolites. Only the minor N-desmethyl metabolite was similar to rizatriptan in its 5-HT_{1D} and $_{1A}$ affinities. The major metabolite (rizatriptan-IAA; L-749,335) was devoid of 5-HT receptor affinity.

Distribution:

Plasma Protein Binding : Test range =

Species	% Bound
rat	18
mouse	19
rabbit	27
dog	12
human	14

Partitioning into Erythrocytes:

Rizatriptan partitioned into rat, dog and human erythrocytes (
suggesting a possible slower clearance from blood than plasma.

SPECIAL POPULATION STUDIES:

TITLE: An Open-Label, Two-Period, Fixed Sequence Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Rizatriptan After a Single Oral Dose and a Single Intravenous Dose in Patients With Defined Degrees of Renal Insufficiency (Protocol-027, volume 46, Page 6285).

The objectives of the study were to: (1) investigate whether the pharmacokinetics of rizatriptan are altered to a clinically significant degree by various levels of renal insufficiency relative to a historical control group with normal renal function; (2) investigate the clearance of rizatriptan by hemodialysis; (3) investigate the effects of renal insufficiency on the apparent bioavailability of rizatriptan; (4) investigate the relationship between creatinine clearance, systemic and renal clearance of rizatriptan; (5) investigate the safety and tolerability of rizatriptan in patients with defined degrees of renal insufficiency; and (6) determine whether a reduction is needed in dose or dosage regimen based on a patient's renal function, and develop guidelines for such dose adjustments if necessary.

Pharmacokinetics of rizatriptan (5-mg oral solution and 2-mg I.V. dose infused over 30 minutes) in 18 patients (11M; 7F) with defined degrees of renal insufficiency (age range less than 70 years) was determined in the following 3 groups based on creatinine clearance:
Group I : 30 to 60 mL/min/1.73 m^2;(N=7); Group II: 10 to 29 mL/min/1.73 m^2;(N=5);
Group III: < 10 mL/min (hemodialysis)/1.73 m^2 ;(N=6).
All patients received single doses of rizatriptan 5-mg oral solution in the first period and rizatriptan 2 mg I.V. in the second period. The two doses were separated by at least 2 weeks. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles are presented in Figure 21 and the pharmacokinetic data for individual patients with different degrees of renal insufficiency are provided in Table 41. The mean (sd) pharmacokinetic parameters for rizatriptan in patients with different degrees of renal insufficiency compared to a historic control group (protocol 16) following oral administration are summarized in the following Table.

Parameter	Renal Insufficiency Patients			Control Group (N=16)		
	Group I (n=7)	Group II (n=5)	Group III (n=6)	Male (n=12)	Female (n=12)	Combined
$AUC_{0-\infty}$ (ng.hr/mL)	43.8 ± 18.1	43.9 ± 21.5	51.9 ± 14.3	32.8 ± 8.9	41.7 ± 11.6	37.3 ± 11.1
Cmax (ng/mL)	12.7 ± 3.0	11.4 ± 4.9	12.5 ± 5.7	12.7 ± 4.8	13.2 ± 3.7	12.9 ± 4.2
Tmax (hr)	0.9 ± 0.3	0.8 ± 0.3	0.8 ± 0.6	0.7 ± 0.3	0.9 ± 0.4	0.8 ± 0.4
$T_{1/2}$ (hr)	2.2 ± 0.5	2.2 ± 0.7	2.7 ± 0.7	2.4 ± 0.7	2.6 ± 0.9	2.5 ± 0.8
Clr (mL/min)	110.9±35.9	47.0 ± 11.0	—	339.8±121.5	244 ± 54.0	294 ± 105
Ue (%)	5.5 ± 2.0	2.5 ± 1.4	—	13.0 ± 4.7	12.1 ± 3.5	12.5 ± 4.1
F	0.56	0.53	0.56	—	—	0.38

Geometric Mean AUC (ng·hr/mL) for Renally Impaired Patients Versus Normal Subjects (Protocol 016) for Rizatriptan Following a 5-mg Oral Dose

	Geometric Mean (90% CI)	Geometric Mean Ratio (Abnormal/Normal) (90% CI)	P-Value
Normal (n=24)	35.70 (31.71, 40.20)		
Group I (n=7)	41.24 (33.09, 51.38)	1.16 (0.90, 1.48)	> 0.250
Group II (n=5)	40.39 (31.13, 52.41)	1.13 (0.85, 1.51)	> 0.250
Group III (n=6)	51.39 (40.46, 65.27)	1.44 (1.10, 1.88)	0.027

Mean (±SD) Pharmacokinetic Parameters for rizatriptan in patients with varying degrees of renal insufficiency following a 2-mg intravenous dose.

Parameter	Group I (N=7)	Group II (N=5)	Group III (N=6)
AUC, ng•h/mL	30 (7)	31 (8)	39 (10)
CL_p†, mL/min	1132	1149	827
V_{ss}, L	69 (17)	63 (35)	67 (33)
$t_{½}$§, h	2.0	1.8	2.5
Urinary excretion, % dose	9.9 (3.8)	4.4‖ (2.2)	---#
CL_r, mL/min	113 (44)	47‖ (16)	---#

Geometric mean Cmax (ng /mL) for renally impaired patients vs normal subjects (Protocol 016) for rizatriptan following a 5-mg oral dose.

	Geometric Mean (90% CI)	Geometric Mean Ratio (Abnormal/Normal) (90% CI)	P-Value
Normal (n=24)	12.29 (10.92, 13.83)		
Group I (n=7)	12.26 (9.85, 15.27)	1.00 (0.78, 1.28)	>0.250
Group II (n=5)	10.53 (8.13, 13.66)	0.86 (0.64, 1.14)	>0.250
Group III (n=6)	11.48 (9.04, 14.56)	0.93 (0.72, 1.22)	>0.250

Geometric Mean Bioavailability for Renally Impaired Patients Versus Normal Subjects (Protocol 016) for Rizatriptan

	Geometric Mean (90% CI)	Geometric Mean Ratio (Abnormal/Normal) (90% CI)	P-Value
Normal (n=12)	0.38 (0.33, 0.44)		
Group I (n=7)	0.56 (0.48, 0.64)	1.46 (1.19, 1.79)	<0.010
Group II (n=5)	0.53 (0.44, 0.63)	1.39 (1.11, 1.73)	0.019
Group III (n=6)	0.53 (0.46, 0.63)	1.40 (1.14, 1.72)	<0.010

Geometric Mean Systemic Clearance (mL/min) for Renally Impaired Patients Versus Normal Subjects (Protocol 042) for Rizatriptan Following a 2-mg I.V. Dose

	Geometric Mean (90% CI)	Geometric Mean Ratio (Abnormal/Normal) (90% CI)	P-Value
Normal (n=24)	1210.2 (1130.8, 1295.2)		
Group I (n=7)	1132.3 (997.3, 1285.5)	0.94 (0.81, 1.08)	>0.250
Group II (n=5)	1149.4 (987.6, 1337.7)	0.95 (0.80, 1.12)	>0.250
Group III (n=6)	827.1 (716.3, 955.1)	0.68 (0.58, 0.80)	<0.010

Mean renal clearance (mL/min) for renally impaired patients vs normal subjects (protocol 042) for rizatriptan following a 2-mg i.v. dose

	Mean	P-Value	
		vs. Normals	vs. Group II
Normal (n=24)	342.3		
Group I (n=7)	113.4	<0.01	0.158
Group II (n=4)	46.6	<0.01	

The above results suggest that in patients with renal insufficiency (creatinine clearance less than 60 mL/min), plasma concentrations (i.e., AUC) of rizatriptan are comparable to those in healthy subjects with normal renal function. However, in dialysis patients, plasma concentrations are slightly greater than in healthy subjects (AUC increased by 40%; 52 vs 37 ng.hr/mL) and may not have any clinical significance. Peak plasma concentrations (Cmax) of rizatriptan are similar in patients with all levels of renal insufficiency compared to healthy subjects. The bioavailability of rizatriptan is slightly greater in patients with renal insufficiency compared to historical controls. This difference may not be clinically significant. Systemic clearance of rizatriptan in patients with creatinine clearance less than 60 mL/min/1.73 m^2 does not differ from systemic clearance in healthy subjects. However, systemic clearance of rizatriptan is reduced significantly in dialysis patients, but may not be clinically significant. In patients with creatinine clearance less than 60 mL/min/1.73 m^2, the renal clearance of rizatriptan is reduced in proportion to reductions in creatinine clearance. Rizatriptan (5 mg p.o. and 2 mg, i.v.) is generally well tolerated in patients with all degrees of renal insufficiency.

SAFETY: All 18 patients were included in the assessment of safety and tolerability. Three patients reported clinical adverse experiences. One of these patients also reported laboratory adverse experiences. There were no serious adverse experiences and no patients died during the study. No patient discontinued the study due to an adverse experience.

In conclusion, renal impairment does not appear to alter the pharmacokinetics of rizatriptan except that the exposure (AUC) increased by about 40% in dialysis patients, but may not have clinical significance.

TITLE: An Open-Label Study to Determine the Influence of Hepatic Insufficiency on the Pharmacokinetics of Rizatriptan (Protocol-041, volume 57, page 13216).

The objectives of the study were to: PART 1: (1) determine the pharmacokinetic profiles of simultaneously administered 0.5 mg stable heavy-labeled isotope [triazole-$^{13}C_2$,$^{15}N_3$] rizatriptan solution intravenously infused over 50 minutes and a single 5-mg oral dose of rizatriptan in healthy male subjects; (2) determine the pharmacokinetic profiles of simultaneously administered

1.0 mg stable heavy-labeled isotope [triazole-$^{13}C_{2,15}N_3$] rizatriptan solution intravenously infused over 50 minutes and a single 5-mg oral dose of rizatriptan in healthy male subjects; PART 2: (1) investigate the pharmacokinetics and bioavailability of a single 5-mg oral dose of rizatriptan in patients with hepatic insufficiency; (2) determine the systemic clearance of a single 0.5-mg i.v. dose of rizatriptan in patients with hepatic insufficiency; and (3) assess the tolerability of a single 5-mg oral dose of rizatriptan in patients with hepatic insufficiency.

This was an open-label, two-part, single-period study in normal healthy male subjects (Part 1) and patients with mild-to-moderate hepatic insufficiency (Part 2; child-pugh's score (CPS); mild <6 CPS; Moderate >6 CPS).
PART 1: Three subjects received rizatriptan treatment provided as a single 5-mg tablet for oral administration and 0.5 mg stable heavy-labeled isotope [triazole-$^{13}C_{2,15}N_3$] rizatriptan solution for i.v. infusion over 50 minutes, both administered at the same time between 8 a.m. and 10 a.m. on the day of dosing. Three subjects received rizatriptan treatment provided as a single 5-mg tablet for oral administration and 1.0 mg stable heavy-labeled isotope [triazole-$^{13}C_{2,15}N_3$] rizatritpan solution for i.v. infusion over 50 minutes, both administered at the same time between 08:00 and 10:00 a.m. on the day of dosing.

PART 2: All 10 of the patients (6M; 4F) with hepatic insufficiency received rizatriptan treatment provided as a single 5-mg tablet for oral administration and 1.0 mg stable heavy-labeled isotope [triazole-$^{13}C_{2,15}N_3$] rizatriptan solution for i.v. infusion over 50 minutes, both administered at the same time between 8 a.m. and 10 a.m. on the day of dosing. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles are presented in Figure 22 and the pharmacokinetic data for individual patients with different degrees of hepatic insufficiency are provided in Tables 42 and 43. The mean (sd) pharmacokinetic parameters for rizatriptan in patients with different degrees of hepatic insufficiency compared to a historic control group (protocol 35) following oral administration are summarized in the following Table:

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Parameter	For Rizatritpan			For mono-N-desmethyl Metabolite of rizatriptan		
	Hepatic Insufficiency Patients		Healthy Subjects (n=16)	Hepatic Insufficiency Patients		Healthy Subjects (n=16)
	Mild (n=7)	Moderate (n=3)		Mild (n=7)	Moderate (n=3)	
$AUC_{0-\infty}$ (ng.hr/mL)	30.2 ± 9.5	42.3 ± 11.1	31.8 ± 6.3	3.1 ± 1.1	2.0 ± 0.3	4.6 ± 0.8
Cmax (ng/mL)	10.9 ± 2.2	14.1 ± 3.8	9.8 ± 2.4	0.9 ± 0.3	0.4 ± 0.2	1.5 ± 0.4
Tmax (hr)	1.1 ± 0.4	0.9 ± 0.5	0.9 ± 0.4	1.4 ± 0.5	1.4 ± 0.3	1.4 ± 0.6
$T_{1/2}$ (hr)	2.0 ± 0.7	2.3 ± 09	2.2 ± 0.4	2.1 ± 1.3	3.3 ± 2.2	1.6 ± 0.5
Clr (mL/min)	325± 114	352 ± 52	202 ± 58	213.5 ± 99.4	197.7 ± 46.6	150.7 ± 55.7
Ue (%)	11.6 ± 4.9	17.8 ± 5.0	7.7 ± 2.8	0.8 ± 0.3	0.4 ± 0.1	0.8 ± 0.3
F	0.44	0.69	0.41	——	—	---

From the above results, it can be concluded that $AUC_{0-\infty}$ and Cmax respectively, in moderately impaired hepatic group compared to control group, with a corresponding decrease in the metabolite concentrations. Further, a significant increase in renal clearance of rizatriptan was observed in both mild and moderate hepatic impaired group compared to control group. However, these observations could be the result of small sample size (n=3) in the moderate group.

The overall geometric means, geometric mean ratios, p-values, and 90% confidence intervals for bioavailability, $AUC_{0-\infty}$, Cmax , and systemic clearance for rizatriptan following a 5-mg oral dose and a 1-mg I.V. dose for patients with hepatic insufficiency vs. healthy subjects from other clinical pharmacology studies (Protocols 007, 013, 016, 032, 040, and 042) with rizatriptan are summarized in the table below:

	Patients With Hepatic Insufficiency		Healthy Subjects		Geometric Mean Ratio Hepatic/Healthy (90% C.I.)	p-Value
	N	Geometric Mean (90% C.I.)	N	Geometric Mean (90% C.I.)		
Bioavailability	10	0.50 (0.44, 0.57)	48	0.41 (0.38, 0.43)	1.24 (1.08, 1.42)	0.013
$AUC_{(0-\infty)}$ ng·hr/mL	10	33.2 (28.0, 39.3)	60	31.7 (29.6, 34.0)	1.05 (0.87, 1.25)	>0.250
C_{max} (ng/mL)	10	11.7 (9.7, 14.0)	60	10.6 (9.8, 11.4)	1.10 (0.90, 1.35)	>0.250
Systemic Clearance (mL/min)	10	1261.8 (1123.3, 1417.4)	74	1062.2 (1017.5, 1108.9)	1.19 1.05, 1.34)	0.023

Geometric means obtained using least squares estimation.

The medians for pharmacokinetic parameters ($AUC_{0-\infty}$, Cmax, and elimination rate constant) for the metabolite (L-706,248), and the AUC and Cmax ratios of metabolite to parent drug following a 5-mg oral dose of rizatriptan for patients with hepatic insufficiency vs. healthy subjects are summarized in the following Table.

Median (Min, Max) for Pharmacokinetic Parameters for L-706,248 Following a 5-mg Oral Dose of Rizatriptan for Patients With Hepatic Insufficiency vs. Healthy Subjects

Parameter	Patients With Hepatic Insufficiency N=10	Healthy Subjects N=40	p-Value
$AUC_{(0-\infty)}$ (ng·hr/mL)	2.50	8.44	<0.010
C_{max} (ng/mL)	0.75	2.10	0.033
$AUC_{(0-\infty)}$ Ratio (L-706,248/MK-0462)	0.08	0.137	<0.010
C_{max} Ratio (L-706,248/MK-0462)	0.72	0.122	<0.010
Half-Life (hr)	1.8	1.8	
Elimination Rate (hr^{-1})	0.420	0.379	>0.250

Harmonic Mean - Half-life.

The results indicate that bioavailability and systemic clearance are statistically significantly different in hepatically impaired (pooled data of mild and moderate) compared to control group, but may not be clinically significant. Metabolite concentrations decreased to a significant extent in hepatically impaired compared to control group, but may not have clinical significance.

SAFETY: There were no serious clinical, laboratory, or other adverse experiences during the study. No subjects in Part 1 of the study and no patients with hepatic insufficiency in Part 2 of the study discontinued from the study.

In conclusion, the systemic clearance of rizatriptan is altered to a statistically significant extent in patients with mild-to-moderate hepatic insufficiency relative to a control group of healthy subjects (p=0.02), but may not have clinical relevance. Patients with moderate hepatic insufficiency had a greater bioavailability than patients with mild hepatic insufficiency. Plasma concentrations of mono-N-desmethyl rizatriptan are reduced in patients with mild-to-moderate

hepatic insufficiency in comparison to concentrations in healthy subjects. However, these observations could be result of small sample size for moderate group (n=3). Single-dose oral administration of 5 mg rizatriptan in patients with mild-to-moderate hepatic insufficiency is well tolerated.

TITLE: A Double-Blind, Parallel, Randomized, Placebo-Controlled Single-Dose Study to Investigate the Pharmacokinetics and Safety of Rizatriptan in Healthy Elderly (Greater Than or Equal to 65 Years of Age) Subjects (Protocol-036, volume 52, page 10431).

The objectives of the study were to: (1) investigate the plasma concentrations of rizatriptan in elderly subjects (>65 years of age); (2) compare plasma concentration profiles of rizatriptan following administration of a 10-mg tablet in elderly (>65 years of age) with historical data from young subjects; and (3) assess the safety and tolerability of a single dose of rizatriptan in elderly subjects.

Single-dose of rizatriptan was given to 20 healthy elderly subjects (10M (Age: 65-77); 10F (Age: 65-75)). Each subject received a single oral dose of either 10 mg Rizatriptan (E-8484R) or matching placebo (E-8414). Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles for elderly females and males are presented in Figure 23 and the pharmacokinetic data for individual subjects are provided in Table 44. The mean (sd) pharmacokinetic parameters for rizatriptan in elderly subjects (age>65 yrs) compared to a control group (age< 45 yrs; protocol 35) following oral administration are summarized in the following Table:

Parameter	Healthy Elderly Subjects (N=16)	Healthy Young Subjects (N=16)
$AUC_{0-\infty}$ (ng.hr/mL)	79.6 ± 18.0	63.6 ± 12.6
Cmax (ng/mL)	24.9 ± 12.8	19.6 ± 4.9
Tmax (hr)	1.1 ± 0.6	0.9 ± 0.4
$T_{1/2}$ (hr)	1.8 ± 0.2	2.2 ± 0.4
Clr (mL/min)	194.6 ± 39.2	292 ± 58
Ue (%)	9.3 ± 2.5	12.5 ± 4.8

The results indicate that mean $AUC_{0-\infty}$ and Cmax are about in elderly subjects than the young subjects. Further, the sponsor compared the pharmacokinetic results from the healthy elderly subjects in this study to results from healthy young subjects in Protocols 013, 016, 019, and 033 also (Tables 40, 8-22i, 45, and 35, respectively) and found no significant difference between elderly and young subjects. The estimated geometric mean AUC for elderly subjects was 77.65 ng.hr/mL and for the comparator group of young subjects was 81.27 ng.hr/mL. The estimated geometric mean ratio of elderly to young AUC was 0.96, and the 90% confidence interval for the geometric mean ratio ranged from The estimated geometric mean Cmax for elderly subjects was 21.91 ng/mL and for the comparator group of young subjects was 24.73 ng/mL. The estimated geometric mean ratio of elderly to young Cmax was 0.89, and the 90% confidence interval for the geometric mean ratio ranged Thus, it can be concluded that plasma concentrations in the elderly healthy subjects are not significantly different from those observed in young healthy subjects.

Further, it was observed that there were no significant differences in the pharmacokinetic parameters between elderly males and females (Table 44).

SAFETY: There were no serious or drug-related adverse events in this study. One subject (AN 004) experienced a laboratory adverse event of hematuria. No subjects experienced a clinical adverse event and no subjects discontinued this study.

In conclusion, the $AUC_{0-\infty}$ and Cmax of rizatriptan are not altered to a clinically significant degree in the elderly compared to healthy young subjects. Renal clearance and urinary excretion tend to be lower in the elderly. Plasma concentrations of rizatriptan are similar in males and females in elderly. Single oral 10-mg doses of rizatriptan are well tolerated in elderly subjects.

RACE: The sponsor did not conduct a formal study to evaluate the effect of race on the pharmacokinetic differences of rizatriptan. However, a retrospective analysis of data from three studies (protocols 035, 040, and 043) which enrolled black and caucasian subjects who received single 10 mg doses of rizatriptan indicated no significant differences in the plasma concentrations of rizatriptan.

Parameter	Males		Females	
	Black (n=11)	Caucasian (n=17)	Black (n=10)	Caucasian (n=4)
AUC (ng.hr/mL)	58.6 ± 21.9	57.4 ± 13.2	64.9 ± 11.5	75.4 ± 14.2
Cmax (ng/mL)	20.3 ± 8.5	18.6 ± 5.3	19.9 ± 5.1	16.7 ± 5.3

The data suggests that there are no differences in the pharmacokinetics of rizatriptan between black males and females. However, AUC in caucasian females was observed to be higher by about 30% and this observation seem to be similar to other studies.

DRUG INTERACTION STUDIES:

TITLE: A double-blind, two-period, crossover study to investigate the effect of oral doses of rizatriptan 10 mg on oral contraceptive pharmacokinetics in healthy female volunteers (Protocol-017, Volume 39, page 2240).

The objectives of the study were to: 1) determine the effect of rizatriptan on the plasma concentration profiles of oral contraceptive components (ethinyl estradiol (EE) and norethindrone (NET), and 2) assess the safety of the concurrent administration of rizatriptan and oral contraceptives in healthy women.

Eighteen healthy female volunteers, during each study period, received either 10 mg rizatriptan or matching placebo once daily for 6 days starting with days 1, 2, 3, or 4 of the oral contraceptive treatment cycle. On study days 7 and 8, subjects received 10 mg rizatriptan or matching placebo every 4 hrs for a total of three doses per day. A combination of EE (35 μg) and NET (1 mg) oral contraceptive tablets were taken as Ortho-Novum 1/35. On study day 8, blood samples were drawn over 0-24 hrs after dosing to assay rizatriptan, EE and NET. An additional blood sample one hour post dose on day 1 was drawn to assay for rizatriptan.

RESULTS: The sponsor reported that, because there were no unexpected clinical results nor unusual pharmacokinetic results for EE and NET, rizatriptan was not assayed. The mean plasma concentration time profiles for EE and NET with or without rizatriptan are presented in Figures 23. The mean (sd) pharmacokinetic parameters obtained for all treatments are summarized in the following Table:

ETHINYL ESTRADIOL	Mean ± SD	p-value
AUC_{0-24} (pg.hr/mL)		
Rizatriptan	7.28 ± 0.19	0.297
Placebo	7.25 ± 0.19	
Cmax pg/mL		
Rizatriptan	4.81 ± 0.23	0.624
Placebo	4.83 ± 0.24	
NORETHINDRONE		
AUC_{0-24} (pg.hr/mL)		
Rizatriptan	11.99 ± 0.34	0.367
Placebo	11.96 ± 0.35	
Cmax pg/mL		
Rizatriptan	9.77 ± 0.33	0.337
Placebo	9.82 ± 0.33	

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The results indicate that concurrent administration of rizatriptan with the oral contraceptive Ortho-Novum 1/35 does not alter the plasma concentrations of the oral contraceptive components EE and NET. Concurrent administration of oral contraceptives with rizatriptan is well tolerated by healthy women.

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SAFETY: There were no serious clinical, laboratory or other adverse experiences were reported.

TITLE: A Double-Blind, Randomized, Three-Period, Placebo-Controlled, Crossover Study to Investigate the Effects of Propranolol on the Pharmacokinetics of Rizatriptan and the Effects of Rizatriptan on the Pharmacodynamics of Propranolol in Healthy Volunteers (Protocol-019, Volume 40, page 2893).

The objectives of the study were to: (1) determine the effect of multiple-dose propranolol on the plasma concentration profile (AUC and C_{max}) of single-dose rizatriptan in healthy volunteers, (2) compare the effects of propranolol 120 mg q12h, rizatriptan 10 mg as a single dose, and propranolol 120 mg q12h plus rizatriptan 10 mg as a single dose on the heart rate, blood pressure, and heart rate times blood pressure responses to submaximal exercise, and (3) assess the safety and tolerability of the concurrent administration of rizatriptan and propranolol in healthy volunteers.

In this cross over study 11 subjects (6M; 5F) received oral doses of propranolol (120 mg) or placebo every 12 hours for 7½ days. On Day 7 and Day 8, subjects received either single oral doses of rizatriptan (10 mg) or placebo. Plasma samples were collected 0-24 hrs post dose to assay rizatriptan.

RESULTS: The mean plasma concentration time profiles are presented in Figure 25 and the pharmacokinetic data for individual subjects with or without propranolol are provided in Table 45. The mean (sd) pharmacokinetic parameters for rizatriptan with or without propranolol are summarized in the following Table:

Parameter	Rizatriptan without propranolol	Rizatriptan with propranolol	p-values
$AUC_{0-\infty}$ (ng.hr/mL)	93.4 ± 32.7 *90.0	159.0 ± 59.7 *150.2	0.0002
C_{max} (ng/mL)	25.6 ± 9.4 *24.2	46.8 ± 23.6 *42.4	0.0013
T_{max} (hr)	1.3 ± 1.0	1.0 ± 0.6	0.295
$T_{1/2}$ (hr)	2.3 ± 0.8	3.0 ± 1.0	0.025

* Geometric mean

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The geometric mean ratio for $AUC_{0-\infty}$ of the combination to monotherapy was 1.7, with 90% confidence interval limits of 1.44 and 1.93. The geometric mean ratio for Cmax of the combination to monotherapy was 1.8 with 90% confidence interval limits of 1.41 and 2.17. Propranolol attenuated the heart rate and supine blood pressure × heart rate response to submaximal exercise. This effect was not altered by administration of rizatriptan with propranolol. The sponsor did not investigate the effect of rizatriptan on propranolol pharmacokinetics.

SAFETY: There were no serious clinical, laboratory or other adverse experiences were reported.

In Conclusion, administration of 10 mg rizatriptan to healthy subjects taking 120 mg propranolol b.i.d. results in an average increase of approximately 70% in rizatriptan plasma concentrations. Propranolol's effects on the cardiovascular response to submaximal exercise are not affected by rizatriptan. Administration of 10 mg rizatriptan to healthy subjects taking 120 mg propranolol b.i.d. is well tolerated.

TITLE: A Double-Blind, Randomized, Placebo-Controlled, Two-Period Crossover Study to Investigate the Effects of Moclobemide on the Pharmacokinetics of Rizatriptan in Young Healthy Subjects (Protocol-037, volume 53, page 11025).

The objectives of the study were to: (1) determine the effect of multiple doses of moclobemide on the plasma concentration profile (AUC0-∞ and Cmax) of a single dose of rizatriptan in young healthy subjects; (2) compare the effects of moclobemide on rizatriptan concentrations in young healthy subjects; (3) assess the effects of moclobemide on plasma concentrations of dihydroxy-phenylglycol (DHPG), a marker of MAO-A inhibition, and to investigate the relationship between decreases in DHPG and increases in rizatriptan concentrations; and (4) assess the safety and tolerability of the concurrent administration of rizatriptan and moclobemide in young healthy subjects.
Twelve healthy subjects (6M; 6F) received moclobemide 150 mg (GB-A358) or placebo moclobemide (GB-A358) t.i.d. for 4 consecutive days (450 mg total daily dose) and single-dose rizatriptan 10 mg (GB-A358) on the morning of Day 4 (1 hour after the first dose of moclobemide/placebo). Each treatment period was separated by 14 days. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles for rizatriptan and N-desmethyl rizatriptan (L-706,248) are presented in Figure 26 and the pharmacokinetic data for individual patients for rizatriptan and N-desmethyl rizatriptan with or without moclobemide are provided in Tables 46 and 47. The mean (sd) pharmacokinetic parameters for rizatriptan and N-desmethyl rizatriptan with or without moclobemide are summarized in the following Tables:

Parameter	Rizatriptan with moclobemide			Rizatriptan with placebo		
	Males (n=6)	Females (n=5)	Combined (n=12)	Males (n=6)	Females (n=6)	Combined (n=12)
$AUC_{0-\infty}$ (ng.hr/mL)	141.6±32.1	174.8±58.7	158.2±48.3	66.6 ±20.3	76.2 ± 13.9	71.4 ± 17.3
Cmax (ng/mL)	30.3 ± 13.5	32.4 ±8.2	31.3 ± 10.7	23.2 ± 11.4	22.1 ± 7.7	22.6 ± 9.3
Tmax (hr)	2.1 ± 1.2	2.8 ± 0.9	2.4 ± 1.0	1.5 ± 0.9	1.4 ± 0.7	1.5 ± 0.8
$T_{1/2}$ (hr)	2.3 ± 0.3	2.4 ± 0.5	2.3 ± 0.3	1.7 ± 0.2	1.8 ± 0.3	1.7 ± 0.3
Clr (mL/min)	252.2±60.6	176.8±71.3	211.1±74.6	271.5±78.7	233.8± 52.7	252.7±66.9
Ue (%)	21.6 ±6.4	18.2 ± 9.2	19.7 ± 7.9	10.1 ± 1.4	10.4 ± 1.7	10.2 ± 1.5

Parameter	N-desmethyl rizatriptan with moclobemide			N-desmethyl rizatriptan with placebo		
	Males (n=6)	Females (n=5)	Combined (n=12)	Males (n=6)	Females (n=6)	Combined (n=12)
$AUC_{0-\infty}$ (ng.hr/mL)	47.0 ± 7.7	57.9 ± 9.2	52.5 ± 9.9	9.7 ± 3.6	10.3 ± 2.3	10.0 ± 2.9
Cmax (ng/mL)	6.4 ± 0.7	7.9 ± 1.6	7.2 ± 1.4	3.0 ± 1.5	2.7 ± 0.8	2.8 ±1.2
Tmax (hr)	3.3 ± 1.0	3.7 ± 0.8	3.5 ± 0.9	2.0 ± 0.8	1.7 ± 0.8	1.8 ± 0.8
$T_{1/2}$ (hr)	3.1 ± 0.4	3.3 ± 0.7	3.2 ± 0.6	1.4 ± 0.3	1.8 ± 0.3	1.6 ± 0.4
Clr (mL/min)	186.9±52.7	127.8±41.3	154.6±54.0	200.8±64.7	174.2±40.4	187.5±53.3
Ue (%)	5.6 ± 1.8	4.5 ± 1.2	5.0 ± 1.6	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2

The geometric means, geometric mean ratios, and 90% confidence intervals for $AUC_{0-\infty}$ and Cmax of rizatriptan and N-desmethyl rizatriptan (L 706,248) are summarized by treatment in the tables below.

Pharmacokinetic Parameters ($AUC_{(0-\infty)}$ and C_{max}) for Rizatriptan (N=12)

	Geometric Mean		Geometric Mean Ratio (Moclobemide / Placebo)	90% Confidence Interval	P-Value
	Rizatriptan with Moclobemide	Rizatriptan with Placebo			
$AUC_{(0-\infty)}$ (ng·hr/mL)	151.98	69.47	2.19	(1.93, 2.47)	<0.001
C_{max} (ng/mL)	29.86	21.10	1.41	(1.11, 1.80)	0.025

Pharmacokinetic Parameters ($AUC_{(0-\infty)}$ and C_{max}) for L-706,248 (N=12)

	Geometric Mean		Geometric Mean Ratio (Moclobemide / Placebo)	90% Confidence Interval	P-Value
	Rizatriptan with Moclobemide	Rizatriptan with Placebo			
$AUC_{(0-\infty)}$ (ng·hr/mL)	51.60	9.67	5.34	(4.81, 5.91)	<0.001
C_{max} (ng/mL)	7.03	2.66	2.64	(2.23, 3.14)	<0.001

Pharmacokinetic Parameters ($AUC_{(0-\infty)}$ and C_{max}) for Rizatriptan (N=12)
Rizatriptan with Placebo

	Geometric Mean		Geometric Mean Ratio	90% Confidence	
	Females	Males	(Females/Males)	Interval	P-Value
$AUC_{(0-\infty)}$ (ng·hr/mL)	75.10	64.26	1.17	(0.89, 1.54)	0.322
C_{max} (ng/mL)	20.87	21.34	0.98	(0.63, 1.52)	0.929

Pharmacokinetic Parameters ($AUC_{(0-\infty)}$ and C_{max}) for L-706,248 (N=12)
Rizatriptan with Placebo

	Geometric Mean		Geometric Mean Ratio	90% Confidence	
	Females	Males	(Females/Males)	Interval	P-Value
$AUC_{(0-\infty)}$ (ng·hr/mL)	10.10	9.25	1.09	(0.79, 1.50)	0.625
C_{max} (ng/mL)	2.52	2.80	0.90	(0.60, 1.35)	0.651

The results indicate that mean $AUC_{0-\infty}$ and Cmax of rizatriptan increased by two-fold and 40% respectively, where as that of N-desmethyl rizatriptan increased by 5-fold and 3-fold respectively, following co-administration of moclobemide and rizatriptan compared to placebo and rizatriptan. However, mean $AUC_{0-\infty}$ and Cmax of rizatriptan and N-desmethyl rizatriptan were not statistically significantly different between females and males (p=0.322 and p=0.929; p=0.625 and p=0.651; respectively), indicating no gender differences in the pharmacokinetics of rizatriptan.

Plasma Concentrations of DHPG: The mean plasma concentration time profiles of DHPG receiving moclobemide or placebo are presented in Figure 27. Summary statistics for plasma concentration (mean±sd) parameters for DHPG are summarized in the following Table.

Parameter	Moclobemide	Placebo	p-value
Average Base line concentration (nmol/L)	6.7 ± 1.2	6.7 ± 1.2	——
AUC_{0-11} (nmol*hr/L)	41.7 ± 6.4	73.3 ± 14.1	<0.001
Cavg (nmol/L)	3.8 ± 0.6	6.7 ± 1.3	<0.001
C_0 (nmol/L)	5.1 ± 1.1	6.9 ± 1.2	<0.001
Max Decrease (nmol/L)	3.4 ± 1.2	0.3 ± 1.3	<0.001
Time to Max Decrease (hr)	3.5 ± 1.4	2.7 ± 2.1	0.264

Plasma concentrations of DHPG measured on Day 4 were reduced following administration of moclobemide as compared to levels during placebo (p<0.001). Plasma concentrations of DHPG on Day 4 were also reduced prior to dosing with moclobemide compared to placebo (p<0.001). Following moclobemide, there was a larger maximum decrease in plasma DHPG concentration

than during placebo ($p<0.001$). The time to maximum decrease was not significantly different between treatments ($p=0.264$).

Safety: All 12 subjects completed the study as planned. There were no serious adverse experiences in this study. Ten (83.33%) of the 12 subjects reported a total of 30 clinical adverse experiences, while 2 subjects (16.67%) reported no adverse experiences. Of the 30 clinical adverse experiences, 29 of them were reported with a maximum intensity rating of mild, and only 1 was reported as moderate in intensity. Overall, the incidence of clinical adverse experiences (total and drug related) was similar for both Test Drug Treatments. The most frequently occurring clinical adverse experiences for both treatments were headache and asthenia/fatigue. All subjects recovered from their adverse experiences.

In conclusion, $AUC_{0-\infty}$ and Cmax of rizatriptan and its active metabolite, L-706,248 (N-desmethyl rizatriptan), are increased following administration of rizatriptan with moclobemide as compared to administration of rizatriptan with placebo. The increase in concentrations of the metabolite is greater than that of rizatriptan. However, increase in these parameters of rizatriptan and N-desmethyl rizatriptan with moclobemide are similar between females and males. As expected, plasma concentrations of DHPG were reduced during moclobemide administration, confirming the role of MAO-A in the metabolism of rizatriptan. The sponsor is proposing to contraindicate the administration of MAO inhibitors with rizatriptan.

TITLE: A Double-Blind, Randomized, Two-Panel, Placebo-Controlled Study to Investigate the Effects of Nadolol and Metoprolol on the Pharmacokinetics of Rizatriptan in Healthy Male and Female Subjects (protocol-038, volume 54, page 11703).

The objectives of the study were to: (1) determine the effect of multiple doses of nadolol on the plasma concentration profile (AUC and Cmax) of a single 10-mg dose of rizatriptan in healthy subjects; (2) determine the effect of multiple doses of metoprolol on the plasma concentration profile (AUC and Cmax) of a single 10- mg dose of rizatriptan in healthy subjects; and (3) assess the safety and tolerability of the concurrent administration of rizatriptan and nadolol or metoprolol in healthy subjects.

Twelve healthy subjects (M6; F6) per panel were studied to assess the effects of nadolol 80 mg q12h on the pharmacokinetics of 10 mg rizatriptan (Panel I) and metoprolol 100 mg q12h on the pharmacokinetics of 10 mg rizatriptan (Panel II). Each panel consisted of a randomized, two-period crossover design. This was a two-panel study; 7 days per period, with at least a 13 day wash out between each period. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles for rizatriptan with or without nadolol and metoprolol are presented in Figure 28, and the pharmacokinetic data for individual patients for rizatriptan with or without nadolol and metoprolol are provided in Table 48. The mean (sd) pharmacokinetic parameters for rizatriptan with or without nadolol and metoprolol are summarized in the following Table.

Parameter	Rizatriptan without Nadolol (n=12)	Rizatriptan with Nadolol (n=12)	p-values	Rizatriptan without Metoprolol (n=12)	Rizatriptan with Metoprolol (n=12)	p-values
$AUC_{0-\infty}$ (ng.hr/mL)	59.5 ± 14.1	65.3 ± 19.9	0.266	66.0 ±20.6	70.6 ± 20.4	0.087
Cmax (ng/mL)	18.3 ± 5.9	21.4 ± 6.9	0.201	21.7 ± 6.0	19.6 ± 4.6	0.223
Tmax (hr)	0.8 ± 0.4	1.1 ± 0.9	0.25	1.0 ± 1.0	1.1 ± 0.7	0.504
$T_{1/2}$ (hr)	2.3 ± 0.7	2.0 ± 0.6	0.134	1.7 ± 0.2	1.8 ± 0.3	0.418

The results indicate that concomitant administration of nadolol and metoprolol do not affect the pharmacokinetics of rizatriptan. However, the sponsor did not investigate the affect of rizatriptan on the pharmacokinetics of nadolol or metoprolol.

SAFETY: In general, administration of a single 10-mg dose of rizatriptan with nadolol or metoprolol under conditions of this study was well tolerated. There were no serious clinical, laboratory, or other adverse experiences and no subjects died during this study.

In conclusion, neither nadolol nor metoprolol affect the plasma concentration profile of rizatriptan, 10 mg, to a clinically significant degree (i.e., AUC and Cmax). Administration of rizatriptan on a background of nadolol or metoprolol is generally well tolerated.

TITLE: A Double-Blind, Randomized, Placebo-Controlled, Two-Period Crossover Study to Investigate the Tolerability of Rizatriptan on a Background of the Selective Serotonin Reuptake Inhibitor (SSRI), Paroxetine, and the Effects of Paroxetine on the Pharmacokinetics of Rizatriptan in Young Healthy Subjects (protocol-043, volume 60, page 14827).

The objectives of the study were to: (1) assess the safety and tolerability of the concurrent administration of rizatriptan and paroxetine in young healthy subjects; and (2) determine the effect of multiple doses of paroxetine on the plasma concentration profile ($AUC_{0-\infty}$ and Cmax) of rizatriptan in young healthy subjects.

Twelve subjects (6M; 6F) received Treatments A and B and 4 subjects (2M; 2F) received Treatments C and D. Each treatment period consisted of 14 days of dosing. There was a washout of 2 weeks' duration between treatment periods. Plasma samples were collected over 0-24 hrs post dose for all treatments.

Treatment A: Paroxetine 20 mg tablet p.o. once daily for 14 days Plus rizatriptan 10 mg tablet p.o. once daily on day 14.
Treatment B: Placebo-paroxetine tablet p.o. once daily for 14 days Plus rizatriptan 10 mg tablet p.o. once daily on day 14.
Treatment C: Paroxetine 20 mg tablet p.o. once daily for 14 days Plus placebo-rizatriptan 10 mg tablet p.o. once daily on day 14.
Treatment D: Placebo-paroxetine 20 mg tablet p.o. once daily for 14 days Plus placebo-rizatriptan 10 mg tablet p.o. once daily on day 14.

RESULTS: The mean plasma concentration time profiles for rizatriptan and N-desmethyl rizatriptan (L 706-248) with or without paroxetine are presented in Figure 29, and the pharmacokinetic data for individual subjects for rizatriptan and N-desmethyl rizatriptan with or without paroxetine are provided in Table 49. The mean (sd) pharmacokinetic parameters for rizatriptan and N-desmethyl rizatriptan with or without paroxetine are summarized in the following Table:

Parameter	Rizatriptan without Paroxetine (n=12)	Rizatriptan with Paroxetine (n=12)	p-values	N-desmethyl rizatriptan without Paroxetine (n=12)	N-desmethyl rizatriptan with Paroxetine (n=12)	p-values
$AUC_{0-\infty}$ (ng.hr/mL)	65.7 ± 21.2	72.4 ± 25.0	0.212	7.7 ± 2.7	7.3 ± 2.4	0.425
Cmax (ng/mL)	17.7 ± 7.8	18.6 ± 6.6	0.399	1.7 ± 0.4	1.6 ± 0.5	0.402
Tmax (hr)	1.1 ± 0.9	1.0 ± 0.6	0.582	1.3 ± 0.3	1.2 ± 0.5	0.572
$T_{1/2}$ (hr)	1.8 ± 0.6	2.1 ± 0.3	---	2.1 ± 0.7	2.2 ± 0.4	----
Clr (mL/min)	340.7 ± 65.1	326.6 ± 87.6	0.436	250.9 ± 65.4	233.7 ± 59.4	0.279
Ue (%dose)	12.4 ± 3.9	13.8 ± 5.6	0.507	1.0 ± 0.3	0.9 ± 0.2	0.310

The results indicate that paroxetine does not affect the pharmacokinetics of rizatriptan. For AUC, Cmax, Tmax, Clr, and Ue the gender-by-treatment interaction was found to be nonsignificant ($p>0.1$) indicating no gender differences in the pharmacokinetics of rizatriptan.

SAFETY: There were no serious adverse experiences in this study. No laboratory adverse experiences were reported.

In conclusion, (1) Mean AUC and Cmax of rizatriptan and its active metabolite, L-706,248 (N-desmethyl rizatriptan) were not affected to a significant extent following administration of rizatriptan (10 mg) with paroxetine (20 mg daily for 14 days) as compared to administration of rizatriptan (10 mg) with placebo-paroxetine (once daily for 14 days). Concurrent administration of a single 10 mg dose of rizatriptan with multiple doses of 20 mg paroxetine (administered once daily for 14 days) is well tolerated in healthy young male and female subjects.

PHARMACOKINETICS IN PATIENTS DURING MIGRAINE AND MIGRAINE FREE PERIOD:

TITLE: A Randomized, Double-Blind, Three-Period, Placebo-Controlled, Inpatient Study to Compare the Pharmacokinetic Profiles of Intranasal (I.N.) rizatriptan and Oral rizatriptan 5 mg (Protocol-026, volume 45, page 6014).

The objectives of the study were to: (1) compare the mean $AUC_{0-\infty}$ values of rizatriptan 5 mg p.o. when administered during and between acute migraine attacks; and (2) compare the mean $AUC_{0-\infty}$ values of rizatriptan 5 mg I.N. when administered during migraine attacks and rizatriptan 5 mg p.o. when administered between migraine attacks.

This was an inpatient study in which initially (Part 1), 21 fasted patients received a single dose of rizatriptan 5 mg p.o. (n=18; 7M; 11F) or placebo (n=3) when free of migraine for >72 hours. In Part 2, the same 18 patients who received active treatment during Part 1 then received treatment for two separate moderate/severe migraines with rizatriptan 5 mg p.o. or rizatriptan and 5 mg I.N. according to a randomized, double-blind, crossover design; these attacks were separated by >72 hours. The other 3 patients received placebo, so that the same 3 patients received placebo during Parts 1 and 2 of the study. Optionally, up to 9 patients randomized to treatment received rizatriptan 5 mg I.N. at least 72 hours after the end of Part 2. For each period each patient received test medication, active or placebo depending on sequence, by the oral and intranasal routes. Plasma concentrations of rizatriptan over 0-12 hrs were collected.

RESULTS: The 5-mg tablet used in this study was the final market composition. An investigational intranasal dosage form also was evaluated in this study, but those results are not discussed here. The mean plasma concentration time profiles for rizatriptan during and between

migraine attack are presented in Figure 30, and the pharmacokinetic data for individual subjects for rizatriptan during and between migraine attack are provided in Table 50. The mean (±SD) pharmacokinetic parameters for rizatriptan in migraineurs following administration of rizatriptan benzoate 5 mg during a migraine attack and while migraine-free are presented in the following Table:

Parameter	Males (N=7)		Females (N=11)	
	During Migraine	Migraine-Free	During Migraine	Migraine-Free
C_{max}, ng/mL	13 (6)	10 (3)	27 (24)	18 (10)
T_{max}, h	1.1 (0.4)	0.9 (0.3)	1.0 (0.5)	0.9 (0.6)
AUC, ng•h/mL	43 (14)	39 (14)	69 (45)	65 (37)
$t_{½}$†, h	2.5	2.4	1.7	1.8

† Harmonic mean.

$AUC_{(0-\infty)}$ and C_{max} (Geometric Means, Geometric Mean Ratios, and 90% Confidence Intervals) for Rizatriptan 5-mg Tablet During and Between Attacks

Measurement	Geometric Mean p.o. During an Attack N=18	Geometric Mean p.o. Between Attacks N=18	Geometric Mean Ratio p.o. During/p.o. Between	90% C.I. for the Ratio
$AUC_{(0-\infty)}$ (ng·hr/mL)	47.39	45.22	1.05	(0.96, 1.15)
C_{max} (ng/mL)	14.93	12.79	1.17	(0.96, 1.42)

These data indicate that a migraine attack itself has no significant effect on the rate or extent of rizatriptan absorption in male or female migraineurs. Higher degree of variability in Cmax data in females was noted. However, the AUC for rizatriptan did not change in males or females, when drug was given during or between migraine attacks. As shown in other studies, there was, however, an apparent difference between males and females in Cmax and AUC. Mean Cmax was nearly twofold higher in females, while mean AUC was approximately 60% higher. This may be attributable to differences in body weight for the patients in this study. For females, body weight ranged from 113 to 176 lb (mean = 137 ± 19 lb), while for males body weight ranged from 174 to 261 lb (mean = 204 ± 38 lb). Regardless, the sponsor reports that there was no difference in the efficacy and safety of rizatriptan for the male and female patients participating in this study.

Pain relief was observed at 2 hours in 12 of 18 (67%) patients on rizatriptan 5 mg p.o. and mean time to relief was 1 hr.

SAFETY: No serious adverse experiences were reported.

In conclusion, the pharmacokinetic characteristics (geometric mean AUC, geometric mean Cmax, and mean Tmax) of the rizatriptan 5 mg tablet, dosed in the presence of a migraine attack, are comparable to those observed in the absence of migraine attacks.

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APPENDIX I

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APPENDIX II

2 PAGES REDACTED

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APPENDIX III

FIGURE 1

Mean (± S.D.) or Individual Plasma Concentration-time Profile(s) of L-705,126 or Sumatriptan in Healthy Males Receiving A Single Oral Dose of 5, 10, 20, 40, 60 mg (n = 4 or 6), or 80 mg (n = 1) of L-705,126, or A Single Oral Dose of 100 mg of Sumatriptan (n = 16).

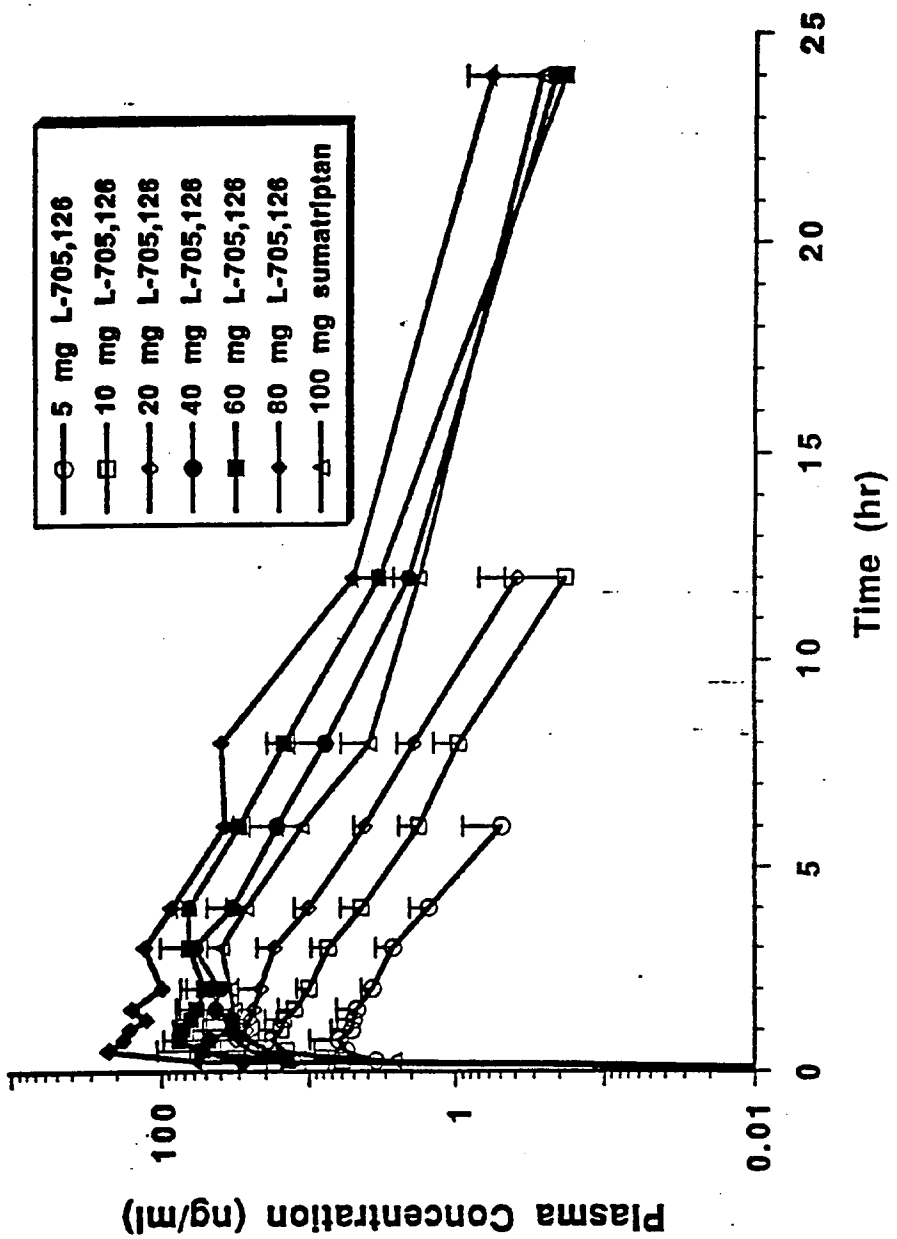


FIGURE 2. Mean Plasma Concentration Versus Time Profiles Following Intravenous Administration of MK-0462 10 to 120 µg/kg

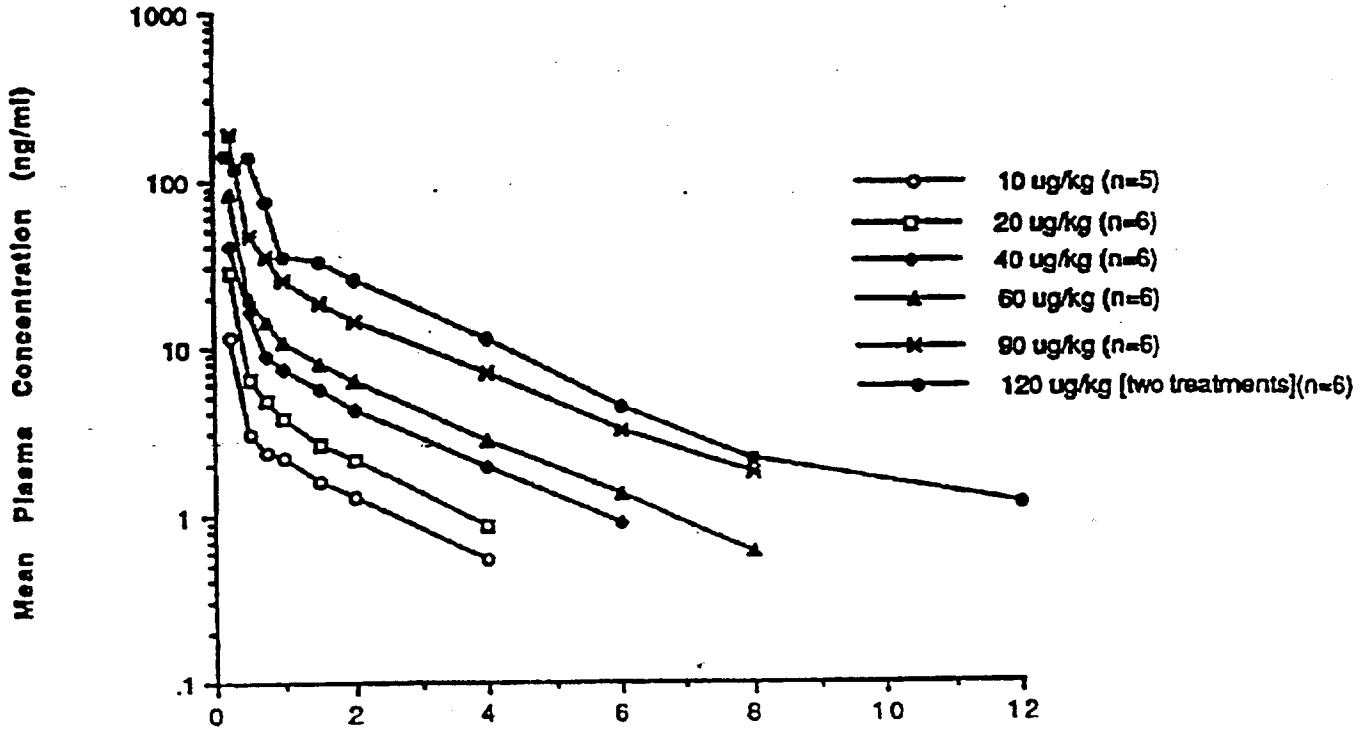


Figure 3

Mean Plasma Concentration Versus Time Profiles Following Oral Administration of MK-0462 mg in the Fed and Fasted States

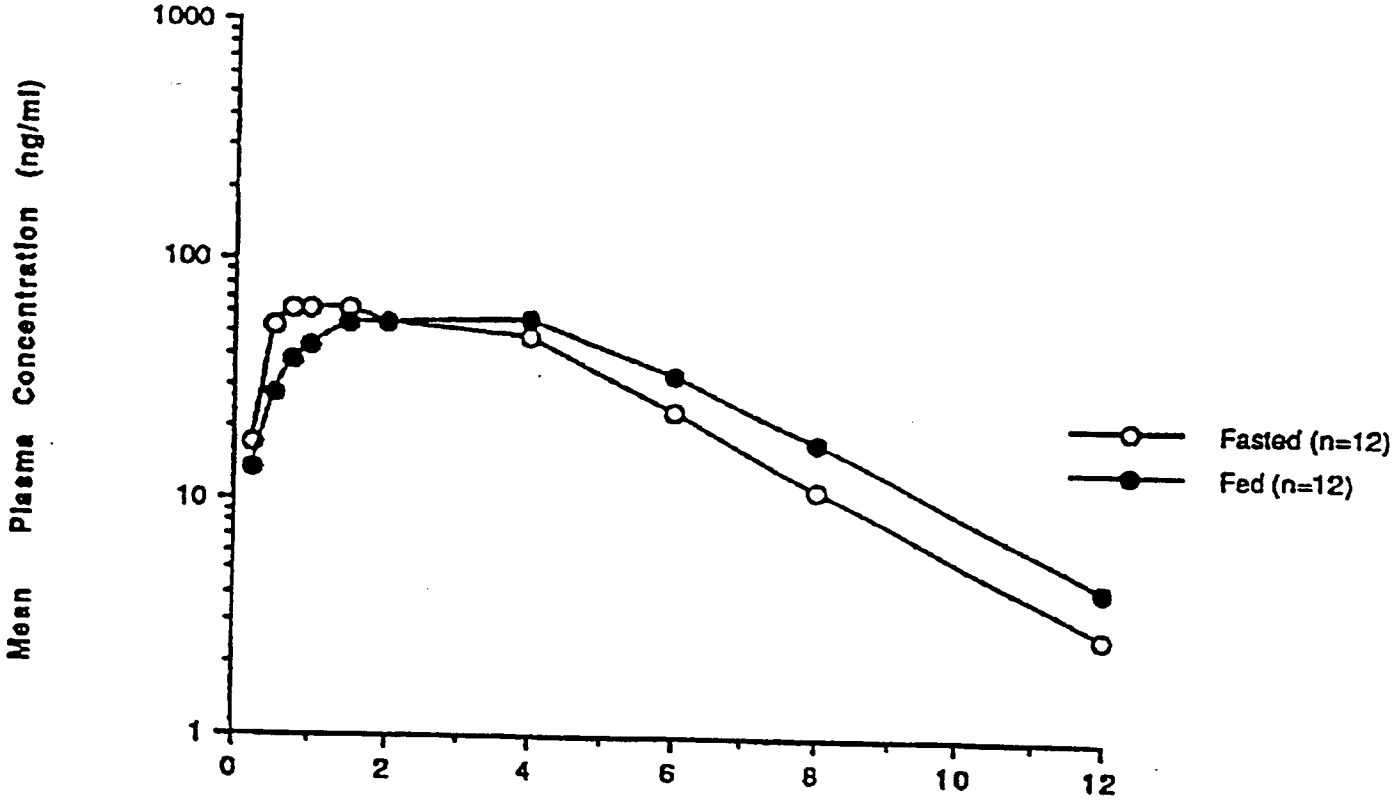


Figure 4

Mean (± S.D., N = 12) Plasma Concentration-time Profiles of MK-462 in Healthy Males and Females Following Intravenous Administration of 4 mg of MK-462

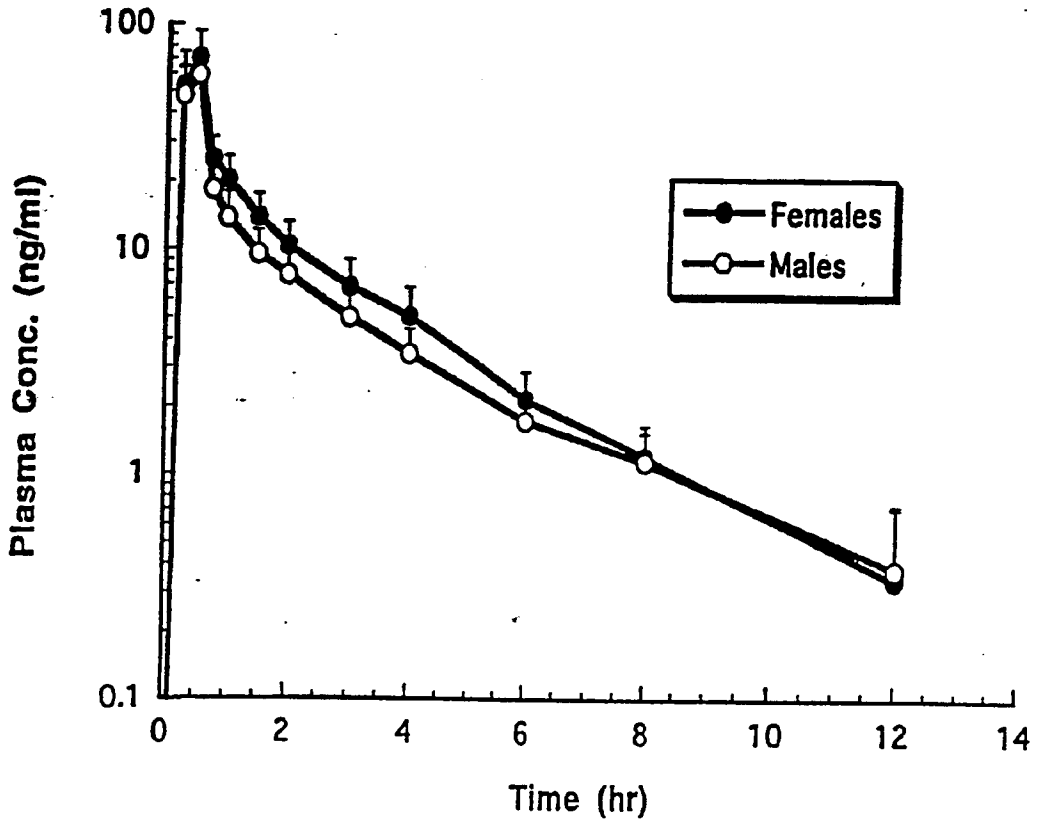


FIGURE 5

Mean (± S.D., N = 12) Plasma Concentration-time Profiles of MK-462 in Healthy Males and Females Following Separate Oral Administration of 2.5-15 mg of MK-462

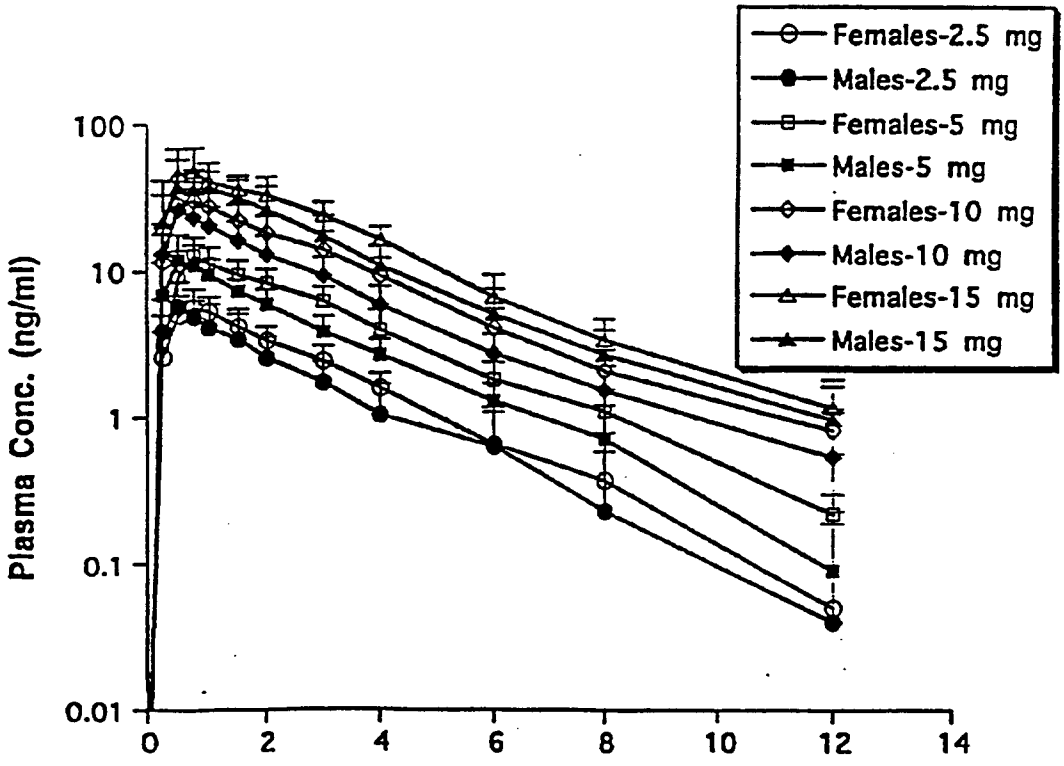
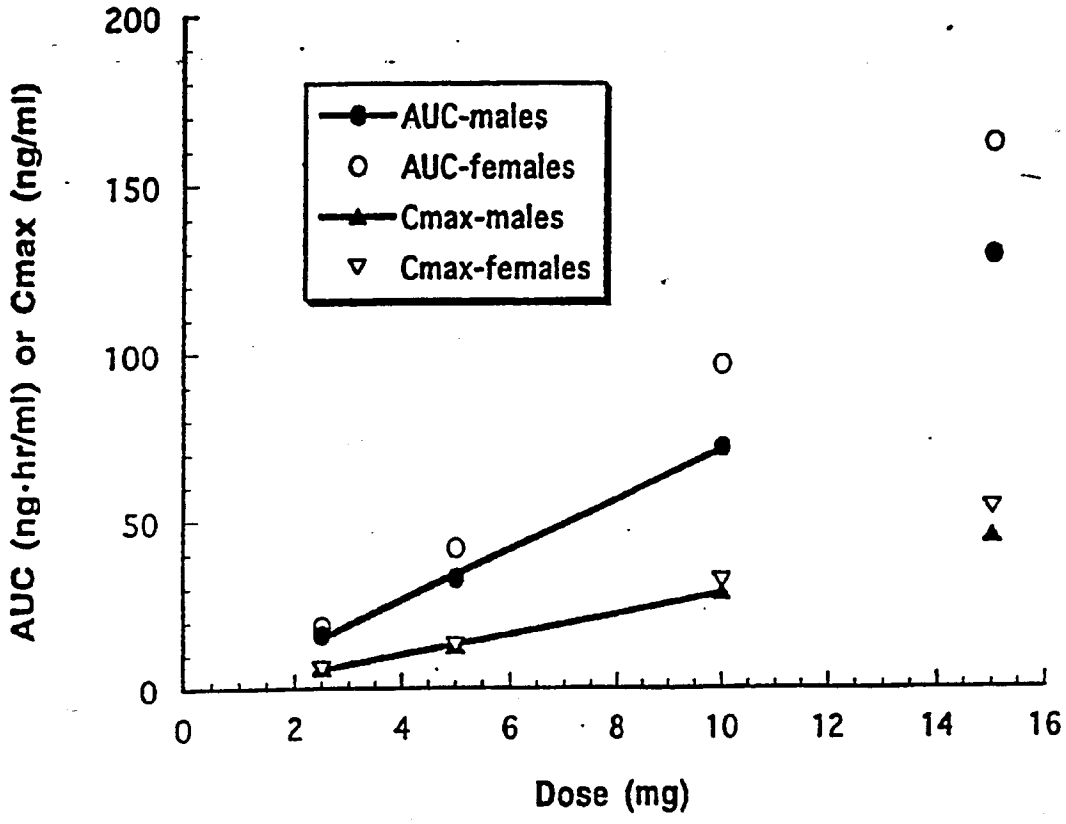


Figure 5a

A Plot of Mean Dose-Normalized AUC and C_{max} versus Oral Dose of MK-462
(the Dosage Range is 2.5-15 mg)



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