DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Maxalt Tablets**
Generic Name:	**rizatriptan benzoate**
Sponsor:	**Merck**
Indication:	**migraine**
NDA Number:	**20-864**
Original Receipt Date:	**6/30/97**
Clinical Reviewer:	**Armando Oliva, M.D.**
Review Author:	**Armando Oliva, M.D.**
Review Completed:	**3/25/98**

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1. Review Sources

The Maxalt NDA was an entirely electronic submission. I used primarily electronic sources on the Merck server maintained by OIT (office of information technology).

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Table 1: Review Sources

Source	Submission Date	Material
Vol 1.1	6/30/97	Index
Vol 1.2	6/30/97	NDA Summary
electronic NDA	6/30/97	Maxalt NDA in electronic format
electronic datasets	6/30/97	electronic datasets
updated efficacy datasets	2/98	electronic datasets

2. Background

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2.1 Indication

Rizatriptan is a selective $5HT_{1D}$ agonist, which is being developed for the treatment of migraine with or without aura.

2.2 Important Information from pharmacologically related agents

Rizatriptan is pharmacologically similar to sumatriptan. Because of the potential for this class of compounds ($5\text{-}HT_{1D/1B}$ agonists) to cause coronary vasospasm, they should not be used in patients with coronary artery disease (CAD) or in patients in whom unrecognized CAD is likely without a prior evaluation.

2.3 Administrative History

Key administrative dates for the rizatriptan development program is shown in Table 2. MG/KG-462, a selective $5HT_{1D}$ receptor agonist which is now known as rizatriptan.

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In the 10/24/96 meeting, the format of the electronic submission was agreed upon. On 3/27/97, the FDA granted the sponsor a waiver of "hard copy" requirements of 21 CFR 314.50(f) in lieu of an electronic version.

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2.4 Proposed Labeling

The highlights of the proposed labeling are summarized here. A more detailed review of the labeling is located in Section 10 of this review.

2.4.1 Indication

Maxalt is indicated for the treatment of acute migraine attacks with or without aura.

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2.4.2 Dosing

The recommended initial dose is 10 mg tablet or RAPIDISC™. Five (5) mg has also been shown to be effective, but is less so. The dose may be repeated every two hours for recurrence, up to a maximum of 30 mg in a 24 hour period. Patients on propranolol should take 5 mg.

2.4.3 Contraindication, Warnings, and Precautions

Maxalt in contraindicated in patients with established coronary artery disease, uncontrolled hypertension, known hypersensitivity to the formulation, or to anyone using an MAO inhibitor within two weeks.

Maxalt should not be used in patients with basilar or hemiplegic migraine, or in patients without a clear diagnosis of migraine. Other $5HT_{1D}$ agonists should not be used with Maxalt. Ergotamine type medications (*e.g.*, ergotamine tartrate, DHE) should not be given within 6 hours of Maxalt use.

Rare reports of serious coronary events with another drug in this class have been reported. Prior to the use of this drug, a cardiovascular assessment should be considered in patients with know risk factors for coronary artery disease.

Phenylketonurics should be aware that the RPD formulation contains phenylalanine.

Maxalt may cause drowsiness in some patients.

2.4.4 Drug Interactions

MAO-A inhibitors can cause significant elevations in Maxalt serum concentrations (up to 400%). The use of MAO inhibitors in this setting is contraindicated.

Propranolol 240 mg/day caused a 70% increase in Maxalt serum concentrations.

2.4.5 Carcinogenesis, Mutagenesis, Fertility

No evidence of carcinogenicity, genotoxicity, mutagenicity, clastogenicity was seen. No adverse effects on fertility, reproductive performance, and no fetal toxicity was seen in rats and rabbits. Pregnancy: Category B.

2.4.6 Special Populations

Nursing Mothers: no data exist in human. Rizatriptan is excreted in rat milk with a very high transfer rate, with milk levels exceeding plasma levels by 5 fold or more.

Safety and efficacy in pediatric patients have not been established.

The PK of rizatriptan was similar in elderly and young adults. Experience in the elderly is limited (n=17 over age 65) but there were no apparent differences in efficacy or safety in this population.

2.4.7 Adverse Events

Maxalt was generally well tolerated. Most common AE's were dizziness (8%), somnolence (8%), asthenia/fatigue (5%), nausea (4%), chest pain (3%) , and paresthesias (3%). No serious adverse events were reported.

2.4.8 Drug Abuse and Dependence

None seen.

2.4.9 Overdose

None seen. In a clinical pharmacology study, 12 subjects received a cumulative dose of 80 mg over 4 hours. Two subjects experienced syncope and/or bradycardia (including 3rd degree AV block treated with atropine and a 5 second systolic pause after a painful venipuncture).

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2.5 Foreign Marketing

Rizatriptan has not been marketed in any country. As of the NDA submission date, 6/30/97, there were no pending applications in any other country.

3. Chemistry, Manufacturing and Controls

Rizatriptan benzoate is a white to off-white powder. Five (5) mg and 10 mg tablets have been developed.

Generic Name:	**rizatriptan benzoate**
Trade Name:	**Maxalt™**
Chemical Name:	***N,N*-Dimethyl-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1*H*-indole-3-ethamine monobenzoate**
Alternative Name:	**MK-0462**
Molecular Formula:	**$C_{15}H_{19}N_5 \bullet C_7H_6O_2$**
Molecular Weight:	**391.47**

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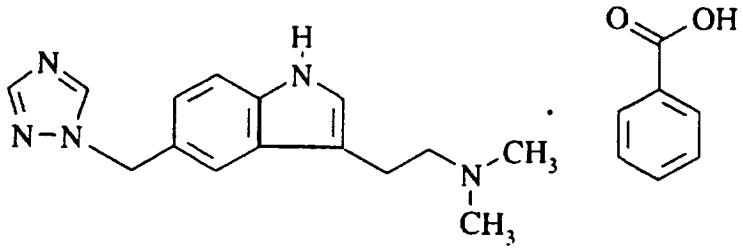
Figure 1: Rizatriptan, chemical structure



Long-term stability studies have been done up to 36 months at 30°C/60% RH and for 24 months at 40°C/75% RH. The results have demonstrated acceptable chemical and physical stability.

4. Animal Pharmacology & Toxicology

4.1 Pharmacology

Rizatriptan is a $5HT_{1D}$ receptor agonist. Recent molecular biology investigations have shown that $5HT_{1D}$ has two subtypes, $5HT_{1D\alpha}$ and $5HT_{1D\beta}$. The latter has been renamed $5HT_{1B}$ and the former subtype is now known simply as $5HT_{1D}$. Therefore, rizatriptan is now known as a $5HT_{1B/1D}$ agonist. Older literature still reflects only the $5HT_{1D}$ interaction. The $5HT_{1B}$ receptor is found in the smooth muscle of meningeal blood vessels. They are also present in the trigeminal neurons in rats. $5HT_{1D}$ are likely to be expressed prejunctionally both on the peripheral and central terminals of the trigeminal nerve fibers.

The pharmacological profile of rizatriptan has been examined in radioligand binding and function pharmacological assays in vitro using animal and human receptors and tissues to characterize its receptor specificity and potency.

Rizatriptan has also been assessed in animal assays in vivo that were designed to mimic some of the pathophysiological processes that are thought to occur during a migraine attack.

The potential safety of rizatriptan was investigated using human coronary arteries in vitro and pharmacodynamic animal assays in vivo, with an emphasis on cardiovascular and behavioral functions. The potential of rizatriptan of unwanted cardiovascular interactions with some therapeutic agents that could be used concomitantly by migraineurs was also examined.

4.1.1 Vasoconstriction

The vasoconstrictor activity of rizatriptan was assessed using a rabbit saphenous vein preparation, where contractions evoked by serotonin agonists are mediated via $5HT_{1B}$. Its action was blocked using the antagonist methiothepin. It was also shown to have vasoconstriction activity in human middle cerebral artery preparations.

It also has vasoconstrictor activity at human isolated coronary arteries. A craniovascular selectivity ratio was calculated by comparing vasoconstrictor effects at cranial arteries vs. coronary arteries. For rizatriptan, the ratio is 5.6, compared to 2.1 for sumatriptan and 1.8 for serotonin (5-HT), suggesting rizatriptan is more cranioselective in its vasoconstrictor properties compared to the other two.

In vivo experiments were done in ferrets and dogs. In anesthetized ferrets, rizatriptan induced a dose-dependent reduction in carotid blood flow, indicative of vasoconstriction of the carotid vascular bed. Similar findings were seen in anesthetized dogs.

4.1.2 Trigeminal Nerves

Perivascular inflammation in migraine appears to be mediated via the trigeminal nerves. Stimulation of trigeminal sensory nerves induces release of pro-inflammatory substances (predominantly substance P). Rizatriptan appears to block this response.

4.1.3 Central Pain Processing

Rizatriptan crosses the blood brain barrier in rats. Rizatriptan produces a dose dependent inhibition of responses of single trigeminal neurons to noxious stimulation of the dura mater in the vicinity of the middle meningeal artery. This indicates that rizatriptan interrupts pain transmission within the medullary trigeminal nucleus caudalis.

4.1.4 Cardiovascular Effects

In dogs, using 5 mg/kg, there were sustained dose-related increases in blood pressure and heart rate. A similar effect on blood pressure was seen in rhesus monkeys, but no consistent pattern with heart rate was seen in this species.

Rizatriptan also demonstrates a sympatholytic effect, presumably by binding to pre-synaptic 5HT inhibitory receptors. This activity has also been seen with sumatriptan, and zolmitriptan, suggesting it is a class effect of $5HT_{1D}$ agonists.

4.2 Toxicology

The potential toxicity of rizatriptan has been studied in a series of in vitro and in vivo studies, including oral and i.v. studies in mice, rats, dogs, and rabbits.

4.2.1 Single Dose Toxicity

The approximate oral LD_{50} in female mice and rats were 700 mg/kg and 2227 mg/kg, respectively. The approximate i.v. LD_{50} were 89 and 141 mg/kg, respectively. The oral mouse LD_{50} is approximately 3,500 times higher than the intended clinical dose in migraine.

4.2.2 Multiple Dose Toxicity

In sub-chronic oral and i.v. toxicity studies in Beagle dogs at doses up to 5 mg/kg/day for 14 weeks and 1 mg/kg/day for 2 weeks, respectively, no organ toxicity was observed. Pharmacological signs included mydriasis, hyperactivity, and increased heart rate at doses as low as 1 mg/kg/day orally and 0.05 mg/kg/day intravenously.

A 53 week oral toxicity study in Beagle dogs with a 27 week interim necropsy was completed at doses of 0.2, 1, and 5 mg/kg/day. There were no treatment related toxicities. The only compound-related change was mydriasis in all dosage groups.

A 53 week oral toxicity study in Sprague-Dawley rats with a 27 week interim necropsy was done at doses of 10, 50, and 250 mg/kg/day. There were no observed treatment related toxicities.

A 14 week oral toxicity study in Sprague-Dawley rats at doses up to 125 mg/kg/day revealed no drug related findings. Similarly, in a 15 day i.v. study at doses up to 10 mg/kg/day, there were no drug related findings.

Sub-chronic oral toxicity studies of up to 14 weeks in CD-1 mice at doses from 25 to 500 mg/kg/day resulted in 10% mortality. Also seen were decreased activity, slight decreases in body weight gain, and decreases in erythroid parameters.

Rizatriptan is not genotoxic, mutagenic, or carcinogenic in laboratory animals. Developmental and reproductive toxicity studies in rabbit and rats indicate there

are no contraindications for clinical use of rizatriptan in women of child bearing potential.

5. Clinical Data Sources

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5.1 Primary Data Sources

5.1.1 Study Type

In addition to the clinical pharmacology studies, the Maxalt tablet development program consisted of six phase 2 studies and four phase 3 controlled trials. Three of the four phase 3 trials had a long-term extension phase. These studies are listed in Table 3. A complete list of all studies, including the phase 1 trials is located in Appendix A, page 129.

Table 3: Phase 2/3 Studies

Protocol No.	Short Study Title
	Phase IIa
004	Safety, Tolerability, and Preliminary Efficacy of Oral L- 705,126 in Patients with Acute Migraine
005	Comparison of Clinical Profiles of Oral L- 705,126 (Rizatriptan) and Oral Sumatriptan in Patients with Acute Migraine (Discontinued Study)
	Phase IIb
008	Dose- Ranging Study of Rizatriptan in Acute Migraine
014	Dose- Finding Study of Rizatriptan in Acute Migraine
020	Cardiovascular Safety of Rizatriptan in Otherwise Healthy Migraineurs
026	Comparison of Pharmacokinetic Profiles of Intranasal MK- A462 and Oral Rizatriptan 5 mg (Not Utilized in Evaluation of Efficacy)
	Phase III
022*	Examination of the Safety and Efficacy of Rizatriptan 10 mg P. O. and Rizatriptan 5 mg P. O. in Outpatients with Acute Migraine and Migraine Recurrence
025*	Examination of the Safety and Efficacy of Rizatriptan 10 mg P. O. in Outpatients with Multiple Attacks of Acute Migraine and Migraine Recurrence
029*	Comparison of the Efficacy and Safety of Rizatriptan 5 mg P. O. and Sumatriptan 50 mg P. O. in Outpatients with Acute Migraine
030	Examination of the Safety and Efficacy of Single Oral Doses of Rizatriptan 5 mg, Rizatriptan 10 mg, and Sumatriptan 100 mg in Outpatients with Acute Migraine

*patients were allowed to enter an open label extension

5.1.2 Demographics

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5.1.2.1 Phase 1 Demographics

The demographic characteristics of subjects in Phase 1 studies are summarized in sponsor Table 4 (ISS Table D-59, page D-171). The majority were male (~70%) and the mean age was about years of age. About were 65 years of age or older. About 82% were Caucasian, and 14% were black. There were no meaningful differences in demographic characteristics between subjects who received rizatriptan and those who received placebo.

Table 4: Demographics of the Phase 1 Studies

	All Subjects Exposed to Rizatriptan Tablets (N= 313)	All Subjects Exposed to Placebo (N= 134)
Gender		
Male	216 (69%)	95 (71%)
Female	97 (31%)	39 (29%)
Age (Years)		
18 to 29	215 (69%)	105 (78%)
30 to 39	54 (17%)	19 (14%)
40 to 49	22 (7%)	6 (4%)
50 to 59	5 (2%)	0 (0%)
60 to 64	1 (0.3%)	0 (0%)
≥65	16 (5%)	4 (3%)
Mean	*29.8*	*27.5*
Median	*26*	*25*
Range		
Origin		
Caucasian	255 (82%)	111 (83%)
Negro	43 (14%)	15 (11%)
Hispanic	6 (2%)	4 (3%)
Asian	7 (2%)	3 (2%)
Other	2 (0.6%)	1 (0.7%)

5.1.2.2 Phase 2 Demographics

Sponsor Table 5 (ISS Table D-60, page D-173) summarizes the demographic characteristics of patients in the phase 2 studies.

Table 5: Demographics of the Phase 2 Studies

	All Patients Treated With Rizatriptan (N= 974)	All Patients Treated With Rizatriptan and/ or Control Agents (N= 1142)	All Patients Randomized (N= 1370)
Gender			
Male	144 (15%)	169 (15%)	205 (15.0%)
Female	830 (85%)	973 (85%)	1165 (85.0%)
Age (Years)			
18 to 29	173 (18%)	205 (18%)	274 (20%)
30 to 39	264 (27%)	311 (27%)	371 (27%)
40 to 49	390 (40%)	444 (40%)	513 (37%)
50 to 59	134 (14%)	168 (15%)	198 (14%)
60 to 64	4 (0.4%)	4 (0.4%)	4 (0.3%)
≥65	9 (0.9%)	10 (0.9%)	10 (0.7%)
Mean	*39.8*	*39.9*	*39.3*
Median	*41*	*41*	*40*
Range			
Origin			
White	904 (93%)	1067 (93%)	1280 (93%)
Black	31 (3%)	33 (3%)	41 (3%)
Hispanic	19 (2%)	20 (2%)	22 (2%)
Asian	4 (0.4%)	4 (0.4%)	6 (0.4%)
Other	15 (2%)	17 (2%)	20 (1%)
Unknown	1 (0.1%)	1 (0.1%)	1 (0.1%)

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Some patients were treated with both rizatriptan and placebo, but are counted only once in the "all patients randomized" column. This explains why the numbers don't add up. The vast majority (85%) were female and white (93%), a pattern which is similar in the phase 3 studies. The mean age was about 40 years. One percent (1%) were 65 years of age or older. There were no patients over the age of 75.

5.1.2.3 Phase 3 Demographics

The demographic characteristics of the phase 3 controlled trials population are very similar to that seen in the phase 2 program. Sponsor Table 6 (ISS Table D-61, page D-173) summarizes the data.

Table 6: Demographics of the Acute Phase 3 Studies

	All Patients Treated With Rizatriptan (N= 2296)	**All Patients Treated With Rizatriptan and/ or Control (N= 3516)**	**All Patients Randomized (N= 4147)**
Gender			
Male	349 (15%)	570 (16%)	681(16%)
Female	1947 (85%)	2946 (84%)	3466 (84%)
Age (Years)			
18 to 29	406 (18%)	613 (17%)	765 (18%)
30 to 39	709 (31%)	1051 (30%)	1239 (30%)
40 to 49	789 (34%)	1220 (35%)	1414 (34%)
50 to 59	341 (15%)	546 (16%)	629 (15%)
60 to 64	43 (2%)	75 (2%)	88 (2%)
≥65	8 (0.3%)	11 (0.3%)	12 (0.3%)
Mean	*39.7*	*40.0*	*39.7*
Median	*40.0*	*40.0*	*40.0*
Range			
Origin			
White	2051 (89%)	3108 (88%)	3666 (88%)
Black	43 (2%)	51 (2%)	61 (2%)
Hispanic	142 (6%)	283 (8%)	313 (8%)
Asian	24 (1%)	29 (0.8%)	40 (0.9%)
Other	36 (2%)	45 (1%)	67 (2%)
Headache Type			
Aura	300 (14%)	517 (15%)	NA
No Aura	1843 (86%)	2992 (85%)	NA
Missing	1 (0.0%)	7 (0.2%)	NA

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As in the phase 2 studies, patients were overwhelmingly female (84%) and white (88%). The mean age was also 40 years of age.

Since this table does not directly compare the demographics of the rizatriptan patients to the placebo patients, I derived this information directly from the electronic datasets provided by the sponsor in the NDA. Placebo patients in study 022 were able to take rizatriptan 5mg or 10mg for up to two recurrences. I categorize them as placebo patients since they were randomized to receive

placebo as their initial treatment. Patients in study 025 treated up to 4 consecutive migraine attacks with either 10mg or placebo. Since these patients were exposed to both agents throughout the course of the study, I analyzed demographic information from the first attack only.

There were 3,516 patients that received study medication for the treatment of a 1st migraine attack in all four studies (022, 025, 029, 030). FDA Table 7 summarizes the demographic characteristics of the patients according to initial treatment (rizatriptan vs. control). The total numbers differ from those in the sponsor's Table 6 since I count each patient only once in study 025 as described above. The demographic characteristics differ very little between the two treatment categories.

Table 7: Demographics for Acute Phase 3 Studies, Rizatriptan vs. Control

	All Patients Treated With Rizatriptan (N=2144)	All Patients Treated With Control (N=1372)	All Patients Randomized (N=3516)
Gender			
Male	327 (15%)	243 (18%)	570 (16%)
Female	1817 (85%)	1129 (82%)	2946 (84%)
Age (Years)			
Mean	39.6	40.5	40.0
Median	40	41	40
Range			
Origin			
White	1909 (89%)	1199 (87%)	3108 (88%)
Black	38 (2%)	13 (1%)	51 (1%)
Other	197 (9%)	160 (12%)	357 (10%)

5.1.3 Extent of Exposures

The NDA contains information on 3949 unique subjects/patients who received one or more doses of an oral formulation of rizatriptan (Table 8, ISS Table D-48, page D-156).

Table 8: Number of Individuals on Rizatriptan Formulations

	Formulation			
Category	Tablets Subjects/ Patients (N)	RAPIDISC™ Subjects/ Patients (N)	Intranasal Subjects/ Patients (N)	Other † Subjects (N)
Phase I (Subjects)	313	36	44	188
Phase II (Patients)	974		21	
Phase III (Patients)	2742	214		
Total exposures	4029	250	65	188
Subjects/ patients in >1 study with formulation	80	0	0	
No. unique individuals in the database	3949	250	65	

† intravenous, oral solution, dry filled capsule

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5.1.4 Exposures in Phase 1 Studies

Sponsor Table 9 (ISS Table D-49, page D-157) summarize exposures to rizatriptan in phase 1 studies. Volunteers who received both rizatriptan and placebo on separate occasions are counted more than once in this table. Most subjects were treated for 6 days or less.

Table 9: Exposures in Phase 1 Studies

	Total Daily Dose (mg) Rizatriptan Tablets (mg/day)							
Days Treated	<5	5	10	15	20	30	>40	Placebo
1	45	80	111	44	5	0	34	68
2- 4	4	0	104	0	13	52	14	35
>4	0	0	19	0	0	0	0	31
TOTAL	49	80	234	44	18	52	48	134

5.1.5 Exposures in Phase 2 Studies

Sponsor Table 10 (ISS Table D-50, page D-158) summarizes the exposures in phase 2 studies. As in the phase 1 studies, patients are counted multiple times if they received more than one agent. The duration of treatment in these studies was one attack treated with one or two doses (inter-dose interval = 2 hours). Patients who took placebo as a second dose following rizatriptan are not included in the placebo column below.

Table 10: Exposures in Phase 2 Studies

	Rizatriptan Total Dose Per Headache (mg)					Control Agents		Total
Days (Attacks) Treated	2. 5	5	10	20	40	Placebo (as Initial Treatment)	Suma 100 mg	Riza 2.5 to 40 mg
1	76	153	253	169	323	214	89	974

5.1.6 Exposures in Phase 3 Controlled Studies

Sponsor Table 11 (ISS Table D-51, page D-160) summarizes exposures in controlled phase 3 trials.

Table 11: Exposures in Phase 3 Studies, by Dosage, Strength, and Extent

	Rizatriptan Tablet Strengths		Control Agents	
Number of Attacks Treated	5 mg (1, 2, or 3 Doses/Attack)	10 mg (1, 2, or 3 Doses/Attack)	PBO (as an Initial Treatment)	Sumatriptan 50 or 100 mg
1	1012	927	836	745
2		34		
3		255		
4		68		
TOTAL	1012	1284	836	745

Study 025 treated up to 4 migraine attacks with rizatriptan 10mg and this accounts for the data for 2-4 attacks treated.

Sponsor Table 12 (ISS Table D-52, page D-161) contains the same information as the previous table, but broken down by number of tablets taken per attack, and by study.

Table 12: Exposures by Dose, Number of Tablets, and Number of Attacks

		Rizatriptan Tablet Strengths (N Doses Per Attack)						Control Agents (N Doses Per Attack)			
		5 mg			10 mg			PBO† (initial treatment)			Suma†
Prot	Attacks Treated	1	2	3	1	2	3	1	2	3	
022	1	403	66	24	401	63	38	306	1		
029	1	355						80			357
030	1	164			387			160			388
025	1				114	137	57	204	61	24	
	2				107	62	24				
	3				97	14	12				
	4				17	1	2				
TOTAL (All Attacks)		**922**	**66**	**24**	**1123**	**277**	**133**	**750**	**62**	**24**	**745**
First Attack All Studies		**922**	**66**	**24**	**984**	**155**	**73**	**612**	**15**	**4**	**745**

† Suma = sumatriptan (357 on 50 mg sumatriptan and 388 patients on 100 mg sumatriptan); PBO = Placebo. Of those patients who treated with rizatriptan 5 or 10 mg, the following numbers treated with placebo for the initial headache and used active drug only to treat a recurrence.

This table shows that 24 patients took 3 doses of 5mg during a 24 hour period, and 133 patients took 3 doses of 10mg during a 24 hour period for treatment of the original migraine and 2 recurrences.

From these tables, 1,012 patients treated 1,012 attacks with rizatriptan 5mg. Ninety-one percent (91%) of the attacks were treated with 1 tablet, 7% with 2 tablets, and 2% with 3 tablets.

One thousand eighty-four (1,084) patients treated 2,032 attacks with rizatriptan 10mg. Eighty percent (80%) of the attacks were treated with 1 tablet, 13% with 2 tablets, and 7% with 3 tablets.

Eight hundred thirty-six (836) placebo patients treated one attack each with placebo. Ninety percent (90%) of the attacks were treated with 1 tablet, 7% with 2 tablets, and 3% with 3 tablets.

Not all patients had the opportunity to remedicate. In particular, patients in studies 029 and 030 did not take study medication for recurrence. Therefore the incidence of the us of a 2nd and 3rd dose are low by design in these groups. A

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more useful measure of the use of a second or third dose is contained in the extension studies discussed below.

Three hundred fifty-seven (357) patients on sumatriptan 50mg and 388 patients on sumatriptan 100mg treated one attack with 1 tablet medication. Redosing was not allowed in either study that utilized sumatriptan as a control.

5.1.7 Exposures in Phase 3 Uncontrolled Studies

Patients in studies 022, 025, and 029 were eligible to enter into long-term extension studies using open label treatment. A total of 1512 patients treated a total of 40,293 attacks with rizatriptan 5mg or 10mg, and 329 patients treated a total of 8126 attacks with "standard care" (most often sumatriptan). Sponsor Table 13 (ISS Table D-54, page D-164) lists the exposures by dose and number of attacks in the extension studies.

Table 13: Exposures in Open Label Extensions, by Dose and Attacks

	Rizatriptan Tablet Strengths		Control
Number of Attacks	5 mg (1, 2 or 3 Doses/ Attack) n=695	10 mg (1, 2 or 3 Doses/ Attack) n=817	Standard Care n=329
1 to 7	218	171	71
8 to 17	179	198	89
18 to 39	160	207	98
40 to 194	138	241	71
TOTAL	**695**	**817**	**329**
Average Number of Attacks Per Patient	23.4	29.4	24.7
Average Interval Between Treated Attacks (Days)	8.3	7.3	9.0

From a separate table in the ISS which is not shown here (Table D-55, page D-165), 25% of all attacks were treated with 2 doses, and 11% were treated with 3 doses. The percentages were exactly the same whether one used 5mg or 10mg.

Sponsor Table 14 (ISS Table D-58, page D-169) summarizes the number of patients exposed to rizatriptan by various time intervals.

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Table 14: Exposures in Open Label Extensions, by Dose and Time; ≥2 migraines/mo.

	Rizatriptan 5 mg				Rizatriptan 10 mg				Standard Care
Time in Extension (Months)	N Pts	Mean % of Attacks Treated With % 1 Tab	% 2 Tabs	% 3 Tabs	N Pts	% 1 Tab	% 2 Tabs	% 3 Tabs	N Pts
>0	449	61	26	13	601	62	26	12	215
≥6	245	59	27	15	390	62	27	12	140
≥12	93	58	27	15	135	59	28	13	59

It only includes patients who had an average of ≥2 migraines per month. It serves to show that the long-term extension program does meet and exceed ICH guidelines for long-term exposures. By adding the columns for 5mg and 10mg exposures, it shows that 635 patients experiencing ≥2 migraines/month were exposed to rizatriptan for at least six months, and 228 patients were exposed for over 12 months.

5.2 Adequacy of Human Experience

Based on the exposure data submitted, the rizatriptan development program includes a sufficient number of patients, both acute and long term exposures, to permit a reasonable evaluation of the drug's efficacy and safety in humans. The sponsor has met ICH guidelines for long-term exposures of a new drug. As is the case for other migraine medications, the population studies is predominantly female and there is a paucity of data in elderly patients (>65 yrs).

6. Human Pharmacokinetics

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6.1 Absorption

The mean oral bioavailability of the 5 and 10 mg tablets is 40-45%. Mean C_{max} were ~10 ng/mL for the 5 gm tablet and ~20 ng/mL for the 10 mg tablet. T_{max} occurs at 1 - 1.5 hours post-dose. A high fat breakfast tended to delay the absorption slightly, but the extent of absorption was not impaired.

6.2 Distribution

Rizatriptan is not bound to plasma proteins to any appreciable extent (~14%). The steady state volume of distribution in healthy males was , and for females was . For patients on hemodialysis, the V_{dss} was , and for patients with hepatic impairment, 142-178 liters. The red blood cell to plasma concentration ratio in human blood averaged 1.21.

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6.3 Metabolism

Rizatriptan undergoes extensive metabolism following oral and i.v. administration. Although the drug is almost completely absorbed, bioavailability ranges indicating moderate first pass metabolism. Following an i.v. dose, ~30% of plasma clearance is renal, the remaining ~70% representing metabolic clearance. Following i.v. and oral doses of ^{14}C-rizatriptan, just 30% and 17%, respectively, of radioactivity is accounted for by parent drug.

The primary metabolite is an inactive indole-acetic acid moiety, which is renally excreted and accounts for of the i.v. dose, and of the oral dose. The n-oxide metabolite accounts for less than 5% of either dose. Other minor metabolites found include the 6-hydroxy derivative and its sulfate conjugate, and the N-monodesmethyl analog. Except for the N-monodesmethyl metabolite, which is approximately twice as active as rizatriptan itself, all of these are metabolically inactive. This active metabolite accounted for of the AUC for rizatriptan itself.

In vitro studies indicate that MAO-A catalyzes the formation of the indole-acetic acid metabolite. Other in vitro studies indicate that therapeutic plasma concentrations of rizatriptan will not inhibit the metabolism of compounds that are substrates of CYP3A4/5, 1A2, 2C9, 2D6 and 2E1.

6.4 Excretion

The plasma half-life of rizatriptan . The pharmacokinetics are essentially linear in healthy males for doses ≤10 mg and i.v. doses ≤60 µg/kg (~4mg). For females, the pharmacokinetics were slightly non-linear at the upper end of both dose ranges. The plasma clearance averaged in males and in females. Hence, the clearance is less in females resulting in plasma concentrations that are proportionately higher following oral or i.v. doses.

Following an oral dose of radio-labeled rizatriptan of the radioactivity was excreted in the urine, and was found in the feces. Approximately of the of the oral dose was recovered as parent compound in the urine. The renal excretion rate is higher than the glomerular filtration rate, suggesting active renal tubular secretion.

6.5 Special Populations

The PK for rizatriptan in migraine patients was similar to those parameters in healthy young subjects. The relative bioavailability was similar whether or not they were suffering a migraine attack at the time of dosing. The absorption and PK are similar between elderly and young volunteers. Male/female differences were minimal in the elderly.

Plasma clearance in renal insufficiency patients was similar to normal patients except in those with severe disease (creatinine clearance ≤ 10 mL/min/1.73 m^2) on hemodialysis, in which rizatriptan clearance averaged 830 mL/min. The plasma half-life averaged in all groups. AUC, C_{max}, T_{max}, and $T_{1/2}$ were all similar to healthy subjects.

In mild to moderate hepatic disease, the plasma clearance was similar to healthy subjects, averaging . $T_{1/2}$ was also similar (2 hours). Following a single oral dose, mean AUC and C_{max} were not clinically significantly different. However, the bioavailability of rizatriptan in mild to moderate hepatic impairment was , respectively, suggesting reduced first pass metabolism.

6.6 Drug-Drug Interactions

In the presence of an MAO-A inhibitor (moclobemide 150 mg tid), the mean AUC doubled for rizatriptan and the mean AUC for the active N-monodesmethyl-rizatriptan increased nearly 5 fold.

In the presence of propranolol (240 mg/day), the mean AUC for rizatriptan increased by 70%. Plasma N-monodesmethyl rizatriptan did not change.

There were no demonstrable changes when rizatriptan was co-administered with paroxetine, or an oral contraceptive.

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6.7 Pharmacodynamic Effects

6.7.1 Blood Pressure and Heart Rate

The maximum recommended regimen is 10 mg given every 2 hours for three doses. In study 035, 24 subjects received a 10 mg test dose on day 1 and 10 mg every 2 hours for three doses on 4 consecutive days (days 3-6).

Diastolic blood pressure (DBP) tended to increase 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. 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.

In a separate study (002), higher doses of rizatriptan (60mg) were associated with a more substantial rise in systolic and diastolic blood pressure ranging from 10-15 mm Hg.

The MAO inhibitor moclobemide resulted in a roughly threefold increase in rizatriptan and the active metabolite, which resulted in an enhanced duration of pressor action, although no subject actually achieved hypertensive levels. It is worth noting, though, that these were healthy individuals and patients, particularly with comorbid conditions, may have a different response.

Four out of 10 elderly patients had notable (*i.e.*, >20/10 mm Hg) asymptomatic blood pressure elevations after a single 10 mg dose. In patients with renal and hepatic impairment, single 5 mg doses of rizatriptan resulted in modest blood pressure increases.

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6.7.2 Cerebral Blood Flow

Using ^{133}Xenon spectrometry, no changes in cerebral arterial blood velocity was seen 1-3 hours after a 40 mg (which was considered at the time to be the likely migraine treatment dose). Similar results have been seen with sumatriptan (2 mg i.v.) and ergotamine (0.5 mg i.v.).

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6.7.3 Peripheral Vasoconstriction

Study 009 evaluated the peripheral vasoconstrictive effects of rizatriptan 10 mg orally, i.v. ergotamine 0.25 mg, and their combination. Peripheral vasoconstriction was assessed by measuring the blood pressure difference between the arm and the toe. During the first hour after dosing, increases in BP in both extremities were observed on both days ergotamine was given, but not following rizatriptan or placebo. The vasoconstriction caused by ergotamine and rizatriptan in combination is indistinguishable from the vasoconstriction seen with ergotamine alone.

6.7.4 Autonomic Effects

Preclinical data suggest that inhibition of sympathetic transmission could the mechanism of vasovagal syncope observed with rizatriptan and other $5HT_{1D}$ agonists. A study was conducted to evaluate the effects on cardiovascular autonomic responses. It evaluated 10mg, 15mg, sumatriptan 100mg, and clonidine 0.2 mg on a battery of autonomic maneuvers. The only clinically relevant effect of any treatment on an autonomic maneuver was inhibition of the pressor and heart rate responses to cold pressor test by clonidine. Based on this test, in healthy male subjects, rizatriptan induced sympatholytic effects are less than a very modest dose of clonidine.

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6.7.5 Endocrine Effects

The effects of rizatriptan on several anterior pituitary hormones were studied. Increases in plasma growth hormone were observed at rizatriptan doses of 40 and 60mg, but not 20mg, and following the 100 mg dose of sumatriptan. For prolactin, the expected decrease in concentration during the observation period was observed. These are not considered of clinical importance at the doses proposed for marketing, 5mg and 10mg.

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7. Integrated Review of Efficacy

7.1 Introduction

A total of 8 phase 2/3 clinical trials support the efficacy of rizatriptan oral tablets in the treatment of an acute migraine headache (Table 15). In general, the phase 2 studies (004, 008, 014, 020) were preliminary, hypothesis-testing and dose finding studies. They established the doses to be used in phase 3, while the phase 3 studies (022, 025, 029, 030) confirmed the efficacy of the selected doses in a large number of patients (over 2,000). In all these efficacy studies, 2,950 patients received rizatriptan over the dose range 2.5mg-40mg. Eight hundred seventeen (817) patients received sumatriptan (50mg or 100mg), and 838 received placebo. Patient exposures to the various study medications are listed in sponsor Table 15.

Table 15: Phase 2/3 Efficacy Trials, Patient Exposures

		RIZATRIPTAN						SUMATRIPTAN			PBO	
Study	Description	2.5	5	10	20	40	Sub-Total	50	100	Sub-Total		Total All Rx
Phase 2		***76***	***130***	***353***	***90***	***157***	***806***		***72***	***72***	***211***	***1089***
004	Prelim Efficacy				8	36	44				21	65
008	1st Dose Ranging			89	82	121	292		72	72	85	449
014	2nd Dose Ranging	76	130	145			351				67	418
020	Inpt ECG study			119			119				38	157
Phase 3			***977***	***1167***			***2144***	***357***	***388***	***745***	***627***	***3516***
022	Recurrence		458	456			914				304	1218
025	1st attack of mult			324			324				83	407
029	Low Dose Suma		355				355	357		357	80	792

030	High Dose Suma		164	387		551		388	388	160	1099
All 2/3		***76***	***1107***	***1520***	***90***	***157***	***2950***	***357***	***460***	***817***	***838***	***4605***

All efficacy studies shared similar design. All were double-blind, placebo-controlled, parallel group, multicenter studies. All but two were outpatient studies (004, the initial introduction of rizatriptan to migraine patients, and 020, the ECG monitoring study were done in the clinic setting).

Patients enrolled were males and females with a history of migraine with or without aura for at least 6 months. The age range for inclusion in the phase 2 studies were with a range of for the in-clinic ECG monitoring study. The phase 3 studies had an inclusion range of

All studies included a short term acute phase during which the effects of rizatriptan on a single migraine attack of moderate or severe intensity was evaluated. In addition, the phase 3 studies [a] treated up to 4 consecutive attacks, [b] treated headache recurrence (within 24 hours, after achieving a 2 hour response, or [c] compared rizatriptan to oral sumatriptan. In several studies, 2 additional doses of study medication were permitted within 24 hours to treat recurrence (one study, 022, randomized the recurrence doses).

Three of the phase 3 studies (022, 025, 029) also included an optional extension phase, in which patients treated migraine attacks with rizatriptan or "standard care" (the patients usual migraine medication, usually sumatriptan) over periods of up to 12 months. The extension phases were primarily designed to provide safety data, but efficacy data to evaluate the magnitude and maintenance of effect (*i.e.*, consistency of response over time) was also obtained.

Efficacy parameters were assessed at baseline and every 30 minutes through 2 hours, and again at 3, and 4 hours after dosing. The parameters measured were:

- headache severity (0-no pain, 1-mild pain, 2-moderate pain, 3-severe pain)
- time to headache response within the first 2 hours (studies 029 and 030)
- functional disability (0-normal, 1-mildly impaired, 2-mod. impaired, 3-bedrest)
- nausea, vomiting, photophobia, phonophobia (present, absent)

Also measured:

- need for and time to escape medication in phase 3 studies
- headache recurrence (grade 2,or 3 headache within 24 hours after achieving a grade 0, or 1 headache at 2 hours) for all studies except 020
- overall patient satisfaction in phase 3 studies (7 point scale)
- Migraine Specific Quality of Life Questionnaire (15 items in 5 domains)

The primary endpoint in all efficacy studies was the 2 hour headache response rate, defined as the percentage of patients who experience a reduction in headache severity from moderate to severe pain at baseline to no or mild pain at

2 hours[1]. The time it took to achieve a headache response was also the primary endpoint in the sumatriptan active control studies (029, 030). Another important, though secondary, measure of efficacy was the percentage of patients who achieved complete pain relief at a given time point.

All patients who took treatment and provided efficacy data were included in the efficacy analyses (intent to treat, or ITT, analyses). Per-protocol analyses, which excluded protocol violators, were also performed for the primary efficacy variables. The number of protocol violators in each study was small and per-protocol analyses were similar to the ITT analyses.

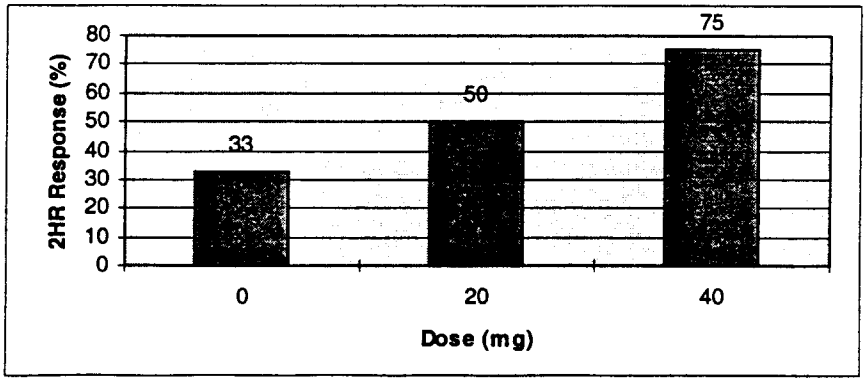
In all studies, escape medication (rescue) was allowed starting at 2 hours.

7.2 Dose Selection - Phase 2 Program Summary

Since there is no clinical surrogate for anti-migraine activity, the phase 1 studies attempted to identify a maximum tolerated dose. During phase 1 trials, doses up to 60 mg appeared to be well tolerated, although blood pressure was increased following this high dose. Based on non-clinical data, it was anticipated that rizatriptan plasma levels somewhat lower than those of sumatriptan might be efficacious, based on their effects on carotid vascular beds. Doses of 20mg and 40mg produced C_{max} in the same range as that for sumatriptan 100mg . It was therefore anticipated that doses of 20-40 mg would be efficacious, and would provide a reasonable margin of safety based on the 60mg maximum tolerated dose.

The first phase 2 trial (004) was a proof of concept study. It enrolled a total of 65 male and female migraine patients. There were two groups. The first group received rizatriptan 20mg or placebo (n=8 and 3). The second group received 40mg or placebo (n=36 and 18). The 2 hour response rate for the 40mg group was 75% vs. 33% for placebo. The 20mg dose also appeared to be effective, with a 2 hour response rate of 50% vs. 33% for placebo (Sponsor Figure 2).

Figure 2: Study 004, Rizatriptan 20mg, 40mg, vs. Placebo (N=65)



[1] The sponsor uses the term "headache relief" throughout the NDA synonymously with "headache response." I avoid using the term "headache relief" in this review since it can be easily confused with "complete relief", which was a separate efficacy measure.

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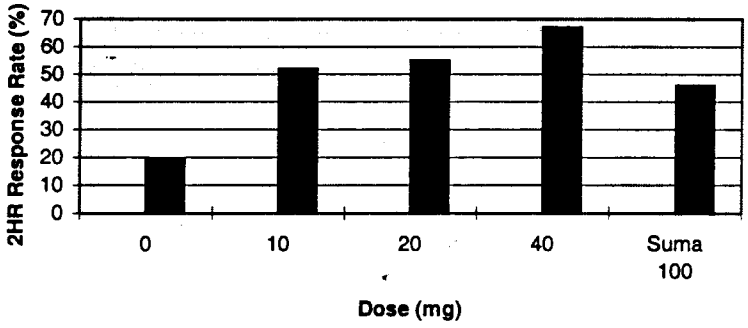
Based on results from study 004, an initial dose-ranging study was undertaken in 449 migraineurs in an outpatient setting (study 008). The doses studied were 10mg, 20mg, 40mg, sumatriptan 100mg, and placebo, in a roughly 1:1:1.5:1:1 randomization scheme. Sumatriptan was included for the purposes of comparison. All active treatments were superior to placebo at 2 hours. There was a dose related increase in efficacy for rizatriptan 10mg-40mg (Sponsor Figure 3).

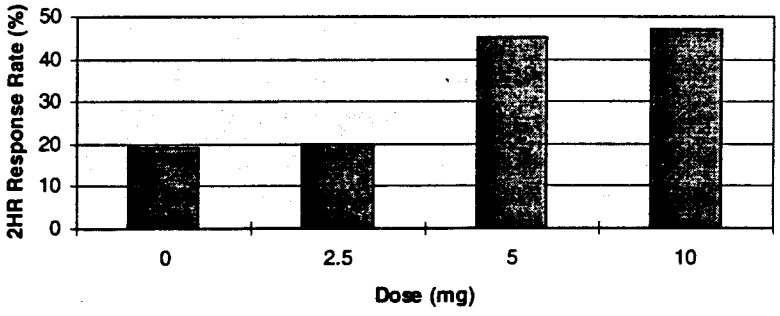
Figure 3: Study 008, Dose-Ranging Study (N=449)



The lowest dose of rizatriptan tested (10mg) was similar in efficacy to sumatriptan 100mg in this study. There was a numerical advantage of rizatriptan 10mg over sumatriptan 100mg at 1.5 hours, suggesting a possible benefit in speed of onset. Approximately 40% of all treatment groups reported recurrence. The study did not establish a no effect dose.

To establish a clear no effect dose, a second dose ranging study (014) was performed. This study enrolled 418 patients, and investigated doses of 2.5mg, 5mg, 10mg, and placebo in a roughly 1:2:2:1 ratio. There was, once again, a dose dependent response to rizatriptan (Figure 4). In this study, 2.5mg was a no effect dose.

Figure 4: Study 014, Low Dose Ranging Study (N=419)



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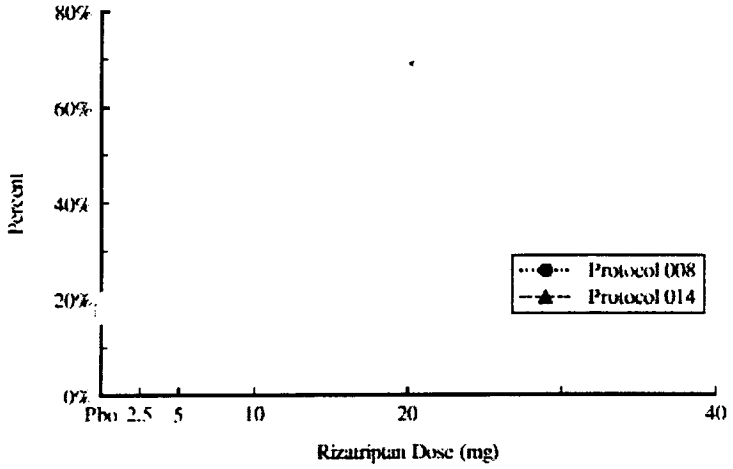
Although the 5mg and 10mg doses were similar in terms of primary efficacy, the 10 mg appeared to be superior in other secondary measures (complete relief, functional ability, etc.) The headache recurrence rate was still about 40% in all groups.

These studies defined a dose-response curve for rizatriptan (Sponsor Figure 5). The 2.5mg dose was a no-effect dose. The curve rises steeply between 2.5mg and 5mg, and begins to flatten thereafter, up to 40mg. On the basis of the phase 2 efficacy data, and an increase in AE's seen with increasing doses, especially above 20mg (dizziness, drowsiness), rizatriptan 5mg and 10mg were chosen for further study in the phase 3 program. Although there was no clear benefit to 10mg over 5mg in study 014, other secondary variables suggested a benefit. In particular, 10mg appeared to result in a higher percentage of patients who were pain-free.

Figure 5: Rizatriptan Dose-Response Curve, Studies 008 and 014



The efficacy of rizatriptan 10mg was also investigated in study 020, the inpatient ECG monitoring study. It enrolled 132 patients with a mean age of 37, and a smaller group of elderly patients (n=25) with a mean age of 62. Although the number of elderly patients were small, and no formal statistical testing was performed, the response rates for young adults were 54% for rizatriptan vs. 33% for placebo, and for elderly patients was 50% for rizatriptan vs. 0% for placebo.

7.3 Pivotal Phase 3 Studies

The sponsor has provided 4 studies (022, 025, 029, 030) that are adequate by design to provide evidence of efficacy of the drug in the acute treatment of migraine headaches. All studies were double-blind, placebo-controlled, randomized, parallel group, multicenter studies. All 4 studies collected efficacy data for the treatment of a single migraine headache of moderate to severe intensity. Patients had a history of migraine headaches greater than six months, and had 1-8 migraines per month at entry.

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Studies 022 and 025 also investigated the treatment of headache recurrence. Study 025 investigated the consistency of the treatment effect over four consecutive migraine headache attacks. Studies 022 and 030 compared both doses of rizatriptan (5mg and 10mg), and studies 029 and 030 also employed an active control (sumatriptan). Escape medication was allowed in all four studies from 2 hours onward.

I review the results of each study in detail in subsequent sections. I first describe the sponsor's efficacy analyses, followed by my own analyses. My own analyses should be regarded strictly as descriptive, and I defer rigorous statistical analysis to the statistician's review. At the end of the efficacy section, I have a included a pooled analysis of all four studies for the purpose of labeling.

I use the various terms throughout the review, which I define in FDA Table 16.

Table 16: Glossary of Terms

study medication	a dose of either active drug or placebo
headache severity	a 4 point scale, 0=no pain, 1=mild, 2=moderate, 3=severe
response	a decrease in headache severity from a grade 2 or 3, to grade 0 or 1
responder	any patient achieving a headache response
recurrence	any headache which recurs to grade 2 or 3 within 24 hours after initial treatment in a patient who achieved a headache response at 2 hours
response rate	proportion of patients in a given treatment group who achieve a headache response at a particular time point
complete relief	absence of any pain (grade 0)
rescue	medication other than study medication, usually an analgesic, anti-emetic, or sedative
time to recurrence	using initial treatment as time zero, the elapsed time until a headache recurrence
time to remedication	using initial treatment as time zero, the elapsed time until remedication (second dose or rescue)
cure	presence of complete relief at 2 hours and the absence of a recurrence and no need for remedication within 24 hours after initial treatment
cure rate	percentage of patients in a given treatment group who achieve a cure

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7.4 Study 022 - Treatment of Migraine Headache and Recurrence

This was a multinational trial which studied both the 5mg and 10mg doses vs. placebo. Up to two additional randomized treatments for recurrence within 24 hours was allowed. Patients randomized to receive 5mg or 10mg at onset were then randomized to receive either the initial rizatriptan dose or placebo for both the 2nd and 3rd recurrence (same dose for both recurrences). Patients randomized to placebo for initial treatment could received either 5mg or 10mg for both recurrences. A more detailed summary of the protocol is located in Appendix B, page 131.

A total of 1218 patients were treated, of which 458 took 5mg as the initial dose, 456 took 10mg, and 304 took placebo.

7.4.1 Results - Sponsor's Analyses

7.4.1.1 Sample Size Rationale

With planned sample sizes of 420 patients in each of the rizatriptan-dose groups and 280 patients in the placebo group, the power to detect a 30-percentagepoint difference in the 2 hour response rates (50% vs. 20%) was ≥95% based on a two-sided test at type I error rate α=0.025 (with multiplicity adjustment).

7.4.1.2 Disposition

The disposition of patients enrolled in study 022 are shown in sponsor Table 17.

Table 17: Study 022 - Patient Disposition

TREATMENT GROUP ENTERED: Total	Riza 5 mg (n= 554)	Riza 10 mg (n= 549)	PBO (n= 370)	Total 1473
Male (Age range, years)	77	66	58	201
Female (Age range, years)	477	483	312	1272
COMPLETED:	450	446	301	1197
DISCONTINUED: Total	104	103	69	276
Adverse clinical experience	1	1	0	2
Adverse laboratory experience	0	0	0	0
Did not take study drug	96	93	66	255
Other	7	9	3	19

7.4.1.3 Efficacy Parameters

Headache severity, functional disability, and associated symptoms were assessed up to 2 hours post dose. The primary efficacy analysis evaluated the 2 hour headache response rate for the initial headache and for the first recurrence. Results for treatment of the initial headache are shown in sponsor Table 18.

The sponsor's primary analysis employed an "all patients treated" approach that included all patients who had at least one record of pain severity within 2 hours after the initial dose (n=1214). Missing data were replaced by a last observation carried forward approach (LOCF). Treatment comparisons were compared using a logistic regression model. The study had ≥95% power to detect a 30% difference between active and placebo groups with planned sample sizes of 420 evaluable patients in each rizatriptan dose group, and 280 in the placebo group, based on a two-sided Type I error rate of α=0.025 (corrected for multiple comparison using Hochberg's procedure). Treatment comparisons were made using Fisher's exact test.

Table 18: Study 022, Efficacy Results**

	Rizatriptan 5 mg		Rizatriptan 10 mg		PBO	
Measure	N	%	N	%	N	%
Headache-Related Measures						
Pain response	457	62*	455	71*§	302	35
Pain-free	457	33*	455	42*§	302	10

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Escape medication	458	22*	456	17*§	304	42
Recurrence (within 24 hr)[1]	285	44	322	47	106	40
Associated Symptoms						
Nausea	455	32*	449	26*§	300	47
Vomiting	452	6	450	4	297	7
Photophobia	457	49*	451	42*§	301	69
Phonophobia	456	38*	452	33*	301	54
Functional Disability Rating[2]		*		*§		
Normal	457	38	454	46	300	18
Mildly impaired	457	35	454	33	300	39
Severely impaired	457	12	454	10	300	18
Requires bed rest	457	14	454	12	300	25
	N	**Mean**	**N**	**Mean**	**N**	**Mean**
Satisfaction with Medication[3]	440	3.96*	439	3.55*§	290	5.10
24 Hour Quality of Life[4]						
Work	423	12.25*	425	12.13*	277	11.21
Social	422	11.96*	425	12.17*	278	10.68
Energy	422	11.36*	425	11.79*	278	9.93
Symptoms	423	12.54*	427	13.11*	278	10.81
Feelings	422	10.68*	427	11.64*§	278	9.51

** all measures are at 2 hours, except for the 24 hour quality of life questionnaire.
1 Not analyzed. The denominator is the number of patients who responded at 2 hours.
2 Analysis based on overall distribution between categories, rather than comparisons within each category.
3 Range of possible scores . A lower score indicates greater patient satisfaction.
4 Range of possible scores for eacn domair A higher score corresponds to better quality of life.
* p<0.05 versus placebo.
§<0.05 versus rizatriptan 5 mg.

The primary efficacy results are shown separately in sponsor Table 19.

Table 19: Study 022 - Two Hour Headache Response Rates

Treatment	N	Responders	%	95% CI
Rizatriptan 5mg	457	285	62.4**	57.5-66.8
Rizatriptan 10mg	455	322	70.8**, ++	66.4-74.9
PBO	302	106	35.1	29.7-40.8

** p<0.01 compared to PBO
++ p=0.007 compared to rizatriptan 5mg

For both the 5mg and the 10mg doses, 2 hour headache response rates were better than placebo (FDA Figure 6). Furthermore, 10mg was statistically better than 5mg.

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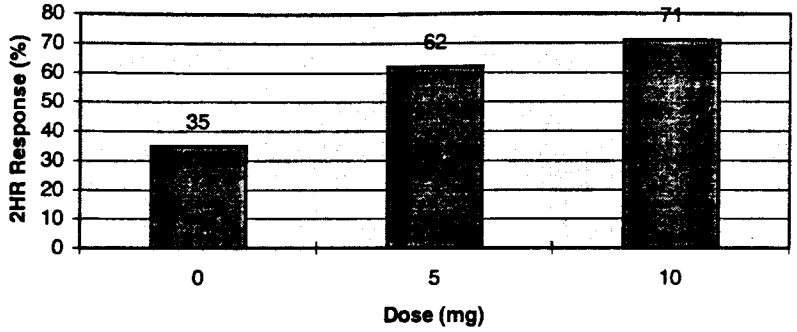
Figure 6: Study 022, Two Hour Headache Response Rates



7.4.1.3.1 SECONDARY EFFICACY PARAMETERS

Secondary endpoints included percentage of patients who were pain free at 2 hours; had no disability at 2 hours; used escape medication after the initial dose; had response 2 hours after treatment for recurrence. The first three are shown in sponsor Table 20, which indicated that all three favored rizatriptan. There was a numerical advantage to the 10mg dose.

Table 20: Study 022 - Secondary Efficacy Parameters

	Rizatriptan 5mg	Rizatriptan 10mg	PBO
2 Hr Pain Free	32.8**	42.4**	9.9
2 Hr No Disability	38.3**	46.0**	18.0
Using Escape Medication	22.1**	16.7**	42.1

** P<0.01 compared to PBO

Study 022 evaluated a randomized second dose for recurrence. Recurrence rates, defined as recurrence of moderate to severe pain within 24 hours in a patient who initially responded at 2 hours, were about the same for the three treatment groups . However, 2 hour response rates for the treatment of the first recurrence were still significantly better for both 5mg and 10mg. In all groups, the response to the second dose was better than the response to the first dose. This may reflect the pre-selection of responders to the first dose, or may indicate that the recurrences were of milder severity or shorter duration than the initial attack. The results for treatment of the first recurrence are shown in sponsor Table 20.

Table 21: Study 022, Efficacy of 1st Recurrence, 2 Hr Response Rate (Complete Relief)

	Recurrence Treatment					
	Rizatriptan 5 mg		Rizatriptan 10 mg		Placebo	
Initial Treatment	N	%	N	%	N	%
Rizatriptan 5 mg	55	71 (36*)	-	-	59	54 (15)
Rizatriptan 10 mg	-	-	65	82** (49**)	75	44 (15)
Placebo	17	71 (41)	22	82 (55)	-	

The total number of patients who had a recurrence; % = the percentage of patients who responded (or were pain-free) 2 hours after treatment of the headache recurrence.
* p<0.05 compared to rizatriptan 5 mg (initial treatment) + placebo (recurrence treatment) group.
** p<0.05 compared to rizatriptan 10 mg (initial treatment) + placebo (recurrence treatment) group.

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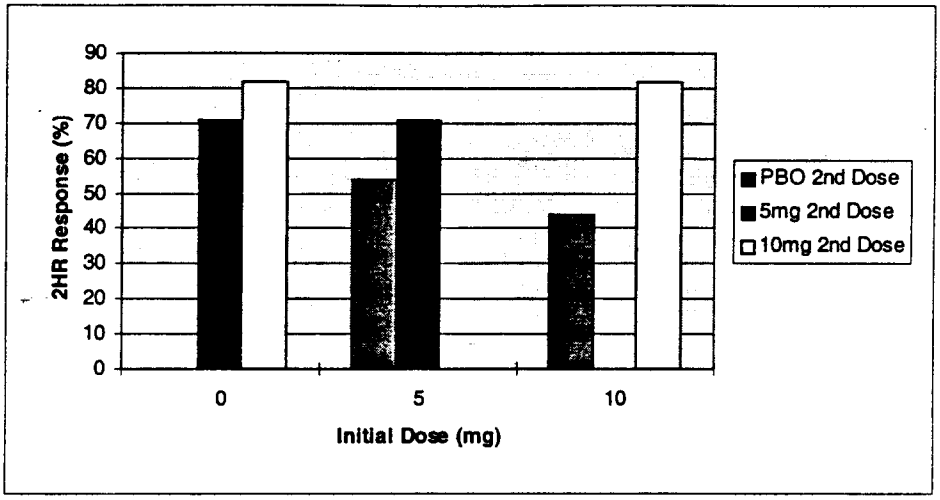
The same results, the 2 hour response rates for treatment of the first recurrence are represented graphically in FDA Figure 7.

Figure 7: Study 022, Treatment of 1st Recurrence, 2 Hour Response Rates



In summary, response rates for treatment of first recurrence favored rizatriptan for both doses (5mg, 10mg) however it achieved statistical significance only for the 10mg+10mg group, when compared to the 10mg+PBO group.

7.4.2 Sponsor's Conclusions

Based on the results of this study, the sponsor concluded the following from study 022:

1. Both doses of rizatriptan (5mg and 10mg) are better than placebo. The 10mg dose was better than the 5mg dose.
2. Both doses of rizatriptan are better than placebo in treatment of recurrence, with 10mg being more effective than 5mg.
3. Both doses of rizatriptan are better than placebo in providing complete headache relief at 2 hours, reducing functional disability at 2 hours, and reducing the need for rescue medication.

7.4.3 Results - Reviewer's Analyses

7.4.3.1 Methods & Demographic Considerations

My analyses of study 022 focused on the SAS efficacy dataset provided by the sponsor. All analyses were done using JMP, version 3.2.1.

I first examined the demographic characteristics of the patients enrolled in the study. There were a total of 1218 patients treated in the efficacy dataset. Of these, 304 received placebo 458 received 5mg, and 456 received 10mg as initial treatment for an acute migraine headache. The summary of the demographics are shown in FDA Table 22. In general, patients were evenly distributed among all three treatment groups with regard to age, gender, and race. The population averaged 41 years of age, and was predominantly female (87%) and Caucasian

(93%), as is typical of migraine trials of this type. The mean age for the men was identical to that of women.

Table 22: Study 022 - Demographic Characteristics (%)

	PBO (n=304)	5mg (n=458)	10mg (n=456)	Total (N=1218)
Mean Age (S.D.)	40.6 (10.5)	40.5 (9.6)	40.7 (9.6)	40.8 (9.8)
Female (%)	259 (85)	394 (86)	402 (88)	1055 (87)
Caucasian (%)	286 (94)	430 (94)	422 (93)	1138 (93)
Black (%)	7 (2)	18 (4)	7 (2)	32 (3)

Prior to doing any efficacy analyses, I analyzed the baseline headache severity for each treatment group. This is important to assure that patients with moderate headaches were evenly distributed among groups, since one might expect they would respond better than those with severe headaches. The results are shown in FDA Table 23. In all three groups, roughly 2/3 of the patients treated a moderate headache (grade 2), and 1/3 treated a severe (grade 3 headache). The number of patients who treated a mild or no headache (*i.e.*, protocol violators in the acute phase) were few.

Table 23: Study 022 - Baseline Headache Severity, by Initial Dose

Initial Treatment	Baseline Headache Severity ?	0 (%)	1 (%)	2 (%)	3 (%)
PBO (n=304)	0 (0)	1 (<1)	6 (2)	202 (66)	95 (31)
5mg (n=458)	1 (<1)	0 (0)	7 (2)	298 (65)	152 (33)
10mg (n=456)	1 (<1)	2 (<1)	6 (2)	316 (69)	131 (29)

Patients were allowed to take up to three doses in 24 hours. Of the 1218 patients, 59 assigned to the 5mg group and 76 assigned to the 10mg group took 3 doses. Not all of these exposures were to active drug, since the second and third doses were randomized to either drug or placebo. Of the 59 who took three doses in the 5mg group, 26 took 5mg for both recurrences. Of the 76 who took three doses in the 10mg group, 38 took 10mg for both recurrences.

7.4.3.2 Primary Efficacy - 2 Hour Response Rate

The primary efficacy parameter was the 2 hour headache response rate. Of the 1218 patients enrolled, 1194 patients had a grade 2/3 headache at baseline. The remaining 24 either treated a mild or no headache (n=22), or failed to record the headache severity at baseline (n=2). Since a headache response requires the presence of a grade 2/3 headache at baseline, I have designated these 24 patients as non-responders. The results of this analysis are shown in FDA Table 24. It confirms the sponsor's analysis that both 5mg and 10mg were better than placebo, and 10mg was more effective than 5mg at 2 hours.

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Table 24: Study 022 - Two Hour Response Rate (Reviewer's Analysis)

Treatment	Response	No Response
PBO (n=304)	96 (32%)	208 (68%)
5mg (n=458)	271 (59%)	187 (41%)
10mg (n=456)	306 (67%)	150 (33%)

p<0.0001 (Fisher's exact test) for 5mg vs. PBO and for 10mg vs. PBO
p=0.0136 (Fisher's exact test) for 10mg vs. 5mg

7.4.3.3 Complete Relief

The 2 hour complete relief rate is shown in Table 25. Again, the 24 protocol violators were designated as failures since they did not start with a moderate or severe headache. The results show that 30% of the 5mg group and 40% of the 10mg group achieved no pain at 2 hours.

Table 25: Study 022- Complete Relief Rate (Reviewer's Analysis)

Treatment	Complete Relief
PBO (n=304)	28 (9%)
5mg (n=458)	141 (30%)
10mg (n=456)	181 (40%)

p<0.0001 (chi-square) for overall analysis

7.4.3.4 Cure Rate

I defined a cure as a patient experiencing a grade 2/3 headache at baseline, no pain at 2 hours, no recurrence by 24 hours and requiring no rescue medication within 24 hours. The proportion of patients experiencing a cure is shown in FDA Table 26. Cure rates for both the 5mg and 10mg were similar at about 20% for both rizatriptan doses, vs. 6% for placebo.

Table 26: Study 022 - Cure Rate (Reviewer's Analysis)

Treatment	Cure
PBO (n=304)	18 (6%)
5mg (n=458)	85 (19%)
10mg (n=456)	97 (21%)

p<0.0001 (chi-square) for overall analysis

7.4.3.5 First Recurrence

The study employed a randomized second dose for treatment of up to two recurrences. A total of 446 patients (37%) experienced and treated at least one recurrence within 24 hours. The recurrence rates, broken down by treatment, were 27% for placebo patients (83/304), vs. 37% (168/458) for 5mg patients, and 42% (191/456) for 10mg patients.

There was a substantial amount of missing data for treatment of the first recurrence. Forty-eight (48) patients fail to record either the baseline recurrence severity or the 2 hour post-treatment severity. Since headache severity for recurrence was recorded only at baseline and at two hours, one cannot use a post-treatment LOCF approach for the missing data. Therefore, I dropped the 48 patients from the recurrent headache response rate analysis. The results are

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shown in FDA Table 27. Patient's taking 5mg+5mg or 10mg+10mg did better than those taking 5mg+0 or 10mg+0, respectively. Response rate for the 5mg second dose was 68% vs. 49% for placebo, and it was 79% for the 10mg second dose, compared to 45% for placebo.

Table 27: Study 022 - Treatment of 1st Recurrence (Reviewer's Analysis)

Initial Treatment	Treatment for 1st Recurrence		
	Rizatriptan 5mg	Rizatriptan 10mg	PBO
Rizatriptan 5mg (n=148)	47/69 (68%*)	--	39/79 (49%)
Rizatriptan 10mg (n=91)	--	63/80 (79%**)	41/91 (45%)
PBO (n=75)	21/35 (60%)	30/40 (75%)	--

* p=0.0296 (Fisher's Exact Test) compared to 5mg+PBO
** p<0.0001 (Fisher's Exact Test) compared to 10mg +PBO

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7.4.3.6 Associated Symptoms

The presence or absence of nausea, vomiting, photophobia, phonophobia were recorded in the patient diary as either present (1) or absent (0). I compared the percentage of patients having the symptom at baseline vs. 2 hours. I adopted the same approach for missing data. I dropped patients who failed to record a baseline measurement. For patients who failed to record a 2 hour measurement, I used an LOCF approach for missing data, using the last post-treatment value recorded, if one was available.

There were 1196 evaluable patients. Sixty-two percent (62%) had nausea at baseline and they were evenly distributed among all three groups. Thirty-four percent (34%) had nausea at two hours, a change of -45%. The results according to treatment group are shown in FDA Table 28. There was a dose-dependent reduction in nausea, with 10mg being most effective.

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Table 28: Study 022 - Nausea (Reviewer's Analysis)

	Nausea at Baseline	Nausea at 2 hours	% Change
PBO (n=299)	187 (63%)	141 (47%)	-25%
5mg (n=452)	276 (61%)	147 (33%)	-46%
10mg (n=445)	279 (63%)	117 (26%)	-58%

p<0.0001 (chi-square) for overall comparison
p=0.04 (Fisher's Exact Test) for 10mg vs. 5mg

For the endpoint vomiting, there were 1185 evaluable patients. Overall, 63 (5%) had vomiting at baseline, and 66 (6%) had vomiting at 2 hours. The numbers were small and there were no significant differences seen among groups. The results are shown in FDA Table 29.

Table 29: Study 022 - Vomiting (Reviewer's Analysis)

	Vomiting at Baseline	Vomiting at 2 hours	% Change
PBO (n=295)	20 (6.8%)	20 (6.8%)	0%

5mg (n=446)	19 (4.3%)	27 (6%)	+39.5%
10mg (n=444)	24 (5.4%)	19 (4.3%)	-20.3%

p=0.37 (chi square) for overall comparison

For the endpoint photophobia, there were 1207 evaluable patients. Overall, 1002 (83%) had photophobia at baseline, and 624 (52%) had photophobia at 2 hours, a net -37% decrease. The results according to treatment group are shown in FDA Table 95. Both 5mg and 10mg were better than placebo at relieving photophobia at 2 hours, and 10mg appears to be slightly better than 5mg.

Table 30: Study 022 - Photophobia (Reviewer's Analysis)

	Photophobia at Baseline	Photophobia at 2 hours	% Change
PBO (n=301)	256 (85%)	209 (69%)	-16%
5mg (n=456)	383 (84%)	224 (49%)	-42%
10mg (n=450)	363 (81%)	191 (42%)	-48%

p<0.0001 (chi-square) for overall analysis
p=0.046 (Fisher's Exact Test) for 10mg vs. 5mg

For the endpoint phonophobia, there were 1204 evaluable patients. Overall, 884 (73%) had phonophobia at baseline, and 483 (40%) had phonophobia at 2 hours, a net -45% decrease. The results according to treatment group are shown in FDA Table 31. Both 5mg and 10mg were better than placebo in relieving phonophobia at 2 hours. There was no difference between 10mg and 5mg.

Table 31: Study 022 - Phonophobia (Reviewer's Analysis)

	Phonophobia at Baseline	Phonophobia at 2 hours	% Change
PBO (n=301)	224 (74%)	162 (54%)	-27%
5mg (n=452)	331 (73%)	172 (38%)	-48%
10mg (n=451)	329 (73%)	149 (33%)	-55%

p<0.0001 (chi-square) for overall analysis
p=0.11 (Fisher's Exact Test) for 10mg vs. 5mg

7.4.4 Reviewer's Conclusions

Based on the data from study 022, I conclude the following:

1. Patients were evenly distributed among all three treatment groups (PBO, 5mg, 10mg) with regard to age, gender, race, and baseline severity.
2. Maxalt 5mg and 10mg were better than placebo for the acute treatment of migraine headache using the 2 hour headache response rate.
3. Both the 5mg and 10mg were also better than placebo at providing complete relief at 2 hours, and both had higher cure rates at 24 hours.
4. Both 5mg and 10mg were effective in the treatment of a 1st headache recurrence within 24 hours.
5. Both 5mg and 10mg were more effective than placebo in the relief of nausea, photophobia, and phonophobia at 2 hours. There was no difference with respect to vomiting.
6. The 10mg dose was better than 5mg in terms of primary efficacy and was generally better than 5mg in most secondary efficacy measures.

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7.5 Study 025 - Treatment of Multiple Migraine Headaches

This US study examined the efficacy of rizatriptan 10mg for the acute treatment of up to 4 consecutive migraine attacks in a total of 407 treated patients. It was a multicenter, double-blind, randomized, placebo-controlled, parallel design. Those who received 10mg for the initial attack were allowed to take 10mg for each of up to 2 recurrences within 24 hours. Those who received placebo for the initial attack also received placebo for recurrences. The repeat doses were not randomized and therefore did not provide information regarding efficacy of a second or third dose. Distinct attacks had to be at least 24 hours apart. There were five parallel treatment groups:

Table 32: Study 025, Treatment Assignment

Group (N)[1]	Attack 1	Attack 2	Attack 3	Attack 4
1 (83)	Placebo	10 mg	10 mg	10 mg
2 (82)	10 mg	Placebo	10 mg	10 mg
3 (84)	10 mg	10 mg	Placebo	10 mg
4 (77)	10 mg	10 mg	10 mg	Placebo
5 (81)	10 mg	10 mg	10 mg	10 mg

[1]Number of patients in group who treated at least the first attack

A more detailed summary of the protocol is located in Appendix B, page 131.

7.5.1 Results - Sponsor's Analyses

7.5.1.1 Sample Size Rationale

The planned sample size was 350 patients, consisting of 70 patients in each of the five treatment sequences. Four of the five treatment sequences had patients treat their first headache with rizatriptan 10mg. Based on this design, 280 patients were expected to treat their first headache with rizatriptan and 70 with placebo. The anticipated 2 hours response rate for 10mg was 50% and for placebo was 20%. The power to detect a 30 percentage point difference was ≥95% based on a two sided test and type I error rate of α=0.05. Based on the actual number of evaluable patients from this study (n=320 on rizatriptan and n=82 on placebo), and the actual observed treatment effect of 40 percentage points (77% for rizatriptan 10mg vs. 37% for placebo), the observed power was ≥99%.

7.5.1.2 Disposition

Table 33 lists the disposition of patients in study 025. Of the 407 patients who treated an initial attack, 367 treated a 2nd attack, 339 treated a 3rd attack, and 316 treated a 4th attack.

Table 33: Study 025 - Patient Disposition

	Sequence					
	P/10/ 10/10	10/P/ 10/10	10/10/ P/10	10/10/ 10/P	10/10/ 10/10	Total
Patients Randomized	*95*	*95*	*95*	*94*	*94*	*473*

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Patients Treated	*83*	*82*	*84*	*77*	*81*	*407*
Patients Not Treated	*12*	*13*	*11*	*17*	*13*	*66*
Patients Treated						
Completed	61	66	66	57	63	313
Total Discontinued	22	16	18	20	18	94 [22]
Clinical AE	2	2	1	1	2	8 [2]
Lost to Follow-Up	9	3	0	6	2	20 [9]
Deviation From Protocol	0	0	1	1	0	2
Withdrew From Study	2	4	2	3	6	17 [2]
Patient Uncooperative	0	1	0	1	2	4
Abnormal Baseline ECG	0	0	0	1	0	1
No Longer Satisfied Inclusion/ Exclusion Criteria	1	1	1	0	0	3 [1]
Not Completed/ Entered Extension	5	1	6	4	3	19 [5]
Study Terminated/ Not Continuing	3	0	3	3	1	10 [3]
Lack of Therapeutic Response	0	4	3	0	1	8 [6]
Pregnancy	0	0	1	0	1	2 [1]
Patients Not Treated						
Lost to Follow- Up	3	1	0	2	5	11
Withdrew From Study	4	7	4	7	2	24
Patient Uncooperative	0	0	0	1	0	1
Abnormal Pre-study Labs	0	0	0	0	2	2
Abnormal Baseline ECG	0	0	1	1	0	2
Lack Migraine Attack Pretreatment	3	5	5	6	4	23
No Longer Satisfied Inclusion/ Exclusion Criteria	1	0	0	0	0	1
Pregnancy	1	0	0	0	0	1
Inclusion/ Exclusion Criteria Not Met	0	0	1	0	0	1

[ ] patients in brackets indicate the number on placebo when they discontinued

7.5.1.3 Efficacy Parameters

The sponsor employed two approaches for the efficacy analysis: an "all-patients-treated" approach and a "per-protocol" approach. The efficacy analysis using the "all-patients-treated" approach was considered the primary efficacy analysis. The two approaches differed with regard to the inclusion/exclusion of protocol violators and the handling of missing data. They are described below.

The "all-patients-treated" analysis included all patients who had at least one record of an efficacy measure after the initial dose. Missing values in the treatment phase (i.e., after the baseline phase) were imputed using an LOCF approach. Values were not carried forward from one attack period to the next. Baseline values were not "carried forward" to impute the missing data in the treatment phase. No imputations were made to missing values at baseline or at 0.5 hour. Patients were included in the analysis starting from the time at which a non-missing value was first recorded after baseline. The efficacy analysis focused on the 2 hour response rate for the first attack only, and the 2 hour response rate over all four attacks. The statistical model of the latter analysis included terms for treatment, period, carryover, and their interactions. Individual

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analyses of the 2nd, 3rd, and 4th attacks were not performed. Efficacy data for 3 and 4 hours were not formally analyzed. The primary analysis was performed on the 2 hour response rate for attack 1 only. I include only the primary analysis in this review.

The two hour efficacy results for all 4 attacks are shown in sponsor Table 34.

Table 34: Study 025, Two Hour Efficacy Measures (N=407)

	Attack 1				Attack 2[a]			
	10mg		PBO		10mg		PBO	
Measure	N	%	N	%	N	%	N	%
Headache Related Measures								
Pain response	320	77*	82	37	291	78	73	37
Pain-free	320	44*	82	7	291	44	73	12
Escape medication	320	15*	82	42	291	14	73	49
Recurrence (within 24 h)	246	42	30	37	228	43	27	59
Associated Symptoms								
Nausea	317	23*	81	42	289	21	73	45
Vomiting	312	2*	79	7	289	3	73	10
Photophobia	319	40*	82	59	289	38	73	71
Phonophobia	318	32*	82	50	289	31	73	66
Functional Disability Rating		*						
Normal	319	48	82	22	291	54	73	16
Mildly impaired	319	39	82	43	291	32	73	44
Severely impaired	319	5	82	16	291	8	73	15
Requires bed rest	319	9	82	20	291	5	73	23

	Attack 3[a]				Attack 4[a]			
	10mg		PBO		10mg		PBO	
Measure	N	%	N	%	N	%	N	%
Headache Related Measures								
Pain response	259	80	75	28	255	75	57	54
Pain-free	259	49	75	11	255	45	57	21
Escape medication	259	14	75	59	255	17	57	32
Recurrence (within 24 h)	207	47	21	33	190	41	31	52
Associated Symptoms								
Nausea	258	21	74	42	256	22	56	29
Vomiting	258	5	74	13	256	3	56	5
Photophobia	258	40	74	72	256	44	56	56
Phonophobia	258	31	74	61	256	35	56	49
Functional Disability Rating								
Normal	259	53	75	12	255	48	57	30
Mildly impaired	259	32	75	41	255	36	57	40
Severely impaired	259	5	75	17	255	7	57	19
Requires bed rest	259	10	75	29	255	8	57	11

* p<0.05 versus placebo.
[a]These attacks were not analyzed separately but were included in a combined analysis of all four attacks, for pain relief measures only.

Rizatriptan was better than placebo for treatment of the first attack. The other three attacks also numerically favored rizatriptan but were not formally analyzed statistically and are supportive only. The response rates were similar across attacks and better than placebo in all four attacks (Table 34). The placebo response rates were highly variable across attacks and probably was related to

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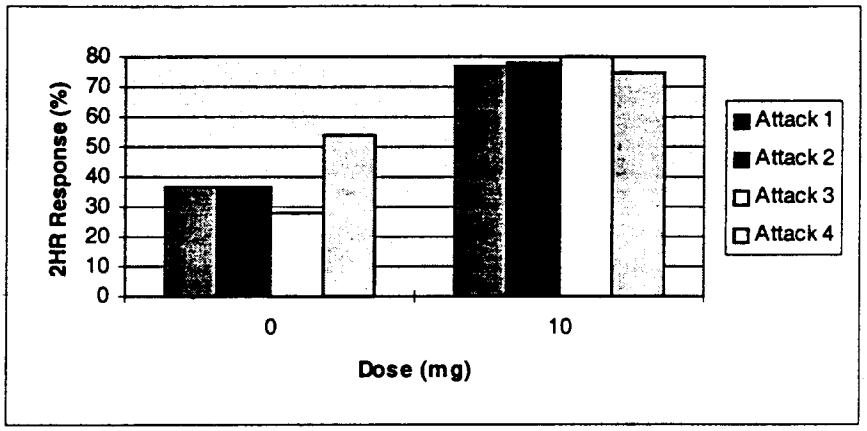
the small number of patients on placebo (n=83). The mean response rates across all 4 attacks was 77% for rizatriptan and 39% for placebo.

Figure 8: Study 025, Two Hour Response Rates in Multiple Attacks (N=407)



Secondary efficacy measures also favored rizatriptan. Complete pain-relief rates at 2 hours for attack 1 was significantly higher in the rizatriptan group (44% vs. 7%) and showed similar trends in subsequent attacks. Use of escape medication was less in the rizatriptan groups (15% vs. 42%, for attack 1). Associated symptoms were also less in the rizatriptan group. There was no statistical difference in recurrence rates between the two groups.

There were 50 patients who did not respond to rizatriptan in the first attack. Of these, 35 (70%) responded to rizatriptan for their second attack. This suggests that patients who fail to respond to initial treatment cannot be labeled as non-responders. Very few patients failed to respond to any attack. Of 315 patients who treated 3 or 4 attacks with rizatriptan, only 12 did not respond to any attacks (4%).

7.5.2 Sponsor's Conclusions

1. Rizatriptan 10mg is highly effective and rapidly acting in the acute treatment of migraine.
2. The efficacy of rizatriptan 10mg is maintained when it is used to treat multiple, discrete migraine attacks; the majority of patients responded in a majority of attacks treated.
3. Rizatriptan 10mg improves quality of life and functional disability, reduces migraine associated symptoms, and reduces the need for additional or escape anti-migraine medications.

7.5.3 Results- Reviewer's Analyses

7.5.3.1 Methods and Demographic Considerations

My analyses of study 025 used the efficacy dataset provided by the sponsor. All analyses were done using JMP version 3.2.1.

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There were 407 patients with efficacy data in the JMP dataset. All 407 treated the first attack, 367 treated the 2nd attack, 339 treated attack 3, and 316 treated attack 4.

For the first attack, 324 received rizatriptan 10mg, the remaining 83 received placebo. The mean age of the population was 40.6. Three hundred forty one (341), or 84%, were female, and the population was predominantly white (382/407 or 94%). Blacks made up 2.4% of the study population (n=10). The demographics, by treatment group, are shown in Table 35.

Table 35: Study 025 - Demographics of the 1st Attack

	PBO (n=83)	Rizatriptan 10mg (n=324)
Mean Age	41.0	40.5
Females	68 (82%)	273 (84%)
White	76 (92%)	306 (94%)
Black	3 (3.6%)	7 (2.1%)
Baseline Severity = 2	58 (70%)	245 (76%)

The two populations were comparable with regard to mean age, gender, race, and baseline severity.

7.5.3.2 Primary Efficacy - 2 Hour Response Rate

Of the 407 patients who treated the first attack, 4 did not record a baseline headache score. I removed them from the analysis. The remaining 403 did, in fact, report a grade 2 or 3 headache at baseline. Eighty-two (82) took placebo and 321 took 10mg as initial treatment. Of these 403 patients, 2 patients recorded a baseline score, but failed to record any post-treatment scores between 0-2 hours. I counted them as treatment failures. An additional 19 patients failed to record a 2 hour score, but I was able to impute an LOCF score from the last post-treatment measurement recorded.

Seventy-six percent (76%) of the 10 mg group (245/321) achieved a response at 2 hours. This is compared with 37% of placebo patients (FDA Table 36).

Table 36: Study 025 - Two Hour Response Rate for 1st Attack (Reviewer's Analysis)

Treatment	Response	No Response
PBO (n=82)	30 (37%)	52 (63%)
10mg (n=321)	245 (76%)	76 (24%)

p<0.0001 (Fisher's Exact Test)

7.5.3.3 Complete Relief

A complete relief was defined as a grade 2 or 3 headache at baseline and no pain (grade 0) at 2 hours. Forty-four percent (44%) of the 10mg patients and only 7% of the placebo patients achieved complete relief at 2 hours (FDA Table 37)

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Table 37: Study 025 - Complete Relief Rate for 1st Attack (Reviewer's Analysis)

Treatment	Complete Relief
PBO (n=82)	6 (7%)
10mg (n=321)	142 (44%)

p<0.0001 (Fisher's Exact Test)

7.5.3.4 Cure Rate

Forty-one percent (41%) of the 10mg group, and 15% of the placebo achieve a cure, using my pre-defined definition of a migraine cure (FDA Table 38).

Table 38: Study 025 - Cure Rate (Reviewer's Analysis)

Treatment	Cure
PBO (n=82)	12 (15%)
10mg (n=321)	132 (41%)

p<0.0001 (Fisher's Exact Test)

7.5.3.5 Consistency of Response

Of the 407 patients who treated an initial attack, 367 treated a 2nd attack, 339 treated a 3rd attack, and 316 treated a 4th attack. Across all attacks, there were 8 attacks without a recorded baseline headache severity (4 in attack 1, 2 in attack 3, and 2 in attack 4). These I excluded from the analysis. This resulted in 403 evaluable patients for attack 1, 367 for attack 2, 337 for attack 3, and 314 for attack 4. They establish the denominator for all response rates. Furthermore, there were 11 patients (2 in attack 1, 3 in attack 2, 4 in attack 3, and 2 in attack 4) that failed to record any post-treatment headache severity through 2 hours. These I designated treatment failures. All patients had baseline severity of 2 or 3 for every attack, so there were no protocol violators in that regard. The two hour headache response rates across attacks are shown in FDA Table 39.

Table 39: Study 025 - Consistency of Response across 4 Attacks (Reviewer's Analysis)

		Placebo			Rizatriptan 10mg		
Attack	N	n	Responders	%	n	Responders	%
1	403	82	30	37%	321	245	76%*
2	367	74	27	37%	293	228	78%*
3	337	75	21	28%	262	206	79%*
4	314	57	31	54%	257	190	74%**

* p<0.0001 compared to placebo (Fisher's Exact Test); ** p=0.006 compared to placebo (Fisher's Exact Test)

The response rates for rizatriptan 10mg across four attacks were similar, and ranged They were all better than placebo, although the placebo rate fluctuated a great deal

7.5.3.6 Associated Symptoms

I compared the percentage of patients having associated symptoms (nausea, vomiting, photophobia, phonophobia) at baseline vs. 2 hours. For missing data, I dropped patients who failed to record a baseline measurement. For patients who failed to record a 2 hour measurement, I used an LOCF approach, using the last

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post-treatment value recorded, if one was available. I used the results from the first attack only for this analysis.

The placebo patients experienced a 30% drop in nausea over 2 hours, whereas the 10mg patients experienced a 58% drop, almost double the change in placebo rate.

Table 40: Study 025 - Nausea During the 1st Attack (Reviewer's Analysis)

	Nausea at Baseline	Nausea at 2 hours	% Change
PBO (n=79)	46 (58%)	32 (41%)	-30%
10mg (n=316)	173 (55%)	73 (23%)	-58%

p=0.0011 (Fisher's Exact Test)

With regard to vomiting, the numbers were too small to draw meaningful conclusions. The placebo patients experienced a 16% drop in vomiting and the 10mg patients a 21% drop, but as can be seen in FDA Table 45, the numbers were small and did not achieve statistical significance when stratified by baseline vomiting (which were quite disparate between the two groups).

Table 41: Study 025 - Vomiting During the 1st Attack (Reviewer's Analysis)

	Vomiting at Baseline	Vomiting at 2 hours	% Change
PBO (n=76)	6 (7.9%)	5 (6.6%)	-16%
10mg (n=311)	9 (2.9%)	7 (2.3%)	-21%

p=0.2233 (Cochran-Mantel-Haenszel, stratified by baseline vomiting)

Both photophobia and phonophobia rates improved more after treatment with rizatriptan 10mg compared to placebo. Both rates decreased approximately 55% with active drug vs. , with placebo (Table 42 and Table 43)

Table 42: Study 025 - Photophobia (Reviewer's Analysis)

	Photophobia at Baseline	Photophobia at 2 hours	% Change
PBO (n=82)	62 (76%)	48 (59%)	-22%
10mg (n=319)	276 (87%)	127 (40%)	-54%

p=0.0027 (Fisher's Exact Test)

Table 43: Study 025 - Phonophobia (Reviewer's Analysis)

	Phonophobia at Baseline	Phonophobia at 2 hours	% Change
PBO (n=80)	52 (65%)	40 (50%)	-23%
10mg (n=318)	232 (73%)	103 (32%)	-56%

p=0.0043 (Fisher's Exact Test)

7.5.3.7 Reviewer's Conclusions

Based on the data from study 025, I conclude the following:

1. Patients were evenly balanced between both treatment groups (PBO, 10mg) with regard to age, gender, race, and baseline severity.

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