CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20864/20865

STATISTICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 4, 1998

FROM: David Hoberman, Ph.D.
Mathematical Statistician

APPEARS THIS WAY
ON ORIGINAL

SUBJECT: NDA 20-864 (MAXALT)

TO: HFD-120 File

This reviewer has concluded that no formal statistical review is needed for this NDA. The clear statistical results showing efficacy, together with Dr. Armando Oliva's comprehensive review and the restricted labelling for this class of drugs makes a supplementary review by the assigned statistician redundent.

/S/

David Hoberman, Ph.D.

cc:
NDA# 20-864
HFD-120/Dr. Leber
HFD-120/Dr. Levin
HFD-120/Dr. Oliva
HFD-120/Dr. Purvis
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Hoberman

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20864/20865

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 22 1998

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Rizatriptan Benzoate (Maxalt®; MLT®)
5 and 10 mg Tablets and Orally Disintegrating Tablets
NDAs 20-864 & 20-865

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486

Submission Dates:
June 30, 1997
October 31, 1997
April 6, 1998
April 27, 1998

Reviewer: **Vijay K. Tammara, Ph. D.**

Indication: **Migraine**
Classification: **1S**
Type of Submission: **Original -- New Molecular Entity**

Rizatriptan (MK-0462 or L-705,126) is a selective 5-hydroxytryptamine$_{1D}$ receptor agonist. The mechanism of action is presumably by acting both centrally and peripherally at 5-HT$_{1D}$ receptors to produce cranial vessel constriction and inhibition of neuropeptide release and thereby exerting its therapeutic effect. The proposed dose is 10 mg. If symptoms persist or return within 24 hours, a second dose can be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose. If patient does not achieve satisfactory relief with 10 mg doses, subsequent migraine attacks can be treated with 10 mg doses, however no more than 30 mg should be taken in any 24 hr period.

The applicant has adequately studied the pharmacokinetics of rizatriptan at the proposed dose.

Absorption

Rizatriptan is rapidly and completely absorbed following oral administration. The mean oral bioavailability of the Maxalt Tablet is approximately , and mean peak plasma concentrations (Cmax) are reached in approximately 1-1.5 hours (Tmax). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delayed the time to reach peak concentration by an hour. In clinical trials, Maxalt was administered without regard to food. The bioavailability and Cmax of rizatriptan were similar following administration of Maxalt Tablets and Maxalt MLT Orally Disintegrating Tablets. However, the apparent rate of absorption is somewhat slower with Maxalt MLT, with Tmax averaging compared to Tmax averaging with tablets.

The pharmacokinetics of rizatriptan are linear in males and nearly linear in females following intravenous doses up to 60 µg/kg. After oral doses of 2.5 to 15 mg, AUC and Cmax of oral rizatriptan increased slightly more than proportionately. Lack of dose proportionality was noted more in females than males. In males nonlinearity was observed at doses above 10 mg, whereas in females nonlinearity was observed at doses above 5 mg. AUC of rizatriptan is approximately 30% higher in females than in males.

When Maxalt 10 mg was administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan increased within each day, consistent with its half-life, but no plasma accumulation of the drug occurred from day to day. Similar results were observed for the N-desmethyl rizatriptan.

Distribution

Rizatriptan is minimally bound (14%) to plasma proteins. The volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects.

Metabolism

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not pharmacologically active. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptor, is formed to a minor degree. This does not contribute significantly to the pharmacodynamic activity of rizatriptan. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of the parent compound, and it is eliminated at a similar rate. Other minor metabolites include the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite. None of these minor metabolites are pharmacologically active.

Based on analyses of urinary radioactivity after oral and i.v. dosing over 120 hrs, approximately of an oral dose of rizatriptan was absorbed. However, absolute bioavailability was only 45%. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about of circulating plasma radioactivity. It was also observed that approximately of an oral dose is excreted in urine as unchanged rizatriptan while is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism. Mean values of plasma clearance (CL) and renal clearance (Clr) of rizatriptan were 1325 and 349 mL/min, respectively, following the i.v. dose. A similar mean renal clearance (Clr) value was obtained following the oral dose. Elimination half-life of radioactivity was about 6 hrs, where as that of rizatriptan was about 2-3 hrs, indicating that metabolites may be circulating longer in plasma than the parent compound.

In Vitro Metabolism

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. However, N-desmethyl rizatriptan was not detected *in vitro*, although it was found to be , of the parent *in vivo*. 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). 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.

Cytochrome P450 isoforms:

The inhibitory activity of rizatriptan versus several P450 isozymes (1A2, 2C9, 2C19, 2D6, 2E1, 3A4/5) was also evaluated *in vitro*. Rizatriptan was found to be not an inhibitor of the activities of human liver cytochrome P450 isoforms; however, rizatriptan was found to be a weak competitive inhibitor (Ki =1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Elimination

The plasma half-life of rizatriptan in males and females averages The plasma clearance of rizatriptan averages about n in males and about in females; about , of this is renal clearance. Following an oral dose of ^{14}C-labeled rizatriptan, about of the radioactivity is excreted in urine, and about of the dose is excreted in feces. This shows that the metabolites are excreted primarily via the kidneys. Approximately , of an oral dose is excreted in urine as unchanged rizatriptan while is excreted as indole acetic acid metabolite.

Special Populations

Renal Impairment: In patients with renal impairment (creatinine clearance 10 - 60 mL/min/1.73 m2), the AUC and Cmax of rizatriptan was not significantly different from that in healthy subjects. However, in hemodialysis patients (creatinine clearance < 2 mL/min/1.73 m2), the AUC for rizatriptan was approximately than that in patients with normal renal function.

Hepatic Impairment: In patients with hepatic impairment (mild to moderate alcoholic cirrhosis), the 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), may not be of 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 a result of small sample size for moderate group (n=3).

Age: The plasma concentrations of rizatriptan observed in elderly subjects (age range 65 to 77 years) were similar to those observed in the younger subjects. However, renal clearance and urinary excretion tend to be lower in elderly.

Gender: The AUC of rizatriptan (10 mg orally) was about in females as compared to males, Cmax was and Tmax occurred at approximately the same time. Based on clinical review, this apparent pharmacokinetic difference was of no clinical significance.

Race: The AUC and Cmax for rizatriptan were measured in Caucasian and African American subjects in several studies, retrospectively. There were no effects of race noted for these parameters.

Drug Interactions

Oral Contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of Maxalt (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Propronalol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70%, and a fourfold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. This increase is most probably due to first-pass metabolic interaction between the two drugs since MAO-A plays a role in the metabolism of both rizatriptan and propranolol.

Monoamine Oxidase Inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). Maxalt 10 mg concomitantly administered with the selective, reversible MAO-A inhibitor (n=12), moclobemide 150 mg t.i.d., showed mean increases in rizatriptan AUC and Cmax of respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased
The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. Administration of Maxalt to patients taking inhibitors of MAO is contraindicated.

Nadolol/Metoprolol: No pharmacokinetic interaction was observed (n=12) between rizatriptan and the beta-blockers nadolol (multiple doses; 80 mg b.i.d) or metoprolol (multiple doses; 100 mg b.i.d). Based on in vitro data, no pharmacokinetic interaction is expected with timolol or atenolol.

Paroxetine: In a study of concurrent administration of the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks, with a single dose of Maxalt 10 mg in healthy subjects (n=12), the plasma concentrations of rizatriptan and its safety profile were not affected by paroxetine.

RECOMMENDATION:

These submissions (NDAs 20-864 & 20-865) have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and have been found to be acceptable for meeting the Office's requirements, provided that the sponsor incorporates all the labeling changes. The sponsor is requested to adopt the dissolution methodology and specification as outlined in **Comment 3.** Please forward **Comments 1-3, Labeling Comments** and this **Recommendation** to the sponsor.

Comments To Be Sent To The Firm:

1) The sponsor is requested to investigate the possible interaction of rizatriptan with drugs that interfere with renal secretion e.g., cimetidine, since rizatriptan is renally secreted.

2) In future studies, the sponsor is requested to construct confidence intervals for drug-drug interaction studies in addition to p-values.

3) The following dissolution methodology and specification for Maxalt 5 and 10 mg Tablets and Orally Disintegrating Tablets (MLT) as requested by the sponsor are acceptable:

For Tablets:
Apparatus: USP Apparatus 2 (paddles)
Medium: Water
Volume: 900 mL
Agitation:
Temperature:
Specification: Q =

For MLT (Orally Disintegrating Tablets):
Apparatus: USP Apparatus 2 (paddles)
Medium: Water
Volume: 900 mL
Agitation:
Temperature:
Specification: Q =

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Labeling Comments:

See OCPB labeling in **Appendix A.**

/S/ 5/21/98

APPEARS THIS WAY
ON ORIGINAL

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

First Draft Prepared on May 5, 1998
First draft initialed by Dr. Sahajwalla on May 11, 1998
Second Draft prepared on May 14, 1998
Second Draft Initialed by Dr. Sahajwalla on May 15, 1998

APPEARS THIS WAY
ON ORIGINAL

Optional Inter-Division CP/B Briefing Date: May 20, 1998
Attendees: Vijay Tammara, Chandra Sahajwalla, Henry Malinowski, Randy Levin, Armando Oliva, Glenna Fitzgerlad, Thomas Steele, Mei-Ling Chen, Arzu Selan, Shiew-Mei Huang, and John Balian.

FT Initialed by C. Sahajwalla, Ph. D. /S/ 5/22/98

CC: NDAs 20,864 & 20,865 (orig.), HFD-120, HFD-860 (Tammara, Sahajwalla, Malinowski), CDR (Barbara Murphy).

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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

NOTE: Figures and Tables referred in the text are provided in Appendix III.

During the review process the name of Rapidisc and RPD has been changed to Orally Disintegrating Tablet (MLT®). Please, make a note of this change.

PHARMACOKINETICS:

SINGLE DOSE STUDIES:

TITLE: A double-blind, placebo-controlled, alternating panel, 4- to 5- period, incremental, single-dose study of the safety and tolerability of rizatriptan followed by an open-label, single oral dose, treatment period of sumatriptan 100 mg in healthy male volunteers (Protocol-002, volume 36, Page 1).

The objectives of the study were to: 1) assess the safety and tolerability of single oral doses of rizatriptan over the dose range of 0.5 to 80 mg; 2) obtain preliminary pharmacokinetic information on rizatriptan administered orally; and 3) obtain comparative pharmacokinetic data for sumatriptan (100 mg) administered orally.

Two panels (8 subjects /panel) underwent 4 treatment periods in an alternating dose fashion. The dose levels for Panel A were 0.5, 2, 10, and 40 mg; dose levels for Panel B were 1, 5, 20, and 80 mg. During each treatment period, 2 subjects in each panel received placebo and 6 received active treatment. However, due to occurrence of adverse clinical experience and hemodynamic changes observed with 80 mg dose received by one subject, the dose for panel B treatment period 4 was decreased to 60 mg. All subjects received oral sumatriptan in an open label treatment period after completion of the rizatriptan treatment periods. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The sponsor reported that the plasma concentrations for doses 0.5, 1, and 2 were not measurable.

The mean plasma concentration time profiles are presented in Figure 1 and the pharmacokinetic data for individual subjects for all treatments are provided in Tables 1 and 2. The mean (sd) pharmacokinetic parameters are summarized in the following Table:

Dose (mg)	$AUC_{0-\infty}$ (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
5 (N=6)	17.4 (3.6)	7.8 (2.9)	1.2 (1)	1.4 (0.2)
10 (N=6)	49.6 (11.7)	19.8 (6.6)	1.0 (0.6)	2.1 (0.5)
20 (N=6)	101 (12)	39.4(16)	1.0 (0.6)	1.9 (0.3)
40 (N=6)	265 (95)	90.8 (47)	1.5 (1.2)	2.5 (1.1)
60 (N=4)	394 (28)	89.6 (16)	2.1 (1.6)	2.2 (0.8)

The mean $AUC_{0-\infty}$ of rizatriptan increased with dose in a greater than proportional manner. After dose normalizing the mean $AUC_{0-\infty}$ to 5 mg dose, the mean $AUC_{0-\infty}$ after administration of 10, 20, 40, and 60 mg were 24.8, 25.3, 33.1, and 32.8 ng.hr/mL respectively, and significant pairwise differences were observed between each of the above doses ($p<0.05$). However, the mean dose-adjusted C_{max} values to 5 mg after administration of 10, 20, 40, and 60 mg were 9.9, 9.9, 11.3, and 7.5 ng/mL respectively, and no significant differences were noted ($p>0.1$). Similarly no significant difference was observed in T_{max} over the dose range of 5-60 mg.

Increases in systolic and diastolic blood pressures were observed following administration of both rizatriptan and sumatriptan, but these increases appeared to be more pronounced after administration of 60 mg of rizatriptan but not 10 mg of rizatriptan. No meaningful differences in heart rate were observed for rizatriptan compared to placebo.

SAFETY: No serious clinical, laboratory, or other adverse events were reported during the study except for 80 mg dose. The first subject dosed at the 80 mg dose level experienced several clinical adverse experiences consisting of headaches, somnolence, dizziness, paraesthesia, anxiety, and cold extremities and it was decided by the sponsor not to proceed with this dosing further and the dose was reduced to 60 mg. Most commonly observed side effects following administration of rizatriptan (5-60 mg) include somnolence, headache, and asthenia/fatigue.

In conclusion, $AUC_{0-\infty}$ of rizatriptan increased with dose in a greater than proportional manner indicating nonlinearity in exposure above 5 mg doses; however such difference was not observed for Cmax.

TITLE: A three-part study to investigate the safety, tolerability, and pharmacokinetics of intravenous rizatriptan, and the effect of food on the oral pharmacokinetics of rizatriptan with in healthy male volunteers (Protocol-007, volume 37, page 759).

The objectives of the study were to:(1) assess the safety and tolerability of intravenously administered rizatriptan; (2) assess the disposition of intravenously administered rizatriptan; (3) evaluate the effect of feeding on the time course and extent of oral absorption of rizatriptan; and (4) evaluate the safety, tolerability, and pharmacokinetics of an infusion regimen designed to maintain therapeutically relevant plasma concentrations for a 20-minute period.

This was a three-part (Parts A, B, and C) study. In parts A and C, the safety, tolerability, and pharmacokinetics of single intravenous doses of rizatriptan were assessed in 8 healthy male subjects (6 on active treatment and 2 on placebo) in a dose-escalation fashion. In part A, the dose levels assessed were 5, 10, 20, 40, and 60 µg/kg as an i.v. infusion over 15 minutes. In part C, the dose levels assessed were 90 µg/kg over 15 minutes and 120 µg/kg over 30 minutes (as a

60 μg/kg loading dose over 10 minutes followed by a 60 μg/kg infusion over the next 20 minutes). Part B was a two-period, crossover, with-in subject assessment of the effects of food on the oral pharmacokinetics of rizatriptan. In this part of the study, 40 mg of rizatriptan was administered orally to 12 subjects following an overnight fast and again following a standard breakfast (two eggs, two strips of bacon, toast with butter, 2-4 oz of hash brown potatoes, and one glass of whole milk). Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS:

Dose Proportionality:

A total of 13 subjects entered the study and 11 completed the study. One subject discontinued due to headaches of increasing frequency during i.v. dose escalation and another subject discontinued due to pre-existing heart condition.

The sponsor reported that the plasma concentrations for 5 μg/kg dose were not measurable.

The mean plasma concentration time profiles are presented in Figure 2 and the pharmacokinetic data for individual subjects for all treatments are provided in Tables 3 and 4. The mean (sd) pharmacokinetic parameters obtained for all treatments following i.v. administration are summarized in the following Table:

Dose (i.v.) (μg/kg)	$AUC_{0-\infty}$ (ng.hr/mL)	V_{ss} (L)	CL (mL/min)	$T_{1/2}$ (hr)
10 (N=5)	10.2 (1.9)	154 (34)	1296 (252)	1.9 (0.5)
20 (N=6)	19.5 (4.6)	117 (27)	1335 (178)	1.7 (0.4)
40 (N=6)	35.2(7.9)	157 (41)	1495 (327)	1.8 (0.3)
60 (N=6)	58.0 (15)	134 (26)	1363 (282)	2.0 (0.3)
90 (N=6)	138.4 (20)	91.6 (27)	807 (133)	2.5 (0.7)

$AUC_{0-\infty}$ increased linearly up to 60 μg/kg, and above this dose increase was nonlinear. Dose proportionality was assessed by dose-adjusted geometric mean AUCs for 10, 20, 40, and 60 μg/kg, which were 12.5, 12.6, 11.4, and 12.4 ng.hr/mL respectively, and no significant difference between these dose groups was observed ($p=0.38$), supporting the conclusion of dose proportionality. However, the dose-adjusted geometric mean AUC for 90 μg/kg dose was 21.7 and is significantly different from other dose levels ($p<0.01$) indicating non-linearity above 60 μg/kg dose level. This is further supported by analyzing geometric mean ratios as displayed in the Table 5.

It also appeared that Vss and clearance were independent of dose over the 10-60 µg/kg dose and decreased for 90 µg/kg dose.

Effect of Food:

The mean plasma concentration time profiles are presented in Figure 3 and pharmacokinetic parameters for individuals are presented in Tables 6 and 7. The mean pharmacokinetic parameters are presented in the following Table:

Parameter (mean ± sd)	Fasted	Fed	Fed/Fasted Ratio (90% Confidence Interval)
$AUC_{0-\infty}$(ng.hr/mL) p-value	330 ± 54	397 ± 95 0.02	1.19 (1.07 - 1.32)
C_{max}(ng/mL) p-value	76.8 ± 32.4	72.3 ± 19.8 0.89	0.98 (0.76 - 1.27)
T_{max} (hr) Range p-value	1.6 ± 1.2 0.5 - 4	2.9 ± 1.4 0.75 - 4 0.04	----

The results indicate that food affected the rate of absorption (mean Tmax prolonged by 1.3 hrs (80%)) and extent of absorption (20% increase in mean AUC) significantly, however peak plasma concentration was not affected. However, dose-ranging and phase III studies of efficacy and safety were conducted in patients without dosing restrictions relative to food consumption.

SAFETY: There were no serious clinical, laboratory, or other adverse events reported during the study.

TITLE: A 4-Period, open, crossover study to examine the dose proportionality of single doses of rizatriptan administered orally in solution followed by an open i.v. arm in healthy male vs female volunteers (Protocol-016, volume 39, page 1863).

The objectives of the study were to: (1) determine the plasma concentration profiles (AUC, Cmax, and Tmax) and dose proportionality of rizatriptan single oral doses of 2.5 to 15 mg administered as solutions to healthy volunteers; (2) compare the pharmacokinetics of rizatriptan between men and women; (3) determine whether the clearance of rizatriptan is independent of dose and whether it differs between men and women; and (4) further investigate the safety and tolerability of single oral doses of rizatriptan from 2.5 to 15 mg.

This was an open-label, 5-period, crossover study in 24 healthy volunteers (12 M: 12 F). Subjects were stratified with regard to gender. Subjects received single oral doses of 2.5, 5, 10, and 15 mg rizatriptan in solution on 4 separate days in Periods 1, 2, 3, and 4 according to a randomized allocation schedule for a balanced, 4-period, crossover design. In Period 5, subjects were given 4 mg rizatriptan i.v. infused over 30 minutes. There was at least a 7-day washout interval between all doses. Plasma samples were collected over 0-24 hrs post dose for all treatments. Urine samples were also collected at specific intervals over a period of 0-24 hrs.

RESULTS: The mean plasma concentration time profiles are presented in Figures 4 and 5; and the pharmacokinetic data for individual subjects for all treatments are provided in Tables 8-22i. The mean (sd) pharmacokinetic parameters are summarized in the following Table:

Mean (±SD, N=12) pharmacokinetic parameters of rizatriptan in healthy males receiving single oral and i.v. solution doses.

Parameter	Dose (mg)				
	4 i.v.	2.5 p.o.	5 p.o.	10 p.o.	15 p.o.
$AUC_{0-\infty}$ (ng.hr/mL)	M:67.8 ± 15.7 F: 84.0 ± 17.3	M:16.0 ± 7.0 F: 18.7 ± 5.1	M:32.8 ± 8.9 F: 41.7 ± 11.6	M:72.0 ± 22.2 F: 96.7 ± 28.0	M:127 ± 45 F: 161 ± 42
C_{max} (ng/mL)	----	M:6.2 ± 2.8 F: 6.1 ± 1.9	M:12.7 ± 4.8 F: 13.2 ± 3.7	M:28.6 ± 13.5 F: 32.1 ± 11.9	M:44.8 ± 17.8 F: 54.0 ± 18.7
T_{max} (hr)	---	M:0.77 ± 0.5 F: 0.81 ± 0.3	M:0.73 ± 0.31 F: 0.94 ± 0.41	M:0.66 ± 0.23 F: 0.73 ± 0.2	M:0.88 ± 0.42 F: 0.96 ± 0.55
$T_{1/2}$ (hr)	M:3.2 ± 0.9 F: 2.7 ± 0.8	M:2.5 ± 1.2 F: 2.5 ± 1.0	M:2.4 ± 0.7 F: 2.6 ± 0.9	M:2.7 ± 1.0 F: 2.6 ± 0.4	M:2.5 ± 0.6 F: 2.5 ± 0.3
Vss (L)	M:141 ± 31 F: 102 ± 29	---	---	---	---
CL (mL/min)	M:1042 ± 281 F: 821 ± 148	---	---	---	---
Clr (mL/min)	M:225 ± 35 F: 174 ± 28	M:225 ± 85 F: 179 ± 27	M:340 ± 122 F: 244 ± 54	M:295 ± 121 F: 242 ± 135	M:271 ± 43 F: 223 ± 59
Ue (% Dose)	M:23.4 ± 7.5 F: 20.8 ± 2.9	M:7.6 ± 2.4 F: 7.9 ± 2.0	M:13.0 ± 4.7 F: 12.1 ± 3.5	M:11.9 ± 6.4 F: 13.5 ± 6.9	M:13.2 ± 4.7 F: 13.8 ± 3.2

For both males and females, slightly greater than dose proportional results were observed for AUC and Cmax across the 2.5- to 15-mg treatments. The extent of the deviations from dose

proportionality was greater in females than in males. Females appeared to have 30% higher AUCs than males. For terminal half-life (t½) and time to maximum plasma concentration (Tmax), generally consistent results were observed for each of the treatments for both males and females.

Renal clearance was observed to be greater in males than females across all doses. Overall, there was no significant difference in renal clearance ($p>0.1$). In females, a significant pairwise difference in the percent of dose excreted in the urine (Urine%dose) between the 2.5 versus 5-mg groups and 5-mg versus 15-mg treatments were observed ($p < 0.050$). Similar results were observed in male subjects for Urine%dose. For systemic clearance (CL), the overall geometric mean for males and females was 1010.8 and 807.8 mL/min, respectively; the difference between sexes was significant ($p = 0.022$). Body weight did not appear to effect the systemic clearance (Figure 6).

SAFETY:

Clinical Adverse Experiences--Number of Subjects						
Evaluated	With an Adverse Experience	With a Serious Adverse Experience	Died	With a Drug-Related Adverse Experience	With a Serious Drug-Related Adverse Experience	Discontinued Due to an Adverse Experience
24	19	1	0	13	0	0

One female subject had severe abdominal cramps and pain at the right colon after a 15 mg rizatriptan oral dose; the adverse experience was diagnosed as spastic colon and rated as serious and probably not drug related. None of the subjects were discontinued from the study due to a clinical adverse experience. There were no laboratory adverse experiences.

In conclusion, (1) the AUC and Cmax of oral rizatriptan increased slightly more than proportionately between 2.5 mg and 15 mg doses; lack of dose proportionality was noted more in females than males; (2) In males nonlinearity was observed at doses above 10 mg, whereas in females nonlinearity was observed at doses above 5 mg; (3) the AUC of rizatriptan is approximately 30% higher in females than in males; (4) the bioavailability of rizatriptan is approximately 40%; (5) the apparent t½ of rizatriptan is between 2 and 3 hours in males and females; (6) the Tmax of rizatriptan is less than 1 hour in males and females; (7) the systemic clearance of rizatriptan is approximately in males (1042 mL/min) than in females (821 mL/min); (8) the majority of the clearance of rizatriptan is nonrenal in males and females; and (9) oral doses of rizatriptan up to 15 mg and an i.v. dose of 4 mg appear to be safe and well tolerated by healthy males and females.

TITLE: An Open, Four-Period Crossover Study to Investigate the Dose Proportionality of Four Intravenous Doses of Rizatriptan in Healthy Female Subjects (Protocol-032, volume 50, page 9093).

The objectives of the study were to: (1) determine the plasma concentration profiles of rizatriptan following single intravenous dose administration of 0.5, 1.0, 2.5, and 5.0 mg and to investigate dose proportionality in healthy female subjects. (2) evaluate the safety and tolerability of single intravenous doses of rizatriptan administered at 0.5, 1.0, 2.5, and 5.0 mg in healthy females.

This was an open, single-dose, four-period crossover study in 8 healthy female subjects to investigate the dose proportionality of four treatments that are single intravenous doses of 0.5, 1.0, 2.5, and 5.0 mg (over 30 minutes) rizatriptan. The treatments were to be separated by 4 to 7 days. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles following i.v. administration of rizatriptan in females are presented in Figure 7 and the pharmacokinetic data for individual subjects are provided in Tables 23-28. The mean (sd) pharmacokinetic parameters for rizatriptan in females following i.v. administration are summarized in the following Table:

Parameter	Dose (mg)			
	0.5	1.0	2.5	5.0
$AUC_{0-\infty}$ (ng*hr/mL)	9.0 ± 1.1	18.7 ± 2.1	49.1 ± 5.7	105.3 ± 8.0
Cl (mL/min)	940.7 ± 132.9	899.9 ± 94.7	858.9 ± 101.4	796.6 ± 62.0
Vdss (L)	90.7 ± 20.0	105.5 ± 25.2	102.8 ± 11.9	90.7 ± 13.0
$T_{1/2}$ (hr)	1.6 ± 0.3	2.0 ± 0.5	2.3 ± 0.4	2.2 ± 0.3
Clr (mL/min)	129.6 ± 50.5	187.3 ± 76.9	239.2 ± 76.3	275.5 ± 70.9
Ue (% dose)	14.5 ± 5.6	20.4 ± 6.6	28.0 ± 9.2	34.6 ± 8.8

In females AUC appear to increase proportionally. Plasma clearance was significantly greater for the 0.5 mg dose than that for the 2.5 and 5 mg doses (p=0.04 and 0.001, respectively). In contrast, renal clearance was significantly less for the 0.5 mg dose than that for the 2.5 and 5 mg dose (p=0.015 and 0.002, respectively). Urinary excretion of rizatriptan increased significantly with increasing doses (p=0.01 and 0.001, respectively, for the 2.5 and 5 mg doses compared to 0.5 mg dose).

The dose-adjusted AUC geometric means and geometric mean ratios (90% confidence interval), and statistical analysis are summarized below:

90% Confidence Intervals for Dose-Adjusted (to 1.0 mg) $AUC_{0-\infty}$ (ng·hr/mL)
Geometric Mean Ratio in Relation to 0.5-mg Treatment

Treatment	N	Geometric Mean	Geometric Mean Ratio	90% CI for Geometric Mean Ratio	Within-Subject SD
0.5 mg	8	17.9	-	-	1.61
1.0 mg	8	18.6	1.04	(0.97, 1.12)	
2.5 mg	8	19.5	1.09	(1.02, 1.18)	
5.0 mg	8	21.0	1.18	(1.09, 1.26)	

Summary Statistics for Dose-Adjusted (to 1.0 mg) $AUC_{0-\infty}$ (ng·hr/mL)

Dose	N	Geometric Mean	Median	Between-Subject STD	Within-Subject CV	p-Values			
						Overall	1.0 vs.	2.5 vs.	5.0 vs.
0.5 mg	8	17.9	18.6	2.4	0.084	0.006	0.338	0.046	0.001
1.0 mg	8	18.6	17.9	2.0				0.262	0.010
2.5 mg	8	19.5	19.6	2.3					0.098
5.0 mg	8	21.0	21.3	1.6					

SAFETY: Eight subjects reported one or more nonserious adverse experiences. Seven of these subjects reported one or more adverse experiences that was rated as possibly, probably, or definitely drug related. No serious adverse experiences were reported. One subject discontinued from the study after experiencing dizziness, tachycardia, and diaphoresis. These experiences, which occurred approximately 23 hours after receiving the 1.0-mg dose of rizatriptan, were considered to be definitely not drug related.

In conclusion, the $AUC_{0-\infty}$ for rizatriptan appear to increase linearly with dose in females up to 5 mg following i.v. administration. Systemic clearance appeared to be independent of dose, however, renal clearance and % dose excreted in the urine increased significantly with increasing doses. Single intravenous doses of rizatriptan from 0.5 mg to 5.0 mg appear to be safe and well tolerated in healthy female subjects.

MULTIPLE DOSE STUDIES:

APPEARS THIS WAY
ON ORIGINAL

TITLE: A two-part, double-blind, placebo-controlled, alternating panel, incremental, multiple dose study of safety, tolerability, and preliminary multiple dose pharmacokinetic profile of rizatriptan in healthy volunteers (Protocol-010, volume 37, page 1119).

The objectives of the study were to: 1) assess the safety and tolerability of rizatriptan given as multiple oral doses within one day and over several days, and 2) obtain preliminary pharmacokinetic information on rizatriptan when given as multiple doses.

Sixteen healthy volunteers participated in this two-part study. In part I of the study incremental multiple doses were given within a single day and in part II multiple-dosing over 5 consecutive days was studied. Subjects were assigned to two panels (Panel A and B; n=8/panel) and each panel has to undergo up to four treatment periods in an alternating dose fashion. Two subjects in

each panel received placebo while the remaining 6 received active drug. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: This study was terminated after the first treatment period due to the occurrence of vasovagal syncope in 2/12 subjects who received 80 mg of rizatriptan over a 2 to 4 hr interval.

TITLE: A 2-Part, Double-Blind, Placebo-Controlled, Multiple Oral Dose Study to Determine the Safety, Tolerability, and Pharmacokinetic Profile of Rizatriptan in Healthy Volunteers (Protocol-018, volume 40, page 2495).

The objectives of the study were to: (1) assess the safety and tolerability of multiple oral doses of Rizatriptan within 1 day and over several days; (2) To obtain pharmacokinetic information on Rizatriptan when given as multiple oral doses; and (3) To assess the day-to-day variability in plasma profile over the first 4 hours post dose for oral doses of Rizatriptan.

This was a 2-part, double-blind, placebo-controlled study in 12 healthy volunteers (6 M: 6 F) to determine the safety and tolerability of rizatriptan when given as multiple oral doses within a single day (Part I) and pharmacokinetic profile of rizatriptan when given as multiple oral doses for 4 consecutive days (Part II). In part I, 5 mg rizatriptan was administered and in part II 10 mg rizatriptan was administered to subjects. Subjects who completed Part I could also participate in Part II; subjects in Part II were not required to have participated in Part I. Plasma samples were collected over 0-24 hrs post dose for all treatments.

RESULTS: The mean plasma concentration time profiles are presented in Figure 8 and the pharmacokinetic data for individual subjects for all treatments are provided in Tables 29 and 30. The mean (sd) pharmacokinetic parameters obtained for all treatments following 10 mg rizatriptan multiple oral dose administration are summarized in the following Table:

	$AUC_{0-\infty}$ (ng.hr/mL)	AUC_{0-24} (ng.hr/mL)	C_{max}	T_{max}	$T_{1/2}$
Day 1	M: 174±106 F: 214±50	M: 172±106 F: 211±52	M: 23.4±17.2 F: 24.4±7.2	M: 6.4±2.1 F: 6.9±4.2	M: 3.3±0.5 F: 3.5±1.0
Day 4	---	M: 175±73 F: 215±49	M: 25.6±9.2 F:30.9±12.7	M: 5.1±3.0 F: 4.8±2.6	M: 3.2±1.0 F: 3.0±0.5

Overall, the rizatriptan plasma concentration versus time profiles for Days 1 and 4 were similar. Geometric mean values for AUC_{0-24} on day 4 and $AUC_{0-\infty}$ on day 1 were 184 and 177 ng.hr/mL, respectively. Thus, the geometric mean ratio (GMR) was 1.04 [90% CI: 94-114)]. Geometric

mean values for AUC_{0-24} on day 4 and AUC_{0-24} on day 1 were 184 and 175 ng.hr/mL, respectively; the GMR was 1.05 [90% CI: 95-115]. Differences in plasma profile over the first 4 hours of dosing (following the first daily dose of rizatriptan) across days also were not significant ($p = 0.1951$); the geometric means for AUC_{0-4} on days 1, 2, 3, and 4 were 38, 44, 42, and 42 ng.hr/mL, respectively. Similarly no difference in Cmax was observed, however, in females, upon multiple dosing the Cmax was found to be greater by 25%, compared to first dose.

SAFETY: None of the subjects had a serious clinical or laboratory adverse experience, discontinued the study because of a clinical or laboratory adverse experience, or died due to a clinical or laboratory adverse experience. In Part I, 1 male subject (AN 003) receiving placebo and 1 female subject (AN 006) at the Rizatriptan 5-mg dose each had 1 incident of mild headache rated as possibly drug related; both subjects recovered without treatment and with no residual effects. None of the subjects receiving rizatriptan reported a clinical adverse experience during Part II. None of the subjects had a laboratory adverse experience considered to be drug related.

In conclusion, rizatriptan was well tolerated by healthy men and women at an oral dosing regimen of 10 mg q4h for 3 doses per day for 4 consecutive days. At the above dosing regimen, there is no evidence of significant accumulation of rizatriptan between Day 1 and Day 4. There is little day-to-day variability in AUC of rizatriptan over the first 4 hours of dosing following a 10-mg dose on consecutive dosing days.

TITLE: A Double-Blind, Parallel, Randomized, Placebo-Controlled Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Multiple Doses of Rizatriptan in Healthy Male and Female Subjects (Protocol-035, volume 51, page 9862).

The objectives of the study were to: (1) investigate the safety and tolerability of a multiple-dose regimen of rizatriptan administered every 2 hours for three doses on 4 consecutive days; (2) evaluate plasma concentration profile and renal clearance of rizatriptan when given as a single 10-mg dose and multiple oral doses q2h; and (3) evaluate plasma concentration profile and renal clearance of the N-desmethyl metabolite of rizatriptan (L-706,248) when rizatriptan is given as a single 10 mg dose and as multiple oral doses q2h.

This was a double-blind, parallel study in 36 healthy subjects (18 M; 18 F). Subjects received a single dose of 10 mg rizatriptan or placebo on Day 1, and 10 mg rizatriptan or placebo orally every 2 hours for three doses on Days 3, 4, 5, and 6. Plasma samples were collected over 0-24 hrs post dose for all treatments.

DOSAGE/FORMULATION NOS.: Rizatriptan 10-mg tablet and matching placebo tablet were used in this study. The formulation numbers are as follows: rizatriptan 10-mg tablet (E-8484R); placebo to match the 10-mg tablet (E-8414).

RESULTS: The mean plasma concentration time profiles following oral administration of 10 mg rizatriptan tablet on days 1, 3, and 6 are presented in Figures 9 and 10 and the pharmacokinetic data for rizatriptan and the N-desmethyl metabolite rizatriptan for individual subjects are provided in Tables 31-34. The mean (sd) pharmacokinetic parameters for rizatriptan and the metabolite following multiple doses are summarized in the following Table:

Parameter (Rizatriptan)	Day 1	Day 3	Day 6
AUC_{0-24} (ng*hr/mL)	M:59.7 ± 13.1 F: 67.3 ± 11.6 Overall: 63.5 ± 12.6	M:196.3 ± 55.0 F:200.4 ± 32.6 Overall: 198.3 ± 43.7	M:197.4 ± 37.6 F: 206.3 ± 54.6 Overall: 201.8 ± 45.5
$AUC_{0-\infty}$ (ng*hr/mL)	M:59.8 ± 13.1 F: 67.4 ± 11.6 Overall: 63.6 ± 12.6	—	—
Cmax (ng/mL)	M:18.6 ± 4.4 F: 20.6± 5.5 Overall:19.6 ± 4.9	M:36.3 ± 9.9 F: 35.2 ± 8.3 Overall: 35.7 ± 8.9	M:33.5 ± 6.9 F: 40.5 ± 16.3 Overall: 37.0 ± 12.6
Tmax (hr)	M:1.1 ± 0.4 F: 0.7 ± 0.3 Overall: 0.9 ± 0.4	M:1.0 ± 0.5 F: 0.9 ± 0.5 Overall: 1.0 ± 0.5	M:0.8 ± 0.4 F: 1.2 ± 0.5 Overall: 1.0 ± 0.4
$T_{1/2}$ (hr)	M:2.2 ± 0.4 F: 2.1 ± 0.3 Overall: 2.2 ± 0.4	M:2.0 ± 0.4 F: 2.0 ± 0.5 Overall: 2.0 ± 0.4	M:2.6 ± 0.3 F: 1.8 ± 0.3 Overall: 2.2 ± 0.5
Clr (mL/min)	M:198.7 ±58.2 F:206.7 ± 63.2 Overall: 202.7 ± 58.8	M:264.6 ± 144.9 F: 278.2 ± 165.8 Overall: 272.4 ±151.4	M:145.4 ± 24.5 F: 212.0 ± 93.5 Overall: 183.6± 77.9

Geometric Mean AUC (ng•hr/mL) for Rizatriptan After Multiple Dosing (Day 6) Compared with Single Dosing (Day 1)

	Geometric Mean Day 6	Geometric Mean Day 1[a]	Geometric Mean Ratio (Day 6/Day 1)	Upper 90% Confidence Limit (One-Sided)	p-Value
Day 6 $AUC_{(0-\tau)}$ vs. Day 1 $AUC_{(0-\infty)}$	196.3	187.0	1.05	1.11	>0.250
Day 6 $AUC_{(0-\tau)}$ vs. Day 1 $AUC_{(0-\tau)}$	196.3	186.8	1.05	1.11	>0.250

[a] Dose-adjusted by a factor of three.

The geometric mean ratio of Day 6 to Day 1 was 1.05, and the upper 90% confidence limit for the geometric mean ratio was 1.11, indicating that there is no accumulation of rizatriptan up on multiple dosing (q2h for 4 days). Further, comparison of pharmacokinetic parameters of rizatriptan between females and males indicated no significant gender effect or day-by-gender interaction (Table 31).

Parameter (N-desmethyl rizatriptan)	Day 1	Day 3	Day 6
AUC_{0-24} (ng*hr/mL)	M:8.4 ± 1.4 F: 8.6 ± 1.4 Overall: 8.5 ± 1.4	M:23.0 ± 2.5 F:24.9 ± 4.7 Overall: 23.9 ± 3.8	M:25.3 ± 1.9 F: 27.1 ± 6.4 Overall: 26.2 ± 4.6
$AUC_{0-\infty}$ (ng*hr/mL)	M:8.4 ± 1.4 F: 8.7 ± 1.4 Overall: 8.5 ± 1.4	—	—
Cmax (ng/mL)	M: 2.1 ± 0.4 F: 2.2± 0.5 Overall:2.2 ± 0.5	M:3.3 ± 0.8 F: 3.5 ± 0.8 Overall: 3.4 ±0. 8	M:3.2 ± 0.3 F: 4.3 ± 1.3 Overall: 3.7 ± 1.1
Tmax (hr)	M:1.4 ± 0.5 F: 1.6 ± 0.5 Overall: 1.5 ± 0.5	M:1.3 ± 0.5 F: 1.3 ± 0.5 Overall: 1.3 ± 0.5	M:1.5 ± 0.5 F: 1.3 ± 0.4 Overall: 1.4 ± 0.4
$T_{1/2}$ (hr)	M:2.7 ± 1.1 F: 1.9 ± 0.8 Overall: 2.3 ± 1.0	M:2.6 ± 0.4 F: 2.4 ± 0.6 Overall: 2.5 ± 0.5	M:3.1 ± 0.6 F: 1.9 ± 0.3 Overall: 2.5 ± 0.8
Clr (mL/min)	M:130.4 ± 56.6 F:171.0 ± 50.2 Overall: 150.7 ± 55.7	M:178.2 ± 83.1 F: 192.2 ± 108.8 Overall: 186.2 ±95.1	M:109.1 ± 34.1 F: 155.4 ± 56.3 Overall: 135.6± 52.1

Geometric Mean AUC (ng•hr/mL) for L-706,248 After Multiple Dosing (Day 6) Compared with Single Dosing (Day 1)

	Geometric Mean Day 6	Geometric Mean Day 1 [a]	Geometric Mean Ratio (Day 6/Day 1)	Upper 90% Confidence Limit (One-Sided)	P-Value
Day 6 $AUC_{(0-\infty)}$ vs. Day 1 $AUC_{(0-\infty)}$	25.8	25.3	1.02	1.08	>0.250
Day 6 $AUC_{(0-24)}$ vs. Day 1 $AUC_{(0-24)}$	25.8	25.2	1.02	1.09	>0.250

[a] Dose-adjusted by a factor of three.

The data above show that the metabolite also does not accumulate. However, the mean Cmax on Day 6 was significantly greater in females than in males ($p<0.01$) upon multiple dosing.

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) were measured at baseline, 30 minutes, and every hour for six hours. On the last day, additional vital sign measurements at 7, 8, 10, 2, 16, and 24 hours were recorded. Diastolic blood pressure (DBP) increased after multiple dosing. This was most apparent on day 3 where an average of 5 mm increase in DBP was seen, and was statistically significant at most time points (Table 34; Figure 11). DBP in placebo patients went down. Systolic blood pressure (SBP) also increased but failed to reach statistical significance. Heart rate changes were similar in the two groups.

SAFETY: All 36 subjects were included in the assessment of safety and tolerability. Twenty-seven subjects reported one or more nonserious clinical adverse experiences. No laboratory adverse experiences were reported and no subjects died during the study. No subjects discontinued the study due to an adverse experience.

In conclusion, rizatriptan regimen of 10 mg every 2 hours for three doses on as many as 4 consecutive days appears to be generally well tolerated. Plasma concentrations (i.e., AUC) of rizatriptan after administration of three 10-mg doses every 2 hours are approximately threefold greater than the plasma concentrations following a single 10-mg dose. There is no unexpected accumulation. A similar result was observed for the N-desmethyl rizatriptan.

BIOAVAILABILITY STUDIES:

TITLE: An Open-Label, Two-Period Crossover Study to Examine the Pharmacokinetics, Taste, Safety, and Tolerability of Single Doses of Rizatriptan 10 mg Rapidisc™ and Rizatriptan 10 mg Tablet in Healthy Male Subjects (Protocol-033, volume 51, page 9551).

The objectives of the study were to: (1) compare the relative bioavailabilities of rizatriptan Rapidisc™ and rizatriptan tablet; (2) compare the mean peak plasma concentrations (Cmax) following a single dose of the rizatriptan 10 mg Rapidisc™ and rizatriptan tablet; (3) evaluate the taste of rizatriptan 10 mg Rapidisc™; and (4) evaluate the safety and tolerability of a single dose of the rizatriptan 10 mg Rapidisc™.

Twelve healthy male subjects received a single dose of rizatriptan 10 mg Rapidisc™, matching placebo, and rizatriptan 10 mg tablet. Plasma samples were collected over 0-24 hrs post dose for all treatments. The formulation numbers are as follows: rizatriptan 10 mg Rapidisc™ (E-8524); placebo to match the 10 mg Rapidisc™ (E-8526); rizatriptan 10 mg tablet (E-8407R).

RESULTS: The mean plasma concentration time profiles following oral administration of 10 mg rizatriptan Rapidisc and tablet are presented in Figure 11 and the pharmacokinetic data for individual subjects are provided in Table 35. The mean (sd) pharmacokinetic parameters for rizatriptan following single dose administration of rizatriptan Rapidisc and tablet are summarized in the following Table:

Parameter	Rapidisc	Tablet	p-values
$AUC_{0-\infty}$ (ng*hr/mL)	119 ± 40	123 ± 44	>0.25
Cmax (ng/mL)	33.7 ± 10.2	44.3 ± 19.6	0.019
Tmax (hr)	1.5 ± 0.6	0.8 ± 0.2	<0.01
$T_{1/2}$ (hr)	2.0 ± 0.3	2.0 ± 0.4	—

The results indicate that the mean AUC for the Rapidisc™ and for the tablet were similar. However, the mean Cmax was significantly lower (p=0.019) for the Rapidisc™than for the tablet. Mean Tmax was statistically significantly longer for the Rapidisc™ than for the tablet formulation, p<0.01.

Taste Assessment: Overall, all 12 subjects rated the placebo Rapidisc™ as tasting better than or average for a medication. Eight of the 12 subjects rated the rizatriptan 10-mg Rapidisc™ as tasting better than or average for a medication. While the placebo Rapidisc™ appeared to have a more acceptable taste than the Rapidisc™, in no subject was the taste so objectionable as to preclude further evaluation of this formulation.

Safety: One subject reported a clinical adverse experience. No serious adverse experiences were reported. No clinically significant trends were identified in blood pressure and heart rate changes.

In conclusion, the relative extent of absorption of the 10 mg rizatriptan Rapidisc™ is equivalent to the 10 mg tablet. However, the Cmax is greater and Tmax shorter for the tablet than the Rapidisc™ and the Rapidisc™ appear to be absorbed more slowly than the rizatriptan tablet. Most subjects rated the rizatriptan 10 mg Rapidisc™ as tasting better than average or average for a medication. A single dose of the rizatriptan 10 mg Rapidisc™ appears to be safe and well tolerated.

TITLE: An Open-Labeled, Four-Period Crossover Study to Compare the Plasma Concentration Profiles and to Estimate the Bioavailability of Single 10-mg Doses of Rizatriptan (in Three Formulations) in Healthy Male Subjects (Protocol-040, volume 56, page 12830).

The objectives of the study were to: (1) compare the plasma concentration profiles of 10 mg rizatriptan tablets used in the Phase IIb dose-finding study to the Phase III FMI formulation; (2) compare the plasma concentration profiles of two 5-mg rizatriptan tablets used in the initial Phase I study to the Phase III FMI formulation; (3) compare the mean peak plasma concentrations (Cmax) following single 10 mg doses of the rizatriptan tablets in three formulations; and (4) estimate bioavailability for each of the tablet formulations used in the study.

This study (randomized crossover for the first three periods) was conducted in 18 healthy male subjects to evaluate the equivalence and pharmacokinetics of single 10 mg doses of rizatriptan tablets in three different formulations, and a fixed treatment in the fourth period with i.v. rizatriptan to estimate the bioavailability for each tablet formulation. Four single-dose treatments (3 oral, one I.V.), with at least 4 to 7 days separating each treatment. Plasma samples were collected over 0-24 hrs post dose for all treatments.
DOSAGE/FORMULATION #S: Treatment A: rizatriptan two 5 mg oral tablets of initial Phase I formulation; E-4845. Treatment B: rizatriptan one 10 mg encapsulated oral tablet of Phase IIb formulation; E-8673. Treatment C: rizatriptan one 10 mg oral tablet of the final Phase III formulation; E-8407R. Treatment D: rizatriptan one infusion over 30 minutes, 4-mL of 1 mg/mL sterile solution for I.V. infusion, for a total dose of 4 mg.

RESULTS: The mean plasma concentration time profiles for rizatriptan of all formulations are presented in Figure 13 and the pharmacokinetic data for individual subjects for rizatriptan for all treatments are provided in Table 36. The mean (sd) pharmacokinetic parameters of rizatriptan for all formulations are summarized in the following Table:

Parameter	Phase I Tablet	Phase IIb Tablet	Phase III Tablet	I.V.
$AUC_{0-\infty}$ (ng.hr/mL)	50.7 ± 15.4	49.5 ± 14.6	53.2 ±14.4	49.4 ± 8.4
Cmax (ng/mL)	18.0 ± 5.6	16.8 ± 5.5	19.6 ± 6.1	----
Tmax (hr)	0.9 ± 0.4	1.3 ± 0.7	1.0 ± 0.6	----
$T_{1/2}$ (hr)	1.9 ± 0.4	1.7 ± 0.3	1.8 ± 0.3	2.0 ± 1.0
Clr (mL/min)	345.7 ± 83.7	353.3 ± 76.7	344.9 ± 61.0	353.9 ± 100.0
Ue (%)	10.2 ± 3.0	10.3 ± 3.0	10.8 ± 2.6	25.4 ± 5.2
F	0.41 ± 0.1	0.40 ± 0.08	0.43 ± 0.09	---

Pharmacokinetic Parameters for Rizatriptan (N=18)

	Geometric Mean			Geometric Mean Ratio with 90% Confidence Interval		
	Phase I	Phase IIb	Phase III	Phase IIb / Phase III	Phase I / Phase III	Phase IIb / Phase I
$AUC_{(0-\infty)}$ (ng•hr/mL)	48.70	47.70	51.35	0.93 (0.86, 1.00)	0.95 (0.88, 1.02)	0.98 (0.91, 1.05)
C_{max} (ng/mL)	17.23	15.96	18.77	0.85 (0.75, 0.97)	0.92 (0.81, 1.04)	0.93 (0.82, 1.05)

Bioavailability for Rizatriptan (N=18)

	Geometric Mean with 90% Confidence Interval		
	Phase I	Phase IIb	Phase III
F	0.40 (0.36, 0.44)	0.39 (0.36, 0.42)	0.42 (0.38, 0.46)

The results indicate that the three tablet formulations are bioequivalent interms of mean $AUC_{0-\infty}$ and Cmax, except for the mean Cmax of Phase IIb formulation vs Phase III formulation. The data also indicates that the time to maximum concentration (Tmax) is longer following dosing of the Phase IIb formulation than the Phase III formulation (p=0.073). The bioavailabilities of the Phase I, IIb, and Phase III formulations of rizatriptan range from 36% to 46% based on 90% confidence intervals. The mean bioavailability for the three rizatriptan tablet formulations in healthy males was observed to be about 40%.

SAFETY: There were no serious clinical, laboratory, or other adverse experiences and no subjects died during the study.

In conclusion, the mean $AUC_{0-\infty}$ of the Phase IIb formulation is equivalent to that of the Phase III formulation of rizatriptan. However, the Phase IIb formulation of rizatriptan produces slightly lower peak plasma concentrations than the Phase III formulation. The $AUC_{0-\infty}$ and Cmax of the Phase IIb and Phase III formulations are equivalent to those of the Phase I formulation. The mean bioavailability for the three rizatriptan tablet formulations in healthy males was observed to be about 40%.

TITLE: An Open-Labeled, Randomized, Two-Panel, Crossover Study to Determine The Absolute Bioavailability of 5-mg and 10-mg Rizatriptan in Final Market Composition (FMC) Tablet and RAPIDISC™ Formulations (Protocol-042, volume 59, page 14390).

The objectives of the study were to: (1) assess the absolute bioavailability of 5-mg and 10-mg rizatriptan FMC tablets in females; (2) assess the absolute bioavailability of 5-mg and 10-mg rizatriptan FMC RAPIDISC™ in females and 10-mg FMC RAPIDISC™ in males; and (3)

compare the rizatriptan plasma concentrations following administration of the FMC RAPIDISC™ to the FMC tablets in females.

This was an open-labeled, randomized, two-panel study. Panel I consisted of 12 healthy males who received the 10-mg rizatriptan RAPIDISC™ in a single period; Panel II consisted of 12 healthy females who received 5-mg and 10-mg rizatriptan tablet, and 5-mg and 10-mg rizatriptan RAPIDISC™, in a four-period, crossover fashion, with each separated by 4 to 10 days. In each period, along with the oral dose, subjects also received a simultaneous intravenous infusion of 1.0-mg stable heavy-labeled isotope [triazole-$_{13}$ C_2,$_{15}N_3$] rizatriptan solution over 50 minutes to permit estimation of absolute bioavailability. Plasma samples were collected over 0-24 hrs post dose for all treatments.
DOSAGE/FORMULATION NOS.: Treatment A = 5-mg rizatriptan oral tablet; (E-8483R) Treatment B = 10-mg rizatriptan oral tablet; (E-8484R) Treatment C = 5-mg rizatriptan oral RAPIDISC™; (E-8724R) Treatment D = 10-mg rizatriptan oral RAPIDISC™; (E-8725R)

RESULTS: The mean plasma concentration time profiles for rizatriptan of all treatments are presented in Figure 14 and the pharmacokinetic data for individual subjects for rizatriptan for all treatments are provided in Tables 37-39. The mean (sd) pharmacokinetic parameters of rizatriptan for all treatments are summarized in the following Table:

Mean pharmacokinetic parameters for rizatriptan following oral administration:

Parameter	Male	Females			
	10 mg Rapidisc	5 mg Tablet	10 mg Tablet	5 mg Rapidisc	10 mg Rapidisc
$AUC_{0-\infty}$ (ng.hr/mL)	56.3 ± 16.9	34.5 ± 13.0	73.9 ±23.4	33.2 ± 9.8	75.9 ± 24.7 ↑ 35%
Cmax (ng/mL)	16.6 ± 6.0	10.4 ± 3.9	21.3 ± 6.9	11.1 ± 4.7	20.3 ± 7.9 ↑ 22%
Tmax (hr)	2.5 ± 0.9	1.0 ± 0.6	1.5 ± 0.8	1.6 ± 0.8	2.5 ± 1.4
$T_{1/2}$ (hr)	2.1 ± 0.7	1.8 ± 0.4	1.8 ± 0.3	1.7 ± 0.4	1.7 ± 0.2
Clr (mL/min)	388.8 ± 78.7	316.2 ± 65.7	320.0 ± 73.2	347.5 ± 117.0	350.7 ± 62.2
Ue (%)	12.6 ± 2.7	12.7 ± 4.5	13.8 ± 3.9	13.3 ± 3.9	15.5 ± 3.9
F	0.47 ± 0.1	0.41 ± 0.08	0.45 ± 0.05	0.42 ± 0.06	0.47 ± 0.06

Mean pharmacokinetic parameters for rizatriptan following i.v. administration:

Parameter	Male	Females			
	10 mg Rapidisc	5 mg Tablet	10 mg Tablet	5 mg Rapidisc	10 mg Rapidisc
$AUC_{0-\infty}$ (ng.hr/mL)	11.9 ± 2.0	16.6 ± 3.6	16.2 ±3.8	15.6 ± 3.5	15.9 ± 3.6
CL (mL/min)	1443.4 ± 247.8	1050.5 ± 224.5	1081.6±239.4	1121.2±241.6	1099.3 ± 251.7
MRT (hr)	1.9 ± 0.5	2.0 ± 0.4	2.0 ± 0.3	1.9 ± 0.5	2.1 ± 0.4
$T_{1/2}$ (hr)	1.8 ± 0.3	1.9 ± 0.4	1.6 ± 0.3	1.6 ± 0.3	1.9 ± 0.5
Clr (mL/min)	371.2 ± 80.2	313.5 ± 82.4	323.6 ± 65.6	312.9 ± 86.5	345.2 ± 69.7
Ue (%)	25.6 ± 2.9	30.2 ± 7.1	30.4 ± 4.6	28.5 ± 7.4	31.9 ± 4.7
Vss (L)	162.4 ± 40.9	125.9 ± 37.3	127.5 ± 25.1	126.0 ± 44.9	134.2 ± 28.5

Pharmacokinetic Parameters ($AUC_{(0-\infty)}$, C_{max}) for Rizatriptan 5-mg Tablet and RAPIDISC™ in Females (N=12)

	Geometric Mean		Geometric Mean Ratio (RAPIDISC™ / Tablet)	90% Confidence Interval	p-Value
	Rizatriptan 5-mg Tablet	Rizatriptan 5-mg RAPIDISC™			
$AUC_{(0-\infty)}$ (ng.hr/mL)	32.37	31.86	0.98	(0.91, 1.07)	0.743
C_{max} (ng/mL)	9.75	10.39	1.07	(0.92, 1.23)	0.460

Pharmacokinetic Parameters ($AUC_{(0-\infty)}$, C_{max}) for Rizatriptan 10-mg Tablet and RAPIDISC™ in Females (N=12)

	Geometric Mean		Geometric Mean Ratio (RAPIDISC™ /Tablet)	90% Confidence Interval	p-Value
	Rizatriptan 10-mg Tablet	Rizatriptan 10-mg RAPIDISC™			
$AUC_{(0-\infty)}$ (ng.hr/mL)	70.70	72.40	1.02	(0.94, 1.11)	0.623
C_{max} (ng/mL)	20.23	18.95	0.94	(0.81, 1.08)	0.452

The results indicate that the mean absolute bioavailability for tablets and rapidiscs in females and males was about 0.45. Further, the data suggests that both $AUC_{0-\infty}$ and Cmax of the two formulations i.e., tablet and rapidisc are equivalent at the 5 and 10 mg dose. However, the time to maximum concentration is longer for both 5 and 10 mg Rapidisc formulation than for the 5 and 10 mg tablets (p=0.005 and 0.021, respectively). In addition, the mean $AUC_{0-\infty}$ was found to be statistically significantly greater in females when compared to males (↑by 35%; p=0.036) following the oral administration of 10 mg Rapidisc, but mean Cmax was not statistically significantly different between females and males (p=0.233).

SAFETY: There was one serious clinical adverse experience of elective abortion. There were no serious laboratory or other adverse experiences and no subjects died during the study.

In conclusion, the mean absolute bioavailabilities of the tablet and rapidisc formulations in females and males ranged Both $AUC_{0-\infty}$ and Cmax of the two formulations were equivalent at the 5 and 10 mg doses, and the Tmax of the tablet formulation is shorter than the Tmax of the Rapidisc™ formulation at both the 5 and 10 mg doses.

MASS BALANCE/METABOLISM:

TITLE: An open study to investigate the disposition of a single oral and a single intravenous dose of ^{14}C-rizatriptan in healthy male volunteers (Protocol-013, volume 38, page 1473).

The objectives the study were to: (1) identify the major metabolites of rizatriptan that are present in plasma, urine, and feces following intravenous and oral administration of ^{14}C-rizatriptan in healthy volunteers and (2) investigate the primary route of elimination of rizatriptan when administered intravenously and orally.

This was an open-label, two-period crossover study in 6 healthy male volunteers. In the first period each subject received an i.v. infusion of 3 mg of ^{14}C-rizatriptan (75μCi) over 30 minutes and in the second period following a two-week washout period each subject received a 10 mg (two 5 mg capsules) oral dose of ^{14}C-rizatriptan (75μCi). Following the i.v., and oral doses blood, plasma, urine, and fecal samples were collected over 0-120 hrs and were analyzed for total radioactivity, parent compound, and metabolites.

RESULTS: The excretion/mass balance of ^{14}C-rizatriptan was determined following i.v., and oral administration. The mean plasma concentration of rizatriptan and total radioactivity time profiles are presented in Figure 15 and the pharmacokinetic data for individual subjects for all treatments are provided in Table 40. The mean (sd) pharmacokinetic parameters obtained for all treatments are summarized in the following Tables:

Pharmacokinetic parameters of rizatriptan and ^{14}C-radioactivity in healthy males receiving a single oral dose of 10 mg of ^{14}C-rizatriptan.

			Rizatriptan			^{14}C-Radioactivity			
	AUC	Cmax	Tmax	t1/2	CLr	AUC	Cmax	Tmax	t1/2
	(ng hr/ml)	(ng/ml)	(hr)	(hr)	(ml/min)	(ng eq hr/ml)	(ng eq/ml)	(hr)	(hr)
Mean	59.8	19.8	1.4	2.2	396	333.8	59.0	1.8	5.6
S.D.	23.6	9.8	1.4	0.3	112	43.4	8.2	1.2	0.5

Pharmacokinetic parameters of rizatriptan and ^{14}C-radioactivity in healthy male receiving a single i.v. dose of 3 mg of ^{14}C-rizatriptan.

				Rizatriptan			^{14}C-Radioactivity	
	AUC	CL	V_{ss}	CLr	CLr/CL	t1/2	AUC	t1/2
	(ng hr/ml)	(ml/min)	(l)	(ml/min)		(hr)	(ng eq hr/ml)	(hr)
Mean	38.1	1325	154	349	0.26	2.5	125.2	5.9
S.D.	5.4	195	28	50	0.04	0.5	10.8	0.9

Mean (±S.D.) ^{14}C-radioactivity in excreta of healthy males (N=6) receiving separately a 3 mg i.v. dose and 10 mg oral dose of ^{14}C-rizatriptan

Dose/Route	Percent Dose excreted (0-120 hr)		
	Urine	Feces	Total
3 mg i.v.	89.5 ± 3.2	4.4 ± 1.4	93.8 ± 2.6
10 mg p.o.	82.4 ± 9.0	11.5 ± 2.4	93.9 ± 8.8

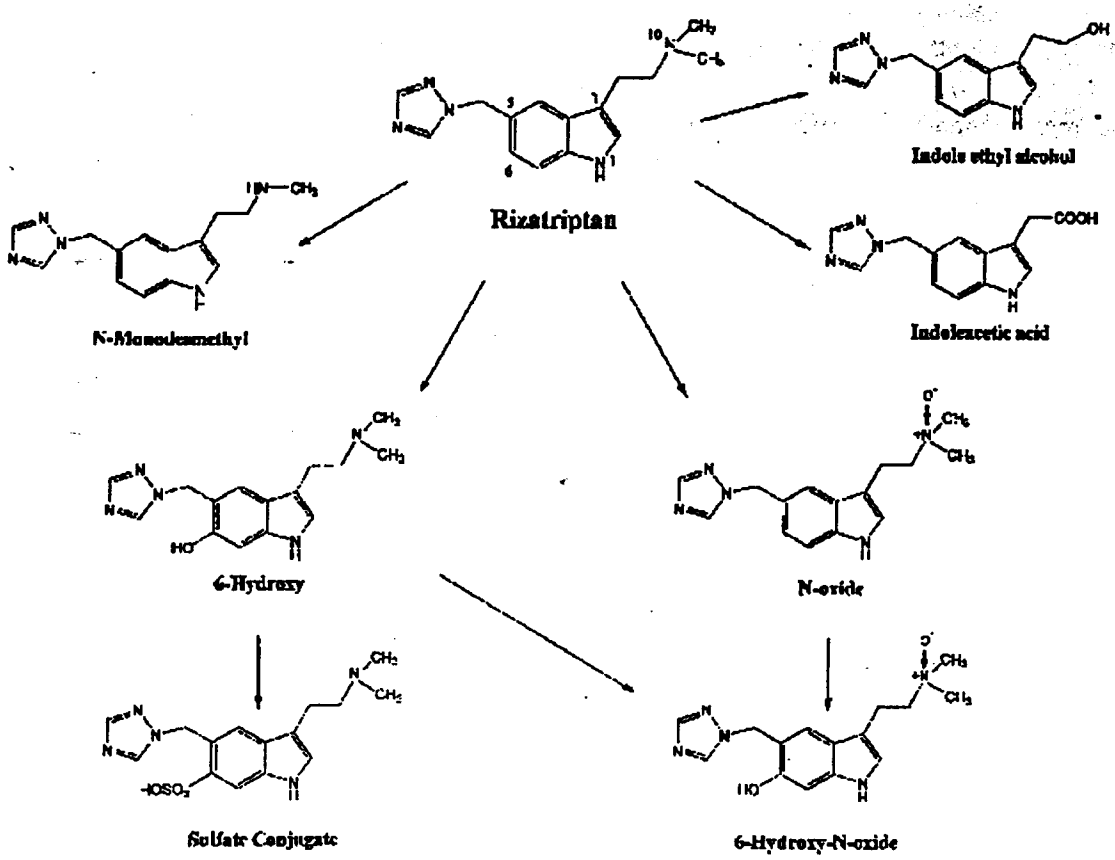
Quantitation of rizatriptan and metabolites (relative to total radioactivity) in human samples following administration of a 3 mg i.v. dose and 10 mg oral dose of ^{14}C-rizatriptan separately in healthy male volunteers (N=6)

Sample		% of Dose		
		Rizatriptan	Rizatriptan-N-10-oxide	Rizatriptan-indole acetic acid
Urine (0-24 hr)	3 mg i.v. 10 mg p.o..	29.3 14.0	3.7 2.3	34.6 51.0
Plasma (1-4 hr)	3 mg i.v. 10 mg p.o..	24.4 26.6	9.0 5.8	35.6 40.2

The major metabolite of rizatriptan in plasma and urine was identified as the indole-3-acetic acid of rizatriptan. A minor metabolite was also identified as rizatriptan-N-10-oxide. Based on analyses of urinary radioactivity after oral and IV dosing, approximately of an oral dose of rizatriptan was absorbed. However, bioavailability was only 45%. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 18% of circulating plasma radioactivity. It was also observed that approximately of an oral dose is excreted in urine as unchanged rizatriptan while is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism. Mean values of plasma clearance (CL) and renal clearance (Clr) of rizatriptan were 1325 and 349 mL/min, respectively, following the i.v. dose. A similar mean renal clearance (Clr) value was obtained following the oral dose. Further, it was noticed that the elimination half-life of radioactivity was about 6 hrs, where as that of rizatriptan was about 2-3 hrs, indicating that metabolites may be circulating longer in plasma than the parent compound.

Further, from a pooled human urine following administration of 60 mg unlabeled rizatriptan in six healthy male subjects, five metabolites were identified of which indole-3-acetic acid is the major metabolite and the rest are minor metabolites which include the N-10-oxide, 6-hydroxy-rizatriptan, the sulfate conjugate of 6-hydroxy-rizatriptan, and N-monodesmethyl rizatriptan. Of these metabolites, N-monodesmethyl rizatriptan was found to have activity similar to that of parent compound at the 5-HT_{1D} receptor, but the plasma concentrations of this metabolite were approximately , of those of parent rizatriptan and is eliminated at a similar rate. Thus, it may not contribute significantly to the pharmacodynamic activity of rizatriptan.

The metabolic pathway of rizatriptan is depicted below.



From the structures of these metabolites, four metabolic pathways are evident, viz., oxidative deamination, oxidative hydroxylation with subsequent sulfate conjugation,, N-dealkylation, and N-oxygenation. A similar metabolic profile is observed in rats and dogs.

SAFETY: Three out of all 6 subjects reported a total of 5 (nonserious) clinical adverse experiences that consisted of headache, nausea, and upper respiratory tract symptoms. All of the clinical adverse experiences were mild in intensity and were rated as possibly or probably not related to study drug. All symptoms resolved. There were no serious clinical adverse experiences. No subjects were discontinued from the study due to a clinical adverse experience.

In conclusion, indole-3-acetic acid of rizatriptan is the major metabolite both in the circulation and in the urine following both oral and IV administration. The major route(s) of elimination of rizatriptan is nonrenal, with the kidneys being the primary route of elimination of the metabolites