2. Maxalt 10mg was better than placebo for the acute treatment of migraine headache, when measured by the 2 hour headache response rate.
3. The 10mg dose was also better than placebo at providing complete relief at 2 hours, and also had a higher cure rate at 24 hours.
4. The response rates were maintained across four consecutive migraine attacks.
5. Maxalt 10mg was more effective than placebo in the relief of nausea, photophobia, and phonophobia at 2 hours. There was no difference with respect to vomiting.

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7.6 Study 029 - Rizatriptan 5mg vs. Sumatriptan 50mg

This was a randomized, double-blind, placebo-controlled and active controlled, non-US multinational study which compared the efficacy of rizatriptan 5mg and sumatriptan 50mg for the acute treatment of a migraine headache. A total of 792 patients were treated. Patients were randomized to single doses of rizatriptan 5mg (n=355), sumatriptan 50mg (n=357) or placebo (n=80). Rescue was permitted at two hours. A second dose was not given. In addition to the 2 hour response rate, the study included the time to a response within the first 2 hours as a primary efficacy measure. A more detailed summary of the protocol is located in Appendix B, page 131.

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7.6.1 Results - Sponsor's Analysis

7.6.1.1 Sample Size

The primary analysis compared the time to response between the rizatriptan and sumatriptan groups. With a planned sample size of 375 patients in both the rizatriptan 5mg and the sumatriptan 50mg groups, the power was 80% to detect a difference of 10 percentage points in the percentages of responders at 1.5 hours post-dose.

7.6.1.2 Disposition

There were 933 patients who entered the study. Only 792 were treated. Of these, 2 did not complete the study (one rizatriptan 5mg patient deviated from the protocol and a placebo patient withdrew from the study). Diary cards were not returned by 4 patients.

Among the 141 patients not treated, the primary reasons were: withdrew from study (53), no migraine (43), or lost to follow up (31). These were classified as "not treated" because there was no evidence that medication was ever taken. Other reasons resulting in no treatment were abnormal pre-study lab results (2), abnormal ECG (4), need for concomitant medications (2), not satisfying inclusion/exclusion criteria (1), pregnancy (1), and other (3). Patient dispositions are summarized in sponsor Table 38.

Table 44: Study 029 - Patient Disposition

	Riza 5 mg	Suma 50 mg	Placebo	Total
Patients Randomized	*418*	*428*	*87*	*933*

Patients Treated	*355*	*357*	*80*	*792*
Patients Not Treated	*63*	*71*	*7*	*141*
Patients Treated				
Completed Study	354	357	79	790
Deviation From Protocol	1	0	0	1
Withdrew From Study	0	0	1	1
Patients Not Treated				
Lost to Follow- up	12	17	2	31
Deviation From Protocol	0	1	0	1
Withdrew From Study	23	27	3	53
Other	3	0	0	3
Abnormal Prestudy Labs	2	0	0	2
Abnormal Baseline ECG	2	2	0	4
Need for Concom. Med.	0	1	1	2
Lack of Migraine Attack	20	22	1	43
No Longer Satisfying Incl/ Excl Criteria	1	0	0	1

7.6.1.3 Efficacy Parameters

The primary efficacy analyses focused on [1] the 2 hour headache response rate of rizatriptan 5mg vs. placebo, [2] the time to headache response within 2 hours for rizatriptan 5mg vs. sumatriptan 50mg. A binary regression model for grouped time to event data was used to compare treatment groups. These data have been summarized by treatment groups in terms of the cumulative percent of patients who first reported a response at each half-hour interval up to 2 hours post dose, using the Life Table method with censoring occurring at the beginning of each interval.

Both rizatriptan 5mg and sumatriptan 50mg were superior to placebo in terms of the 2 hour headache response (FDA Figure 9), but also in terms of other measures (pain-free, need for escape medication, associated symptoms, and functional disability, Table 45).

Figure 9: Study 029, Two Hour Response Rates

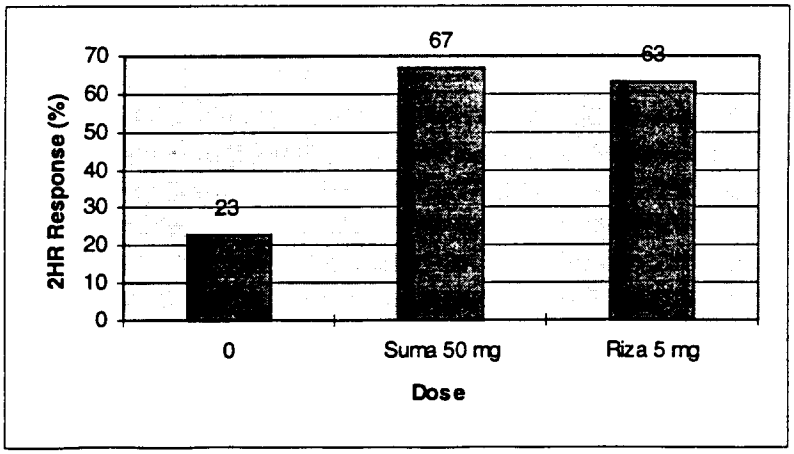


Table 45: Study 029, Efficacy Measures**

	Rizatriptan 5mg	Sumatriptan	PBO

Measure	N	%	50mg N	50mg %	N	%
Headache-Related Measures						
Pain response	352	63*	356	67*	80	23
Pain-free	352	27*	356	32*	80	3
Escape medication	355	21*	357	15*	80	41
Recurrence (within 24 hours)	223	38	238	34	18	33
Cumulative % of patients with first report of pain relief	352	66	356	70	80	24
Associated Symptoms						
Nausea	348	30*†	352	37*	78	62
Vomiting	342	4	342	4	73	8
Photophobia	350	46*	354	43*	80	83
Phonophobia	350	36*	354	35*	80	59
Functional Disability Rating		*		*		
Normal	350	31	355	33	80	5
Mildly impaired	350	43	355	42	80	35
Severely impaired	350	11	355	12	80	23
Requires bed rest	350	15	355	14	80	38
	N	**Mean**	**N**	**Mean**	**N**	**Mean**
Satisfaction with Medication	335	3.86*	337	3.79*	77	5.48
24- Hour Quality of Life						
Work	341	11.92*	339	11.65*	77	9.05
Social	338	11.35*	338	11.19*	77	8.74
Energy	338	11.36*	338	11.63*	77	8.66
Symptoms	341	12.76*	340	12.87*	76	9.72
Feelings	340	12.68*	339	12.87*	76	10.61

** all efficacy measures are at 2 hours except 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 = 1 to 7. A lower score indicates greater patient satisfaction.
[4] Range of possible scores for each domain = 3 to 21. A higher score corresponds to better quality of life.
* $p < 0.05$ versus placebo.
† $p < 0.05$ versus sumatriptan 50 mg.

Although not a primary analysis, there was no difference between rizatriptan 5mg and sumatriptan 50mg with respect to the 2 hour headache response rate. The percentage of experiencing headache recurrence was approximately 35% and similar across treatments.

There were few differences between the two active treatments (Table 46). In particular, the other primary efficacy measure of time to headache response up to 2 hours revealed that there was no difference in the probability of achieving a response between the two active treatments (p=0.514, sponsor Table 47). The only differences between the two treatments were that fewer patients in the rizatriptan groups had nausea at 2 hours (30% vs. 37%), and sumatriptan patients had a higher response rate at 4 hours (81% vs. 72%) and higher pain-free rate at 4 hours (51% vs. 42%).

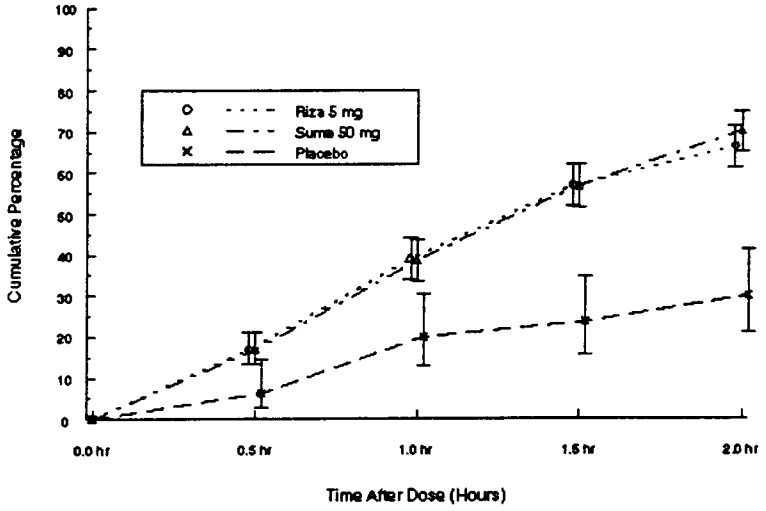
Table 46: Study 029, Time Points at which Significant Differences Occurred

Measure	Riza 5mg Superior to PBO	Suma 50mg Superior to PBO	Riza 5mg Superior to Suma 50mg	Suma 50mg Superior to Riza 5mg

Measures at 0.5, 1, 1.5, 2, 3, 4 Hours				
Pain response	0.5 to 4 hr	0.5 to 4 hr	-	4 hr
Pain-free	1 to 4 hr	1.5 to 4 hr	-	4 hr
Nausea	1 to 4 hr	1 to 4 hr	2 hr	-
Vomiting	1 to 1.5, 3 to 4 hr	3 to 4 hr	-	-
Photophobia	0.5 to 4 hr	0.5 to 4 hr	-	-
Phonophobia	1 to 4 hr	1 to 4 hr	-	-
Functional disability	1 to 4 hr	0.5 to 4 hr	-	-
Measures Assessed at 2 Hours				
Escape medication	2 hr	2 hr	-	-
Satisfaction with medication	2 hr	2 hr	-	-
Measures Assessed at 24 Hours				
Quality of Life: Work	24 hr	24 hr	-	-
Quality of Life: Social	24 hr	24 hr	-	-
Quality of Life: Energy	24 hr	24 hr	-	-
Quality of Life: Symptoms	24 hr	24 hr	-	-
Quality of Life: Feelings	24 hr	24 hr	-	-

"-" indicates no statistically significant difference

Table 47: Cumulative Percentage (Life-Table Estimate) of Patients with First Report of a Headache Response Within 2 Hours (with 95% confidence intervals)



Nausea: About 68% of the patients recorded presence of nausea at baseline, with no significant differences found between treatment groups. Both the rizatriptan and the sumatriptan groups had significantly lower rates of nausea than the placebo group at 1, 1.5, and 2 hours ($p<0.05$). At 2 hours, the percentages of patients reporting presence of nausea were 30.2%, 37.2%, and 61.5% for the rizatriptan 5mg, sumatriptan 50mg, and placebo groups, respectively. At 2 hours after treatment dose, there was a significant difference between rizatriptan and sumatriptan: in the rizatriptan group, fewer patients reported nausea than in the sumatriptan group (30.2% vs. 37.2%, $p=0.049$). At all other time points, the rizatriptan and sumatriptan groups were similar with respect to the percentage of patients reporting nausea.

examining the 2 hour headache response rates, but I don't repeat the other primary analysis (time to response) since no significant difference was observed between the two active groups. I don't repeat the secondary analyses, except for nausea, since the sponsor reports rizatriptan 5mg is better than sumatriptan 100mg in relief of nausea at 2 hours.

There were 792 patients with efficacy data in the JMP dataset. All analyses focused on treatment of the initial attack.

For the initial attack, 355 received rizatriptan 5mg, 357 received sumatriptan 50mg and 80 received placebo. The mean age of the population was 41.2. Six hundred fifty two (652), or 82%, were female, and the population was predominantly white (788/792 or 99%). There were no blacks in the study.

The distribution of demographics, by treatment group, is shown in Table 48.

Table 48: Study 029 - Demographics

	PBO (n=80)	Sumatriptan 50mg (n=357)	Rizatriptan 5mg (n=355)
Mean Age	44.3	41.8	39.9
Females	70 (87%)	291 (82%)	291 (82%)
White	80 (100%)	356 (99.7%)	352 (99%)
Black	0	0	0
Baseline Severity = 2	51 (64%)	221 (70%)	216 (61%)

There were some differences among the three treatment populations. The placebo group was older, and the sumatriptan group had a higher percentage of moderate baseline headaches. The latter difference would tend to favor sumatriptan in the analyses, since it is expected that patients with moderate pain would have higher response rates compared with those that begin with severe pain.

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7.6.3.2 Primary Efficacy - 2 Hour Response Rates

Of the 792 patients who treated the first attack, 14 did not record a baseline headache score. I removed them from the analysis. The remaining 778 did, in fact, report a grade 2 or 3 headache at baseline. Eighty-two (82) took placebo and 349 each took rizatriptan 5mg or sumatriptan 50mg as initial treatment. Of these, 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 26 patients failed to record a 2 hour score, but I was able to impute an LOCF score from the last post-treatment measurement recorded.

Sixty three percent (63%) of the rizatriptan 5 mg group achieved a response at 2 hours, compared to 67% for sumatriptan and 23% for placebo (FDA Table 49).

Table 49: Study 029 - Two Hour Response Rate (Reviewer's Analysis)

Treatment	Response	No Response

Vomiting: The percentages of patients reporting vomiting at baseline ranged from 4.2% (in the placebo group) to 5.4% (in the sumatriptan group). The rizatriptan 5-mg group had significantly lower rates of vomiting than the placebo group at 1 and 1.5 hours ($p<0.01$). At 2 hours after treatment dose, the difference showed borderline significance in favor of rizatriptan (3.5% vs. 8.2%, $p=0.078$). At all time points up to 2 hours, the rizatriptan and sumatriptan groups were similar with respect to the percentage of patients reporting vomiting.

Photophobia: At baseline, the percentage of patients recording presence of photophobia ranged from 77.8% (sumatriptan group) to 86.3% (placebo group), with no significant differences found between treatment groups. Both the rizatriptan 5-mg and sumatriptan 50-mg groups started to show a significant difference from the placebo group as early as 0.5 hours after the treatment dose ($p=0.019$ and $p=0.009$, respectively). At 2 hours, the percentages of patients reporting presence of photophobia were 46.0%, 43.2%, and 82.5% for the rizatriptan 5-mg, sumatriptan 50-mg, and placebo groups, respectively. The rizatriptan and sumatriptan groups were similar with respect to the percentage of patients reporting photophobia at time points up to 2 hours after treatment dose.

Phonophobia: About 66% of the patients in the rizatriptan and sumatriptan groups and about 71% of the patients in the placebo group recorded presence of phonophobia at baseline, with no significant differences found at baseline between treatments. Both the rizatriptan 5-mg and sumatriptan 50-mg groups started to show a significant difference from the placebo group at 1 hour ($p\leq0.005$). At 2 hours, the percentages of patients reporting presence of phonophobia were 36.0%, 35.3%, and 58.8% for the rizatriptan 5mg, sumatriptan 50mg, and placebo groups, respectively. The rizatriptan and sumatriptan groups were similar with respect to the percentage of patients reporting phonophobia at all time points up to 2 hours after treatment dose.

7.6.2 Sponsor's Conclusions

1. Rizatriptan 5mg and sumatriptan 50mg provide relief from moderate and severe migraine headache. Within 2 hours after dosing, rizatriptan 5mg and sumatriptan 50mg are similar with respect to pain response.
2. Rizatriptan 5mg and sumatriptan 50mg are similar with respect to time to response. Both provide relief from as early as 30 minutes after dosing.
3. Rizatriptan 5mg and sumatriptan 50mg are similarly effective in providing total relief (pain-free), and reducing functional disability and associated symptoms, as well as the need for escape medication. Rizatriptan 5mg and sumatriptan 50mg have a similar positive effect on quality of life and provide similar patient satisfaction.

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7.6.3 Results - Reviewer's Analyses

7.6.3.1 Methods and Demographic Considerations

My analyses of study 029 used the efficacy dataset provided by the sponsor. All analyses were done using JMP version 3.2.2. I performed the primary analysis

PBO (n=80)	18 (23%)	62 (77%)
Rizatriptan 5mg (n=349)	221 (63%)	128 (37%)
Sumatriptan 50mg (n=349)	232 (67%)	117 (33%)

p<0.0001 (Chi Square Test) for overall analysis

7.6.3.3 Associated Symptoms - Nausea

I chose to analyze nausea, a secondary efficacy measure, in order to explore the sponsor's comment that rizatriptan 5mg is better than sumatriptan 50mg for the relief of nausea at 2 hours.

Of the 792 patients who treated the initial attack, 23 did not record a baseline nausea measure. I removed these from the analysis. This resulted in 769 evaluable patients. Of these, 2 failed to record any post-treatment nausea measures. One had nausea at baseline and the other did not. I chose to carry forward their baseline nausea score for the LOCF analysis. An additional 30 patients did not record a 2 hour nausea measurement, but I was able to impute an earlier post-treatment measurement for an LOCF analysis.

Five hundred eighteen (518) patients had nausea at baseline (67%). Across treatment groups, the incidences of nausea at baseline were 68%, 65% and 69% for placebo, rizatriptan 5mg, and sumatriptan 50mg, respectively. There was no statistically significant differences noted in baseline nausea scores among the three treatment groups (p=0.483, chi square).

At two hours, the percentages of patients experiencing nausea were 61%, 31%, and 38%, for placebo, rizatriptan 5mg, and sumatriptan 50mg, respectively (p<0.001 chi square for overall analysis). Both active treatments were significantly better than placebo (p<0.001 for rizatriptan 5mg, and p=0.0002 for sumatriptan 50mg, Fisher's Exact Test).

The pair-wise comparison of the 2 hour nausea rates between rizatriptan 5mg and sumatriptan 50 mg was not significant (p=0.0541). This differs from the sponsor's analysis of p=0.049. I therefore conclude that there is no difference between rizatriptan 5mg and sumatriptan 50mg with regard to relief of nausea at 2 hours.

7.6.4 Reviewer's Conclusions

Based on the data from study 029, I conclude the following:

1. Both rizatriptan 5mg and sumatriptan 50mg are more effective than placebo for acute treatment of migraine headache, when measured by the 2 hours headache response rates.
2. There was no difference between rizatriptan and sumatriptan in terms of headache response at 2 hours, or time to response within the first two hours.
3. Although the sponsor states that rizatriptan 5mg was better than sumatriptan 50mg in the relief of nausea at 2 hours post dose, my analysis indicates that there was no statistically significant difference between the two active drugs.

7.7 Study 030 - Rizatriptan 5mg and 10 mg vs. Sumatriptan 100mg

This was a randomized, double-blind, placebo-controlled and active controlled, non-US multinational study which compared the efficacy of high and low dose rizatriptan to high dose sumatriptan for the acute treatment of migraine headache in a total of 1099 treated patients. The study had four treatment arms, rizatriptan 5mg (n=164), rizatriptan 10mg (n=387), sumatriptan 100mg (n=388), and placebo (n=160). As in study 029, a second dose of study medication was not given, and rescue was permitted starting at 2 hours. In addition to the 2 hour response rate, the study included time to headache response as a primary outcome measure. Time to headache response was defined as the time a patient first reported a response in the 2 hours after dosing. A more detailed summary of the protocol is located in Appendix B, page 131.

7.7.1 Results - Sponsor's Analysis

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7.7.1.1 Sample Size

The primary analysis compared the time to response between the rizatriptan 10mg and sumatriptan 100mg. With a planned sample size of 375 patients in both the rizatriptan 10mg and the sumatriptan 100mg groups, the power was 80% to detect a difference of 10 percentage points in the percentages of responders at 1.5 hours post-dose.

7.7.1.2 Disposition

There were 1268 patients who entered the study from 47 sites in 21 countries. There were 1030 females (81%) and 238 males (19%). One hundred sixty nine (169) patients did not take any study medication. They were excluded from any subsequent analyses. This left 1099 evaluable patients.

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Table 50: Study 029 - Patient Disposition

	Riza 5 mg	Riza 10mg	Suma 100 mg	Placebo	Total
Patients Randomized	*180*	*455*	*455*	*178*	*1268*
Patients Treated	*164*	*387*	*388*	*160*	*1099*
Patients Not Treated	*16*	*68*	*67*	*18*	*169*
Patients Treated					
Completed Study	163	386	383	159	1091
Clinical AE	0	0	1	0	1
Lost to Follow-up	0	0	2	0	2
Deviation From Protocol	1	1	2	0	4
Withdrew From Study	0	0	0	1	1
Patients Not Treated					
Clinical AE	0	1	1	0	2
Laboratory AE	0	1	0	0	1
Lost to Follow- up	0	5	5	2	12
Deviation From Protocol	2	0	2	0	4
Withdrew From Study	2	16	11	3	32
Other	0	0	2	0	2
Abnormal Prestudy Labs	0	0	0	1	1
Abnormal Baseline ECG	1	0	0	0	1
Lack of Migraine Attack	9	39	43	12	103

7.7.1.3 Efficacy Parameters

As in study 029, the primary efficacy analyses focused on [1] the 2 hour headache response rate between rizatriptan 5mg and 10mg vs. placebo, and [2] the time to headache response within the first 2 hours for rizatriptan 10 mg vs. sumatriptan 100 mg. Efficacy results are shown in Table 51.

At two hours, all three active medications were better than placebo in terms of headache response (FDA Table 52) and in terms of other measures, including pain-free, need for escape medication (although not significant for rizatriptan 5mg) and presence of associated symptoms.

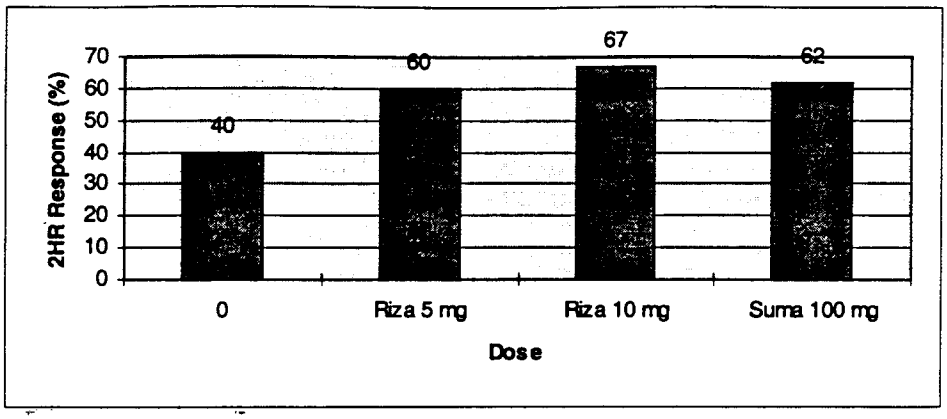
Table 51: Study 030, Efficacy Measures**

Measure	Rizatriptan 5 mg N	Rizatriptan 5 mg %	Rizatriptan 10 mg N	Rizatriptan 10 mg %	Sumatriptan 100 mg N	Sumatriptan 100 mg %	Placebo N	Placebo %
Headache-Related Measures								
Pain response	164	60*	385	67*	387	62*	159	40
Pain-free	164	25*	385	40*†§	387	33*	159	9
Escape medication	164	23	387	18*	388	20*	160	33
Recurrence (within 24 hr)[1]	99	48	258	35	239	32	64	20
Cumulative % of patients with first report of pain relief	164	63	385	69	387	65	159	45
Associated Symptoms								
Nausea	164	23*†	385	25*†	387	33*	159	43
Vomiting	163	5	385	6	386	6	159	10
Photophobia	164	43	385	38*	387	42*	159	53
Phonophobia	164	37*	385	34*	387	40*	159	52
Functional Disability Rating[2]		*		*†§		*		
Normal	164	32	385	42	387	33	159	20
Mildly impaired	164	38	385	32	387	37	159	37
Severely impaired	164	17	385	16	387	17	159	21
Requires bed rest	164	14	385	11	387	13	159	23
	N	**Mean**	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**
Satisfaction with Medication[3]	163	4.10*	380	3.54*§	380	3.75*§	156	4.76
24 Hour Quality of Life								
Work	164	12.37	380	13.52*§	387	13.03	158	12.13
Social	164	12.51	385	13.52*§	387	13.25	158	12.34
Energy	164	12.32	384	13.08*	387	12.86*	158	11.58
Symptoms	164	13.41*	386	13.98*	387	13.69*	157	12.42
Feelings	164	12.03*	386	12.85*	387	12.82*	158	10.87

** all efficacy measures are at 2 hours except the 24 hour Quality of Life Questionnaire
[1] Not analyzed. The denominator is the number of patients who responded at 2 hrs
[2] Analysis based on overall distribution between categories, rather than comparisons within each category
[3] Range of possible scores = 1 to 7. A lower score indicates greater patient satisfaction.
[4] Range of possible scores for each domain = 3 to 21. A higher score corresponds to better quality of life.
* $p<0.05$ vs. placebo
† $p<0.05$ vs. sumatriptan 100 mg
§ $p<0.05$ vs. rizatriptan 5 mg

There was very little difference between either rizatriptan dose and sumatriptan 100mg. Nausea was less with rizatriptan (either dose), and the percentage of pain free patients at 2 hours after receiving rizatriptan 10mg was significantly higher than either rizatriptan 5mg or sumatriptan 100mg.

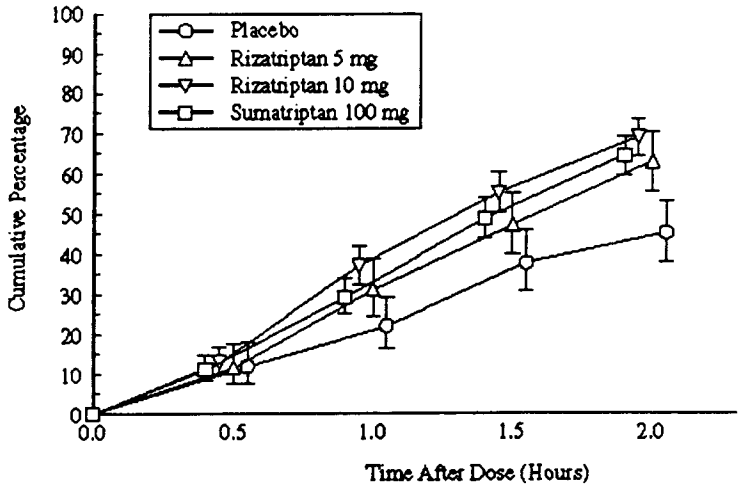
Table 52: Study 030, Two Hour Headache Response Rates (N=1099)



Although rizatriptan 10mg was numerically better than 5mg on various measures, it was statistically better only in percentage of patients becoming pain-free at 2 hours (40% vs. 25%). It also was better than 5mg in functional disability ratings, satisfaction with medication, and 24 hour quality of life parameters.

In terms of the other primary efficacy analysis, the time to headache response within two hours (rizatriptan 10mg vs. sumatriptan 100mg), there was no statistically significant difference between the two drugs. There was a numerical trend favoring rizatriptan 10mg, such that patients on rizatriptan 10mg were more likely to achieve pain response within two hours (hazard ratio = 1.17, p=0.075), but, again, it was not statistically significant (Figure 10).

Figure 10: Cumulative Percentage of Patients with First Report of Pain Relief Within 2 Hours (Life-Table Estimates and 95% Confidence Limits)



Recurrence rates were 32% for sumatriptan, 35% for rizatriptan 10mg, and 48% for rizatriptan 5mg.

Nausea: At baseline, 56%, 59%, 60%, and 62% of patients on 5mg, 10mg, sumatriptan 100mg, and placebo had nausea, with no significant differences among groups. At 2 hours, the percentages of patients reporting nausea were 23%, 25%, 33%, and 43%. All three active treatment groups were better than placebo ($p<0.001$ for rizatriptan groups and $p=0.032$ for sumatriptan). Both rizatriptan groups were significantly better than sumatriptan at 1, 1.5, and 2 hours. The two rizatriptan dose groups were similar at all time points.

Vomiting: At baseline, 9%, 10%, 8%, and 13% of patients on 5mg, 10mg, sumatriptan 100mg, and placebo had vomiting. At 2 hours, the percentages of patients with vomiting were 5%, 6%, 6%, and 10%. The numerical percentages did not achieve statistical significance for any group.

Photophobia: At baseline, 77%, 75%, 76%, and 71% of patients on 5mg, 10mg, sumatriptan 100mg, and placebo, respectively, had photophobia, with no significant differences found among groups. At 2 hours, the percentages of patients with photophobia were 43%, 38%, 42%, and 53%. Rizatriptan 10mg was statistically better than placebo ($p=0.002$). The numerical advantage seen for rizatriptan 5mg did not achieve statistical significance. Sumatriptan 100mg was also better than placebo ($p=0.02$).

Phonophobia: At baseline, 74%, 74%, 72%, and 70% of patients on 5mg, 10mg, sumatriptan 100mg, and placebo, respectively, had photophobia, with no significant differences among groups. At 2 hours, the percentages of patients with phonophobia were 37%, 34%, 40%, and 52%. The two rizatriptan groups were better than placebo ($p=0.007$ for 5mg, and $p=<0.001$ for 10mg). Sumatriptan 100mg was also better than placebo ($p=0.007$).

7.7.2 Sponsor's Conclusions

1. Rizatriptan 5mg and 10mg, and sumatriptan 100mg provide relief from moderate and severe migraines.
2. Rizatriptan 10mg provides relief earlier than sumatriptan 100mg and shows clear activity by 1 hour after dosing.[2]
3. Rizatriptan 5mg and 10mg, and sumatriptan 100mg are effective in providing total pain relief (pain free) and reducing functional disability in patients with migraine headache rizatriptan 10mg is superior to sumatriptan 100 mg on these measures.
4. Rizatriptan 5mg and 10mg, and sumatriptan 100mg are all effective in reducing associated symptoms. Rizatriptan 5mg and 10mg are both superior to sumatriptan 100mg in reducing the associated symptom of nausea.

[2] Reviewer's note: although the analysis favored rizatriptan numerically, it did not achieve statistical significance ($p=0.075$).

7.7.3 Reviewer's Analyses

7.7.3.1 Methods and Demographic Considerations

I used the efficacy dataset provided by the sponsor to perform my own analyses. In all cases, I used JMP version 3.2.2. I analyzed the 2 hour response rates for each treatment group. I did not repeat the sponsor's analysis of time to response, since no statistical significance was seen in the sponsor's analysis between rizatriptan 10mg and sumatriptan 100mg. I did not repeat the secondary efficacy analyses, with the exception of the nausea analysis, since the sponsor reports rizatriptan (either dose) is better than sumatriptan 100mg at relieving nausea at 2 hours.

There were 1009 patients in the efficacy dataset. All 1009 treated the first attack, and 322 took a second dose. All analyses focused on treatment of the initial attack. The mean age of the population was 38.2. Eight hundred ninety-eight (898), or 82%, were female, and the population was predominantly white (800/1099 or 73%). There were 9 blacks in the study. The remaining 290 consisted of Hispanic (222), Mestizo (53) or of other races (15). The demographics, by treatment group, is summarized in FDA Table 53.

Table 53: Study 029 - Demographics

	PBO (n=160)	Sumatriptan 100mg (n=388)	Rizatriptan 5mg (n=164)	Rizatriptan 10mg (n=387)
Mean Age	38.3	39.2	38.3	37.0
Females	132 (83%)	309 (80%)	138 (84%)	319 (82%)
White	120 (75%)	281 (72%)	117 (71%)	282 (73%)
Baseline Severity = 2	75 (47%)	196 (49%)	72 (44%)	174 (45%)

There were some differences among the three treatment populations. The sumatriptan group was slightly older, and had a higher percentage of moderate baseline headaches. The latter difference would tend to favor sumatriptan, since it is expected that patients with moderate pain would have higher response rates compared with those with severe pain.

7.7.3.2 Primary Efficacy - 2 Hour Response Rates

Of the 1099 patients who treated the first attack, 2 did not record a baseline headache score. I removed them from the analysis. The remaining 1097 did, in fact, report a grade 2 or 3 headache at baseline (no violators). One hundred fifty-nine (159) took placebo, 164 took rizatriptan 5mg, 387 took rizatriptan 10mg, and 387 took sumatriptan as initial treatment. Of these 1097 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 13 patients failed to record a 2 hour score, but I was able to impute an LOCF score from the last post-treatment measurement recorded.

Sixty percent (60%) of the rizatriptan 5 mg group achieved a response at 2 hours, compared to 67% for rizatriptan 10mg, 62% for sumatriptan 100mg and 40% for placebo (FDA Table 49).

Table 54: Study 030 - Two Hour Response Rate (Reviewer's Analysis)

Treatment	Response
PBO (n=159)	64 (40%)
Rizatriptan 5mg (n=164)	99 (60%)
Rizatriptan 10mg (n=387)	258 (67%)
Sumatriptan 100mg (n=387)	239 (62%)

p<0.0001 (Chi Square Test) for overall analysis

Pairwise comparison showed no difference between rizatriptan 5mg and 10mg (p=0.17, Fisher's Exact Test), and no difference between rizatriptan 10mg and sumatriptan 100mg (p=0.18, Fisher's Exact Test).

7.7.3.3 Associated Symptoms: Nausea

I chose to analyze nausea, a secondary efficacy measure, in order to explore the sponsor's comment that rizatriptan 5mg and 10mg re better than sumatriptan 100mg for the relief of nausea at 2 hours.

Of the 1099 patients who treated the initial attack, 5 did not record a baseline nausea measure. I removed these from the analysis. This resulted in 1094 evaluable patients. Of these, 2 failed to record any post-treatment nausea measures. Both had nausea at baseline. I chose to carry forward their baseline nausea score for the LOCF analysis. An additional 14 patients did not record a 2 hour nausea measurement, but I was able to impute an earlier post-treatment measurement for an LOCF analysis.

Six Hundred fifty-one (651) patients had nausea at baseline (60%). Across treatment groups, the incidences of nausea at baseline were 62%, 56%, 59% and 60% for placebo, rizatriptan 5mg, rizatriptan 10mg and sumatriptan 100mg, respectively. There was no statistically significant differences noted among the treatment groups with regard to baseline nausea (p=0.79, chi square).

At two hours, the percentages of patients experiencing nausea were 43%, 22%, 25%, and 33%, for placebo, rizatriptan 5mg, rizatriptan 10mg, and sumatriptan 100mg, respectively (p<0.001 chi square for overall analysis). All three active treatments were significantly better than placebo (p<0.0001 5mg vs PBO, p<0.0001 10mg vs. PBO, p=0.39 suma 100mg vs PBO, Fisher's Exact test for all 3 comparisons).

Both rizatriptan 5mg and 10mg were better than sumatriptan in the relief of nausea at 2 hours (p=0.01 for 5mg vs. suma 100mg, and p=0.02 for 10mg vs. 100mg, Fisher's Exact test for both comparisons).

7.7.4 Reviewer's Conclusions

1. Rizatriptan 5mg and 10mg, and sumatriptan 100mg provide relief from moderate and severe migraines.
2. Rizatriptan 5mg and 10mg, and sumatriptan 100mg are all effective in reducing associated symptoms. Rizatriptan 5mg and 10mg are both superior to sumatriptan 100mg in reducing the associated symptom of nausea.

7.8 Other Analyses - Sponsor

The sponsor performed other analyses, generally on pooled data from all 4 studies. These are described below.

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7.8.1 Demographic Analysis

There was no gender effect in any of the studies. Overall, patients ≥40 years had a higher response rates regardless of treatment. There were too few patients >65 years to formally assess efficacy for that age group. There was no race effect in any of the studies.

There was an effect of baseline headache severity. Across all studies, response rates were higher among patients experiencing a moderate headache compared to those with severe headaches. This probably reflects the fact that the criterion for a response is more easily met by patients experiencing a moderate headache, since they only have to improve by one grade.

The presence or absence of an aura did not appear to affect the outcome. Both patients with and without aura appeared to respond equally.

In view of the pharmacokinetic data that rizatriptan plasma levels are increased by 70% when given simultaneously with propranolol, exploratory subgroup analyses were performed in a group of patients taking propranolol vs. those not taking prophylactic medication in studies 029 and 030. (Concomitant use of propranolol was not permitted in 022 and 025). The analyses are descriptive only since sample sizes were small. In study 029, patients on propranolol experienced a higher 2 hours response rate to 5mg compared to those not taking prophylaxis. A similar finding was observed in 030 in patients taking 5mg (n=5), and was also seen for patients taking sumatriptan 100mg, for that matter. Response rate in the 10mg subgroup taking propranolol was similar to that seen in patients who were not taking prophylactic medications.

There was no effect seen in women taking oral contraceptives, suggesting both 5mg and 10mg are effective in women who are taking these drugs. Any effect of rizatriptan on the efficacy of oral contraceptives was not explored.

Treatment effect was similar across multiple countries.

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7.8.2 Long Term Efficacy

Studies 022, 025, and 029 had optional one year extension phases for its participants. The extension phase was single blinded (patients were blinded to

the dose of rizatriptan) except in 025 where only a 10mg dose of rizatriptan was used, and randomized (rizatriptan vs. "standard care"). Standard care could be anything, and was not necessarily a single medication. In practice, sumatriptan was the most common standard care medication (76% treated at least one attack with sumatriptan, and patients who took sumatriptan used in 84% of their attacks).

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Table 55: Extension Phases Designs

Study	Design	Max. Duration (Months)	Treatment		
			Riza 5 mg	Riza 10 mg	Stan. Care
Protocol 022	Single blind	12	X	X	X
Protocol 025	Open label	12	-	X	X
Protocol 029	Single blind	6	X	X	X

Efficacy was measured in the same way as in the placebo-controlled phase. The primary endpoint was the 2 hour headache response rate. The 2 hour complete relief rate was a secondary measure. Patients also recorded any additional migraine medication taken, and well as headache recurrences.

The unit of analysis was the percentage of attacks achieving a response, or becoming headache free at 2 hours. This varies from the controlled trials, which measured the percentage of patients. This is because one patient treated multiple attacks, some of which may have responded and others may not. Distinct attacks had to be at least 24 hours apart.

Treatment comparisons were made on the basis of odds ratios. In comparing treatment A with treatment B, a ratio greater than 1 favors treatment A. All three comparisons (5mg vs. standard care, 10mg vs. standard care, 10mg vs. 5mg) were of equal interest. Analyses were performed separately on each study, and with pooled data. Patients who were non-randomly assigned to rizatriptan 5mg (*e.g.*, patients on propranolol or metoprolol) were excluded from the analysis. Median scores, rather than means, are reported for most measures since skewed distributions were observed in some instances.

A total of 1854 patients enrolled into an extension and treated at least one attack. Of these, 700 were assigned to rizatriptan 5mg, 825 were assigned to 10mg, and 329 to standard care.

The long term exposures are listed in Table 56. The frequency of attacks were 3.6 - 4.1 attacks per month (mean, with median values 3.2-3.7, Table 57).

Table 56: Long Term Exposures, by Dose

Duration	Rizatriptan 5mg	Rizatriptan 10mg	Standard Care
≥6 months	347	496	218
≥1 year	111	157	79

Patients on standard care were less likely to withdraw, since the medication could be changed or adjusted to suit efficacy needs.

Table 57: Long Term Extension Studies: Summary of Attacks

Measure	Rizatriptan 5 mg†	Rizatriptan 10 mg‡	Standard Care
Number of Patients	606 (87)	815	325
Number of Days in Extension:			
Median	183 (171)	204	243
Mean	199 (178)	224	239
Number of Attacks:			
Median	14 (14)	21	19
Mean	24 (19)	29	25
Attack Frequency Per 30 Days:			
Median	3.2 (3.5)	3.7	2.9
Mean	3.6 (4.2)	4.1	3.4

Number in parentheses = nonrandomized patients
† Excluding 5 patients who had not yet treated an attack.
‡ Excluding 8 patients who had not yet treated an attack.

The median percentages of attacks in which patients had a response at 2 hours were 80%, 90%, and 70% for rizatriptan 5mg, 10mg, and standard care, respectively. Rizatriptan 10mg was superior to standard care in each study and in the combined analysis. There was a numerical advantage to rizatriptan 5mg but it failed to reach statistical significance. Rizatriptan 10mg was superior to 5mg in each study and in the combined analysis (Table 58).

Table 58: Efficacy Results of Long Term Extensions

Study	Parameter	Riza 5 mg†	Riza 10 mg‡	Standard Rx
Protocol 022	N	395 (41)	394	183
	Median (%)	82 (80)	91	69
	Odds Ratio vs. Standard Care§	1.65*	2.47*	—
	Odds Ratio vs. Riza 5 mg§	—	1.49*	—
Protocol 025	N	—	206	49
	Median (%)	—	88	59
	Odds Ratio vs. Standard Care§	—	3.64*	—
Protocol 029	N	211 (46)	215	93
	Median (%)	75 (83)	90	78
	Odds Ratio vs. Standard Care§	0.81	1.71*	—
	Odds Ratio vs. Riza 5 mg§	—	2.12*	—
Combined	N	606 (87)	815	325
	Median (%)	80 (83)	90	70
	Odds Ratio vs. Standard Care§	1.16	2.49*	—
	Odds Ratio vs. Riza 5 mg§	—	1.78*	—

N = the number of patients with evaluations at 2 hours for at least one attack.
Number in parentheses = nonrandomized patients.
Median is the percentage of headaches relieved at 2 hours over the N patients (i.e., half the patients had greater than this percentage of headaches relieved, and half had fewer than this percentage relieved).
† Excluding 5 patients who had not yet treated an attack.
‡ Excluding 8 patients who had not yet treated an attack.
§ Analysis performed on randomized patients.
* $P<0.05$.

7.9 Sponsor's Efficacy Conclusions

In summary, based on the sponsor's efficacy analyses, they make the following efficacy conclusions (D. Clinical Efficacy and Safety, B. Efficacy, page D-121).

1. Rizatriptan doses of 5 to 40 mg are effective in the acute treatment of moderate or severe migraine attacks. The efficacy of rizatriptan is dose related. 2.5mg is a no-effect dose, and 40 mg is the most effective dose studied.
2. Rizatriptan 5 mg and 10 mg possess the most favorable therapeutic ratios. Rizatriptan 10 mg is more effective than rizatriptan 5 mg.
3. Rizatriptan 5 mg and 10 mg are effective in treating both the headache and the non-headache aspects of a migraine attack, including associated migraine symptoms (nausea, vomiting, photophobia, and phonophobia) and functional disability. Patients taking rizatriptan 5 mg and 10 mg also have a reduced need for escape medication and had improved quality of life in the 24 hours after dosing.
4. Rizatriptan 5 mg and 10 mg are effective as early as 30 minutes after dosing.
5. The efficacy of rizatriptan 10 mg is maintained when it is used to treat multiple discrete migraine attacks; the majority of patients respond to most of the attacks treated.
6. Migraine headache recurs in approximately one third of patients who initially report relief following rizatriptan 5 mg and 10 mg. Both rizatriptan 5 mg and 10 mg are effective in treating headache recurrence. Rizatriptan increases the duration of relief (time to recurrence) in those patients who experience recurrence.
7. Rizatriptan 10 mg provides pain relief earlier than sumatriptan 100 mg. More patients are pain-free and have reduced functional disability following rizatriptan 10 mg than after sumatriptan 100 mg.
8. Rizatriptan 5 mg and sumatriptan 50 mg show comparable overall efficacy through 2 hours after dosing.
9. Fewer patients report nausea as an associated symptom following rizatriptan 5 mg and 10 mg than after sumatriptan 50 mg or 100 mg.
10. Both rizatriptan 5 mg and 10 mg are highly effective when used long term for the acute treatment of intermittent migraine attacks occurring over a period of up to 1 year. Efficacy is consistent over the course of a year of treatment. Rizatriptan 10 mg is more effective than either rizatriptan 5 mg or standard care treatment.

7.10 Other Analyses - Reviewer

I pooled efficacy data from the initial headache treatment from 4 studies, 022, 025, 029, and 030. The purpose of this analysis is to provide pooled efficacy data for purposes of labeling.

7.10.1 Response Rates - Pooled Data

Using JMP, version 3.2.2, I concatenated the four efficacy datasets. Since study 025 treated four consecutive attacks, I used the data from the first attack only. In the pooled efficacy dataset, 3516 patients treated an initial migraine headache

with study medication. The distribution of these 3516 patients, by protocol and treatment, is shown in FDA Table 59.

Table 59: Distribution of Patients, by Protocol and Treatment

Protocol	Total N	PBO	5mg	10mg	Suma 50mg	Suma 100mg
22	1218	304	458	456	0	0
25	407	83	0	324	0	0
29	792	80	355	0	357	0
30	1099	160	164	387	0	388
TOTAL	**3516**	**627**	**977**	**1167**	**357**	**388**

Of these 3,516 patients, 22 did not record a baseline headache severity score. I removed them from the analysis, resulting in 3494 evaluable patients. Of these, 6 patients did not record any post-treatment headache scores through 2 hours and I counted them as treatment failures. Another 2 only recorded a 4 hour score and I recorded them as treatment failures up until their 4 hour score. For missing headache scores, I used an LOCF approach to impute missing values where possible. Missing values were rare between 0-2 hours but very common at 3 hours (1,220 missing values) and at 4 hours (1,218 missing values). Results for 3 and 4 hours, therefore, should be interpreted with caution.

The response rates at various times are shown in FDA Table 60.

Table 60: Response Rates from Pooled Efficacy Data (Studies 022,025,029,030)

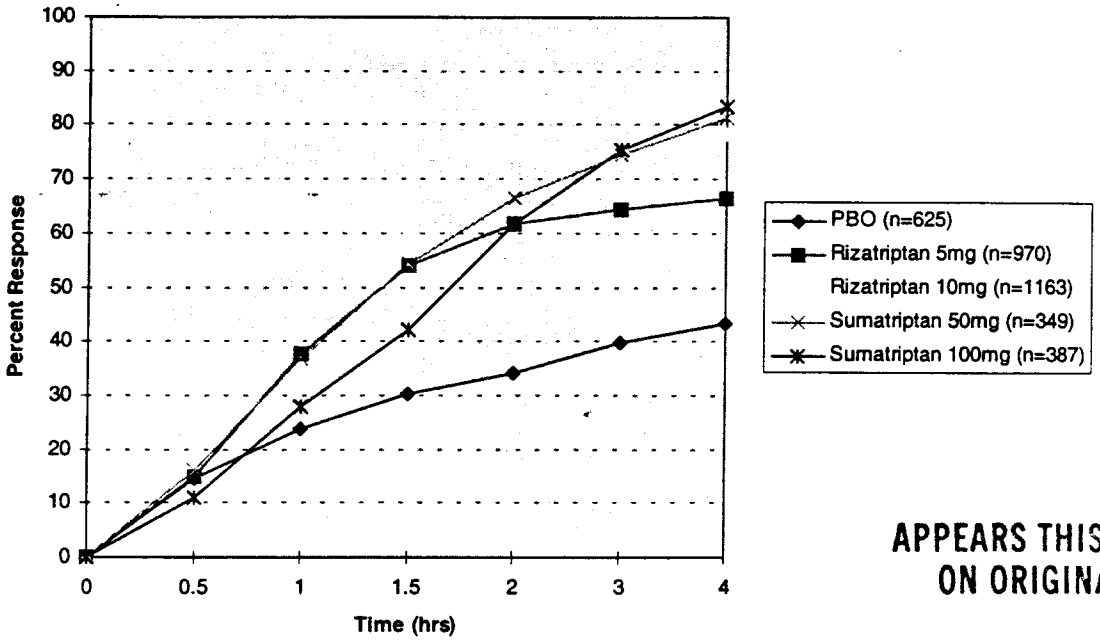
Treatment	0.5 hrs	1.0 hrs	1.5 hrs	2 hrs	3 hrs	4 hrs
PBO (n=625)	90	149	190	214	248	271
	14.4%	23.8%	30.4%	34.2%	39.7%	43.4%
Rizatriptan 5mg (n=970)	143	365	525	598	626	646
	14.7%	37.6%*	54.1%*	61.7%*	64.5%*	66.6%*
Rizatriptan 10mg (n=1163)	231	526	706	820	881	911
	19.9%**	45.2%*	60.7%*	70.5%*	75.8%*	78.3%*
Sumatriptan 50mg (n=349)	56	128	190	232	260	284
	16.0%	36.7%*	54.4%*	66.5%*	74.5%*	81.4%*
Sumatriptan 100mg (n=387)	43	108	182	239	292	323
	11.1%	27.9%	47.0%*	61.8%*	75.5%*	83.5%*

p=0.0002 at 0.5 hrs, p<0.0001 (Chi Square Test) for overall analyses at other times
* p<0.0001 compared to PBO (chi square)
** p<0.01 compared to PBO (chi square)

The data at 3 and 4 hours are also difficult to interpret since it must be remembered that patients were allowed to take rescue after 2 hours. I am unable to determine how many patients took rescue between 2-4 hours since the sponsor did not provide the time rescue was taken. It is possible that some of the response seen at those time points is due to rescue medication. I counted 189 responders at 3 hours and 294 responders at 4 hours took rescue at some point during treatment. This represents of all patients treated at those time points.

At 0.5 hours, only rizatriptan 10mg was significantly better than placebo. Most active treatments (with the exception of sumatriptan 100mg!) beat placebo at 1 hour. All active treatments beat placebo from 1.5 hours onward. Table 60 is displayed graphically in FDA Figure 11.

Figure 11: Response Rates from Pooled Efficacy Data (Studies 022,025,029,030)



7.10.2 Complete Relief Rates - Pooled Data

Of the 3,494 evaluable patients in the pooled efficacy dataset, a total of 1066 reported complete relief of headache at 2 hours. The incidence of complete relief at 2 hours is shown in FDA Table 61. All active treatments were better than placebo. Rizatriptan 10mg was better than 5mg and better than sumatriptan 100mg in this pooled analysis.

Table 61: Complete Relief at 2 Hours from Pooled Efficacy Data

Treatment	n	Complete Relief	%
Placebo	625	53	8
Rizatriptan 5mg	970	286	29
Rizatriptan 10mg	1163	489	42* #
Sumatriptan 50mg	349	111	32
Sumatriptan 100mg	387	127	33
All Treatments	3494	1066	31

p<0.0001 for overall analysis (chi-square)
*p<0.0001 for 10mg vs. 5mg (Fisher's Exact Test)
#p=0.0015 for 10mg vs. sumatriptan 100mg (Fisher's Exact Test)

7.10.3 Recurrence Rates - Pooled Data

Recurrence rates offer insight into the drug's duration of action. It is expected that those with long treatment effects will have low recurrence rates. However, recurrence rates should be interpreted with caution because the rates are based on non-randomized samples conditional upon having an initial headache response.

I defined a recurrence as the presence of a grade 2 or 3 headache within the first 24 hours of treatment in a patient who initially experienced a headache response at 2 hours. Of the 3,494 evaluable patients in the pooled efficacy dataset, a total of 1171 patients experienced a recurrence, however of these, only 873 experienced a response at 2 hours. Therefore, recurrence rates, using the definition stated above, are based on this total number of 873 recurrences. The recurrence rates are shown in FDA Table 62.

Table 62: Recurrence Rates from Pooled Efficacy Data (Studies 022, 025, 029, 030)

Treatment	n	Recurrence	%
Placebo	625	75	12
Rizatriptan 5mg	970	268	28
Rizatriptan 10mg	1163	361	31
Sumatriptan 50mg	349	86	25
Sumatriptan 100mg	387	83	21
All Treatments	3494	873	25

Recurrence rates ranged with sumatriptan 100mg having the lowest recurrence rate. Interestingly, placebo patients had the lowest recurrence rate of all, 12%, and illustrates the problems of using a non-randomized sample to calculate these rates. The numbers are descriptive and I performed no statistical tests on these data.

7.10.4 Cure Rates - Pooled Data

I defined a cure as a patient meeting the following three criteria:

1. complete relief at 2 hours, AND
2. no escape medications within 24 hours, AND
3. no recurrence within 24 hours

The 24 hours cure rates for the various treatments are shown in FDA Table 63.

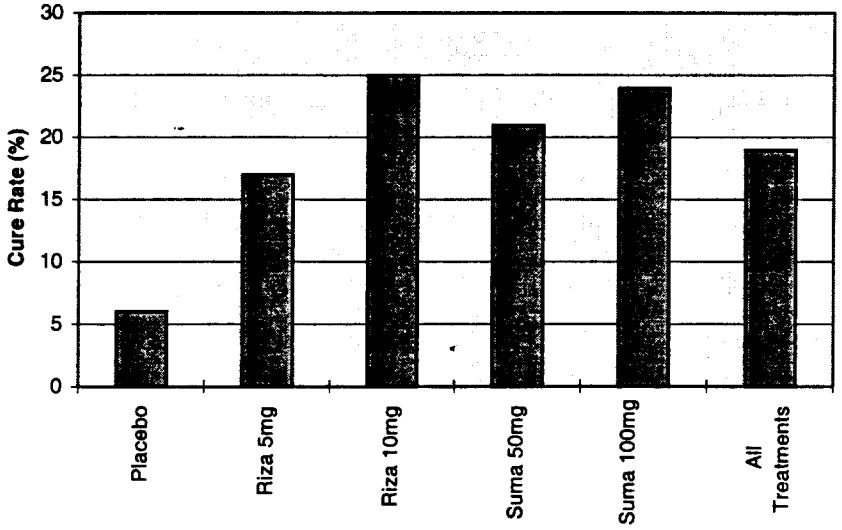
Table 63: Cure Rates from Pooled Efficacy Data (Studies 022, 025, 029, 030)

Treatment	n	Cure	%
Placebo	625	38	6
Rizatriptan 5mg	970	162	17
Rizatriptan 10mg	1163	285	25*
Sumatriptan 50mg	349	72	21
Sumatriptan 100mg	387	93	24
All Treatments	3494	650	19

p<0.0001 for overall analysis (chi-square)
*p<0.001 for rizatriptan 10mg vs. 5mg (Fisher's Exact Test)

This "cure rate" has the advantage over the recurrence rate because the denominator for the analysis is, in fact, the initial randomized population. Cure rates for active treatments ranged from , with rizatriptan 5mg having the lowest, and rizatriptan 10mg having the highest. The 10mg dose was better than the 5mg dose in this analysis. FDA Figure 12 displays the same data graphically.

Figure 12: Cure Rates from Pooled Efficacy Analysis (Studies 022, 025, 029, 030)



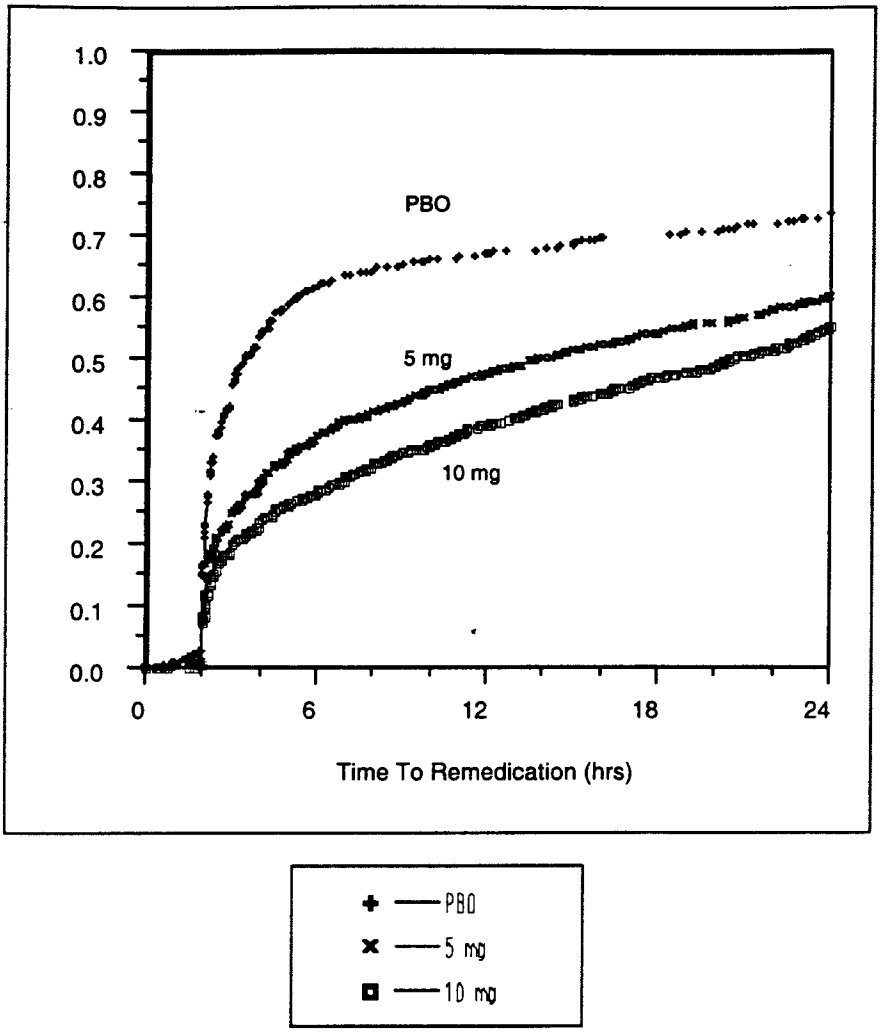
7.10.5 Time to Remedication - Pooled Data

The original efficacy datasets did not contain the time to remedication. We requested that the efficacy datasets be resubmitted with this information included. I received revised efficacy datasets for studies 022, 025, 029, 030 (and Rapidisc study 039) on 2/3/98. Subsequently the sponsor notified us that these datasets contained erroneous data for the variable of interest, time to remedication. They submitted new datasets with the corrected information in mid-March. I used these to generate the graphs in this section.

Remedication was defined as any escape medication or study medication taken within the first 24 hours after the initial dose. For study 025, which treated 4 attacks, I used remedication data for the first attack only. Patients who took no additional medication within the first 24 hours after treatment were censored to 24 hours.

I plotted the probability of not requiring remedication using product-limit survival estimates (Kaplan-Meier method) using JMP version 3.2.2. The graph is shown in Figure 13. It shows that patients taking 10mg had the lowest probability over time of requiring remedication. Placebo patients had the highest. Patients were not allowed to remedicate prior to 2 hours, which explains why the curve is almost flat between 0-2 hours.

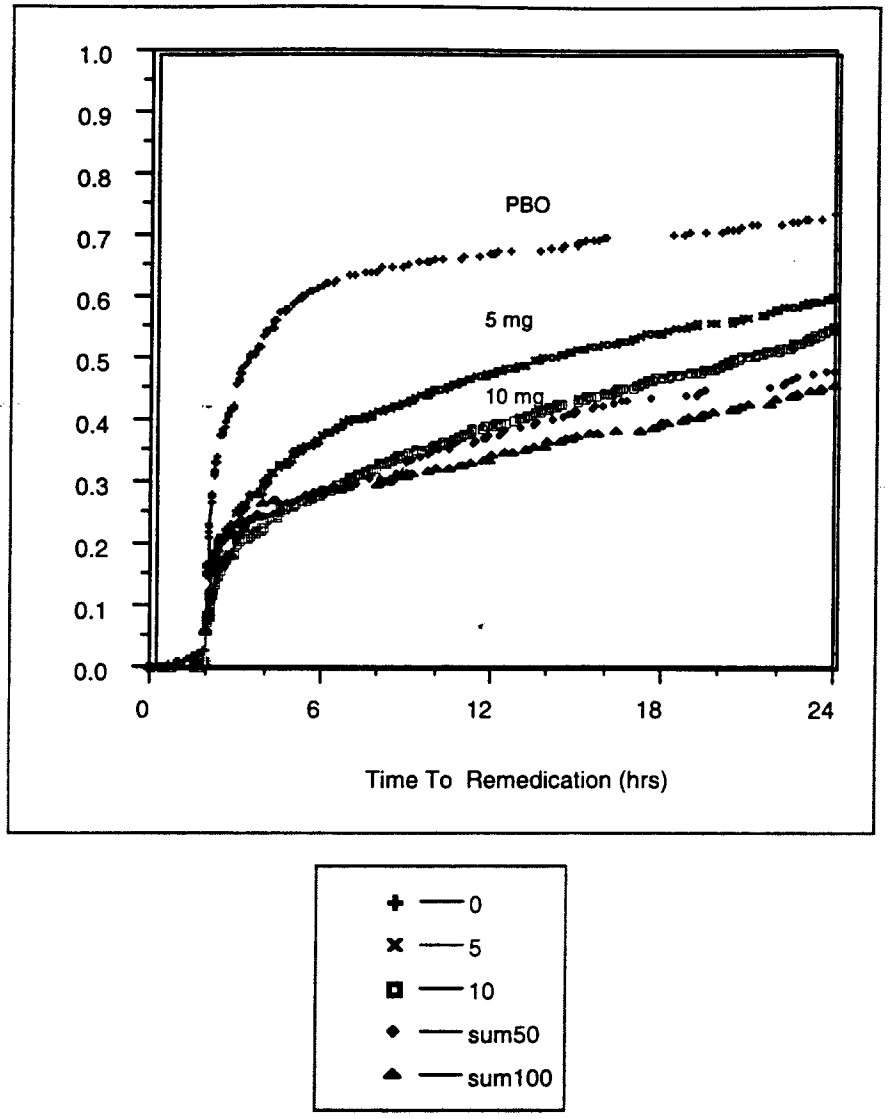
*Figure 13: Estimated Probability of Remedication during the first 24 hours**



* pooled data from studies 022, 025 (first attack), 029, 030, revised data, 3/25/98

Out of interest, I also plotted the same curve including the remedication time data for sumatriptan 50mg and 100mg from studies 029 and 030. This graph is shown in Figure 14 and shows that sumatriptan 50mg and 100mg were numerically better than Maxalt in time to remedication during the first 24 hours.

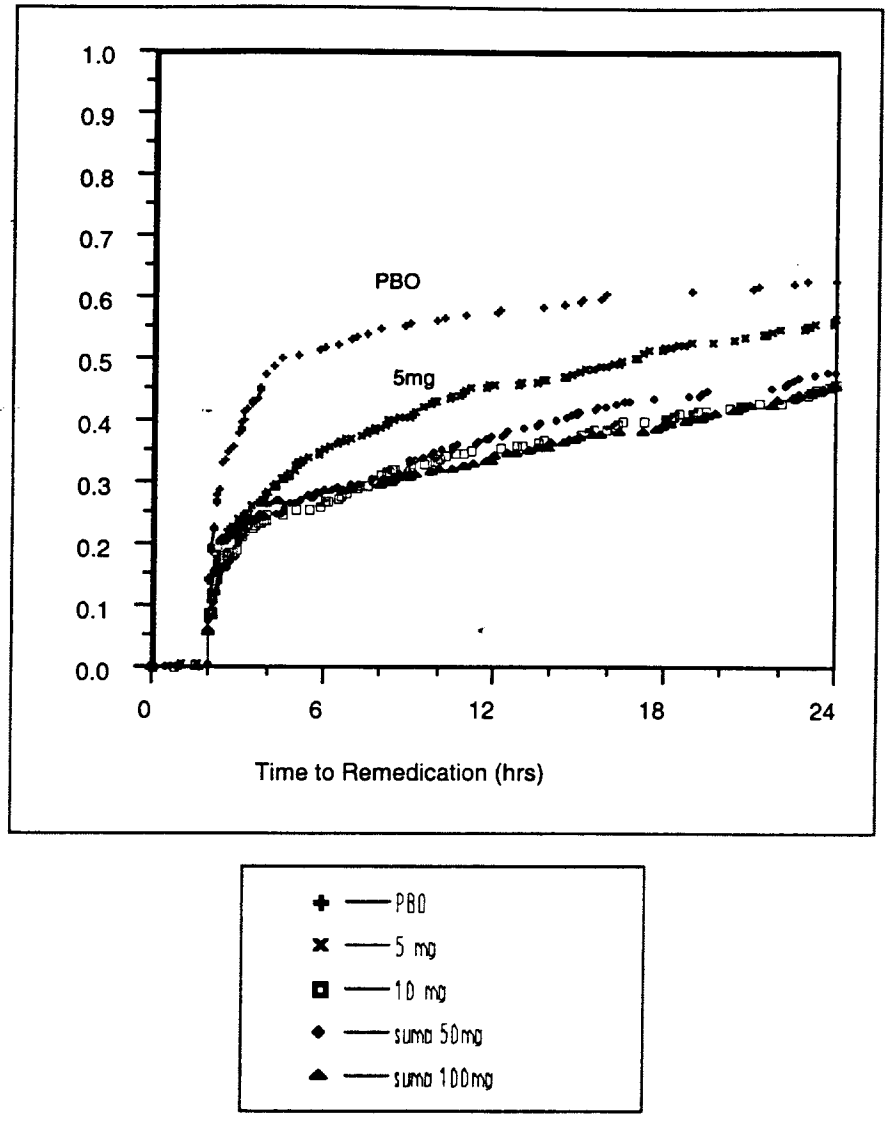
*Figure 14: Estimated Probability of Remedication, Including Sumatriptan**



* pooled data from studies 022, 025 (first attack), 029, 030, revised data 3/25/98

Since studies 022 and 025 did not use sumatriptan, I created a third graph using the data only from studies that included sumatriptan in their design—029 and 030. The graph (Figure 15) indicates that rizatriptan 10mg and both doses of sumatriptan have very similar remedication probabilities over the first 24 hours, with rizatriptan 5mg having generally higher estimated probabilities, but lower than placebo.

Figure 15: Estimated Time to Remedication, Studies 029 and 030



* pooled data from studies 029, 030, revised data 3/25/98

7.11 Reviewer's Comments

Based on four adequate and well controlled trials, the sponsor has demonstrated the efficacy of Maxalt tablets in the treatment of acute migraine headache. Specifically, I conclude the following:

1. Maxalt 5mg and 10mg are effective for the acute treatment of migraine headache, when measured by the 2 hour headache response rate.
2. Both the 5mg and 10mg are effective at providing complete relief at 2 hours, and both had higher cure rates at 24 hours compared to placebo.
3. Both 5mg and 10mg are effective in the treatment of a 1st headache recurrence within 24 hours.

4. Both 5mg and 10mg are effective in relieving nausea, photophobia, and phonophobia at 2 hours. There was no difference from placebo with respect to vomiting.
5. The 10mg dose is more effective than the 5mg dose.
6. The response rates are maintained across four consecutive migraine attacks.
7. The efficacy of rizatriptan 5mg and 10mg are comparable to that seen with sumatriptan 50mg and 100mg and there is little evidence that one drug is better than the other. In particular, There was no difference between rizatriptan and sumatriptan in terms of headache response at 2 hours, or time to response within the first two hours, and although the sponsor states that rizatriptan 5mg was better than sumatriptan 50mg in the relief of nausea at 2 hours post dose, my review suggests that there was no significant difference between the two active drugs.

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8. Integrated Review of Safety

8.1 Background and Methodology

The primary source for the safety review was the sponsor's integrated summary of safety and the 120 day safety update. I also used the individual study reports and safety datasets provided by the sponsor as SAS transport (.xpt) files.

The safety of rizatriptan assessed by monitoring clinical adverse experience reports, laboratory tests, physical examinations, vital signs, and ECG's.

The cutoff date was 9/30/96 for all safety data, with the exception of serious adverse events (SAE's), which was 2/28/97.

The 120 day safety update contained additional safety data through 6/30/97, with the exception of SAE's, whose new cutoff date in the update is 7/31/97 (Table 64). The safety update contains information on 20 patients who were enrolled in open label extensions at the time the NDA was submitted but whose extension data arrived past the original NDA cutoff date. Ten (10) of these took placebo during controlled trials and therefore represent new rizatriptan exposures. This brings the total of rizatriptan exposed patients to 3726 from phase 2 and 3 studies. The safety update contains additional extension data on 578 extension patients whose initial safety data were received by the original cutoff date and were included in the original NDA submission.

Table 64: Cutoff Dates for Safety Data

Data	NDA Cutoff	120 Day Safety Update Cutoff
SAE	2/28/97	7/31/97
All Other	9/30/96	6/30/97

The ISS focused on the safety of rizatriptan when given under the following three circumstances:

1. a single dose for a migraine attack
2. three doses within 24 hours for a single attack and 2 recurrences
3. multiple discrete attacks (long-term safety)

Because cardiovascular ischemic events have occurred with sumatriptan, and vasoconstrictive actions have been noted for the $5HT_{1D}$ agonists as a class, the cardiovascular safety profile of the drug is emphasized throughout the review.

Safety data are summarized according to phase of study (1, 2, or 3), and acute vs. long term exposures. For the acute exposures in the phase 3 studies, the data are further subdivided where appropriate: following a single dose in treatment of a first migraine attack, following up to 3 doses for a single attack within 24 hours, and following up to 3 doses per attack for multiple attacks.

Phase 2 safety data are not combined with phase 3 data except for estimates of infrequent or rare events. For most tabulations, 1% incidence cutoffs are used. Additionally, events which occurred ≥5% are highlighted to provide succinct summaries of the most frequently occurring events, and to examine the effects of other variables (age, gender, race, concomitant medications) on their incidences.

The safety profile of rizatriptan is based on data from 21 Phase 1 studies in 313 healthy subjects, as well as data from six phase 2 and four phase 3 controlled studies and their extensions (Table 65, ISS page D-144). Furthermore, five additional phase 1 studies investigated the intranasal, intravenous, and oral solution formulations of rizatriptan.

Table 65: Phase 2 and 3 Studies Contributing to Safety Data

Phase 2A	
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 (MK- 0462) and Oral Sumatriptan in Patients with Acute Migraine (Discontinued Study)
Phase 2B	
008	Dose- Ranging Study of MK- 0462 in Acute Migraine
014	Dose- Finding Study of MK- 0462 in Acute Migraine
020	Cardiovascular Safety of MK- 0462 in Otherwise Healthy Migraineurs
026	Comparison of Pharmacokinetic Profiles of Intranasal MK- A462 and Oral MK- 462 5 mg (Not Utilized in Evaluation of Efficacy)
Phase 3	
022†	Examination of the Safety and Efficacy of MK- 0462 10 mg p. o. and MK- 0462 5 mg p. o. in Outpatients with Acute Migraine and Migraine Recurrence
025†	Examination of the Safety and Efficacy of MK- 0462 10 mg p. o. in Outpatients with Multiple Attacks of Acute Migraine and Migraine Recurrence
029†	Comparison of the Efficacy and Safety of MK- 0462 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 MK- 0462 5 mg, MK- 0462 10 mg, and Sumatriptan 100 mg in Outpatients with Acute Migraine

† Patients in these studies could enter long-term extension treatment with rizatriptan 5 mg, rizatriptan 10 mg, or standard care.

In the phase 2 studies, patients treated single migraine attacks with total doses of 2.5mg - 40mg. All phase 2 studies were double-blind and placebo-controlled.

One study employed oral sumatriptan as a control. Repeat dosing was permitted after 2 hours in certain phase 2 studies for persistent headache. Headache recurrence was noted but not treated with study medication during phase 2.

The phase 3 controlled studies were all placebo controlled, double-blind, outpatient studies. In two studies (022, 025), patient were allowed to treat up to 2 headache recurrences with 5mg or 10mg or placebo. In protocol 025, consistency of response across four attacks was evaluated using 10mg. Studies 029 and 030 treated a single migraine attack with a single dose of study medication.

The phase 3 extensions evaluated the long term safety of rizatriptan 5mg or 10mg. A total of 347 patients on 5mg and 496 patients on 10mg were treated for ≥6 months, and 114 patients on 5mg, and 157 patients on 10mg were treated for ≥1 year. The details of these exposures, including migraine frequency, are reviewed in section 8.9, Long-Term Safety, page 90.

In addition to placebo, sumatriptan (studies 008, 029, 030) and "standard care" (extension study) were used as comparative agents. Sumatriptan was prescribed according to labeling in doses of 50mg and 100mg. Standard care was used in approximately 18% of the extension patients as prescribed by the investigator on an individual basis. The most common "standard care" regimen used was sumatriptan.

For more additional information regarding exposures to rizatriptan, please refer to section 5.1.3, Extent of Exposures, page 13 of this review.

8.2 Deaths

There were no deaths reported in the rizatriptan clinical development program.

8.3 Serious Adverse Events

As of the NDA cutoff date of 9/30/96, there were 68 serious clinical adverse events (SAE's) reported. The NDA also contains information on any additional SAE's reported through 2/28/97. There were some SAE's which occurred after randomization but before treatment with study drug. These are not included in this review. A complete list of the SAE's supplied in the NDA is located in Appendix C, page 138. The serious adverse events are described below according to the study phase in which they occurred.

8.3.1 Phase 1 SAE's

There were 5 SAE's reported in phase 1 studies. Serious adverse events were observed in 4 our of 313 subjects (1%) on rizatriptan and in 1 subject out of 134 (0.7%) on placebo. Two of the four rizatriptan SAE's occurred at doses of 80mg and were considered drug related. A total of 3 SAE's occurred in these two patients and consisted of syncope, bradycardia, and hypotension. The syncope occurred in association with a venipuncture and could very well have been a vasovagal reaction, perhaps exacerbated by the drug. The other two SAE's were

"elective abortion" in a subject on 10mg, and "irritable bowel" in a subject on 15mg. The placebo subject experienced "agitation." It is possible that the case of irritable bowel, which consisted of abdominal pain and cramps and occurred 9 hours after administration, was due to rizatriptan.

8.3.2 Phase 2 SAE's

Only 1 patient out of the 974 (0.1%) in phase 2 studies had an SAE. The patient was a 26 y/o male enrolled in study 020, the inpatient ECG monitoring study. He exhibited chest pain, arm pain, dyspnea, and tachycardia after treatment with rizatriptan 10mg. ECG examination that day showed sinus tachycardia, supraventricular tachycardia, and possible myocardial ischemia. All events were considered drug-related and serious by the investigator. The event led to discontinuation from the study. Cardiac enzymes and stress test failed to document any ischemia and he completely recovered. The incident illustrates that rizatriptan, like sumatriptan, may be associated with chest pain of possible cardiac origin (*e.g.*, coronary vasospasm?). A more detailed discussion of this case is located in 8.8.1, Study 020 - Inpatient ECG Study, page 85.

8.3.3 Phase 3 (Acute Studies) SAE's

There were a total of 7 SAE's in phase 3 acute treatment studies (022, 025, 029, 030),. Of the 2,296 patients exposed to rizatriptan, six (6) had serious adverse events (0.3%). Five were on rizatriptan 5mg (migraine headache (2), endometriosis, malignant lung neoplasm, and dehydration plus syncope), and one was on 10mg (cellulitis). One placebo patient out of 836 (0.1%) reported anaphylaxis (with concomitant Septra use). None of these appeared to be drug related, in my opinion. The one case of dehydration and syncope was in a 54 y/o woman with a long history of syncope associated with migraines and she had been vomiting extensively on the day of her migraine. She took a total of 15mg within a 24 hour period.

8.3.4 Phase 3 (Extensions) SAE's

A total of 40 SAE's were reported in phase three extension studies. These represent the majority of SAE's reported since there was much more opportunity to develop and report SAE's during long-term treatment. Of the 1,525 patients treated with rizatriptan, 29 (2%) had one or more serious adverse event. Eleven (11) were on rizatriptan 5mg and 18 were on rizatriptan 10mg. By comparison, SAE's occurred in 9 patients (3%) on standard care. These are listed in sponsor Table 66 (ISS Table D-87, page D-278).

Table 66: Incidence of Serious Adverse Events in Phase 3 Extension Studies

Adverse Experience	Riza 5 mg (N= 700) (Avg. No. Attacks/ Pt= 23)	Riza 10 mg (N= 825) (Avg. No. Attacks/ Pt= 29)	Standard Care (N= 329) (Avg. No. Attacks/ Pt= 25)
Patients with any SAE (%)	**11 (2)**	**18 (2)**	**9 (3)**
Body as a Whole	***1 (0.1)***	***2 (0.2)***	***1 (0.3)***
Pain, chest	0	1 (0.1)	0

Pain, abdominal	0	1 (0.1)	0
Hernia, inguinal	0	0	1 (0.3)
Trauma	1 (0.1)	0	0
Cardiovascular System	***0***	***1 (0.1)***	***0***
Embolism/ infarction, pulmonary	0	1 (0.1)	0
Digestive System	***2 (0.3)***	***3 (0.4)***	***1 (0.3)***
Appendicitis	0	1 (0.1)	0
Cholelithiasis	0	1 (0.1)	1 (0.3)
Vomiting	0	1 (0.1)	0
Gastroenteritis	1 (0.1)	0	0
Rectocele	1 (0.1)	0	0
Endocrine System	***1 (0.1)***	***0***	***0***
Neoplasm, thyroid, malignant	1 (0.1)	0	0
Hemic and Lymphatic	***0***	***2 (0.2)***	***0***
Agranulocytosis	0	1 (0.1)	0
Thrombocytopenia	0	1 (0.1)	0
Metabolic/ Nutritional/ Immune	***0***	***1 (0.1)***	***0***
Dehydration	0	1 (0.1)	0
Musculoskeletal System	***4 (0.6)***	***3 (0.4)***	***1 (0.3)***
Fracture, elbow, rt	0	1 (0.1)	0
Fracture, hip, rt	1 (0.1)	0	0
Pain, back	0	1 (0.1)	0
Pain, musculoskeletal	0	1 (0.1)	0
Pain, neck	1 (0.1)	0	0
Pain, shoulder	1 (0.1)	0	0
Bursitis	1 (0.1)	0	0
Exostosis	1 (0.1)	0	0
Trauma, cartilage	1 (0.1)	0	0
Joint disorder	0	0	1 (0.3)
Nervous System and Psychiatric	***2 (0.3)***	***4 (0.5)***	***5 (1.5)***
Migraine	1 (0.1)	3 (0.4)	3 (0.9)
Headache	0	1 (0.1)	0
Depression	1 (0.1)	0	1 (0.3)
Anxiety	1 (0.1)	0	0
Meningitis	0	0	1 (0.3)
Respiratory	***0***	***2 (0.2)***	***0***
Asthma	0	2 (0.2)	0
Wheezing	0	2 (0.2)	0
Bronchitis	0	2 (0.2)	0
Skin	***0***	***2 (0.2)***	***0***
Neoplasm, skin, malignant	0	2 (0.2)	0
Urogenital System	***1 (0.1)***	***4 (0.5)***	***1 (0.3)***
Neoplasm, uterine benign	0	1 (0.1)	0
Surgery, breast	1 (0.1)	0	0
Abortion	0	1 (0.1)	0
Menstruation Disorder	0	1 (0.1)	0
Prostatitis	0	1 (0.1)	0
Cystocele	0	0	1 (0.3)

I reviewed narratives for each of the 29 cases reported. One episode of chest pain may have been drug related. Notable cases are described below (including the woman with chest pain).

Thrombocytopenia: A **47 y/o F (022-037)** was hospitalized for thrombocytopenia 8 days after taking rizatriptan 10mg. She had previously taken 107 doses over a 9 month period. Concomitant therapy included diflunisal (Dolobid, a non-steroidal anti-inflammatory medication) 500mg daily for neck pain x 2 days prior to the reported event. She had also previously taken ibuprofen 400mg daily for about 1 week. Upon admission, the diflunisal was stopped. She

received platelets. A bone marrow biopsy revealed numerous megakaryocytes consistent with peripheral destruction. She was diagnosed with idiopathic thrombocytopenic purpura (ITP). The discharge platelet count two weeks later. Blood and sera for antiplatelet antibodies revealed IgG antibodies dependent on diflunisal glucuronide, a metabolite of diflunisal. The investigator and hematologist concurred that the event was due to diflunisal and not rizatriptan.

Agranulocytosis: A **57 y/o M (025-006)** with a history of prostatitis successfully completed study 025 and entered the extension phase. He uneventfully used 13 doses of rizatriptan 10mg over a 2.5 month period. Two months into the extension, he developed a urinary tract infection and fever secondary to prostatitis. He was hospitalized for 3 days and was treated with a short course of gentamycin and a 3 week course of Bactrim DS. After 3 weeks on Bactrim DS, and one day after his last dose of rizatriptan 10mg, he was admitted with agranulocytosis . Bone marrow showed no WBC precursors but other elements were normal. He recovered completely with Neupogen and poly-antibiotic therapy. Both the investigator and the hematologist concurred that the agranulocytosis was related to Bactrim, and not to rizatriptan. This was confirmed with *in vitro* testing, which revealed the patient had antibodies to sulfonamides, and the protein-sulfa complex. In vitro cytotoxicity assay confirmed Bactrim mediated WBC cell death, similar to that seen in other patients with documented hypersensitivity to sulfonamides.

Chest Pain: A **40 y/o F (022-026)** taking rizatriptan 10mg in the extension phase was hospitalized for chest pain, which occurred during treatment in the emergency room for a worsening migraine 6 hours after a dose of rizatriptan 10mg. She had previously treated 14 migraine attacks with rizatriptan 10mg over a 4 month period. While in the emergency room, she developed non-pleuritic chest pain which was unrelieved by nitroglycerin. She had experienced similar episodes of exertional and non-exertional chest pain in the prior 2 months not associated with any medication use. She was admitted and serial ECG's showed sinus bradycardia (considered normal for the patient), clockwise axis rotation and nonspecific ST-T wave changes, but no acute changes. Cardiac enzymes were normal. A stress test 10 days later was unremarkable. The investigator felt that the headache and chest pain were unrelated to rizatriptan. I think a relationship between rizatriptan and the chest pain is possible.

Pulmonary Embolism: A **45 y/o F (029-026)** was hospitalized due to painful breathing and pain in the forearm and wrist and was diagnosed with a pulmonary embolism. The event occurred 5 days after treatment of an eleventh migraine attack over 105 days with rizatriptan 10mg. She was not taking any concomitant medications, including oral contraceptives. She was discontinued from the study and placed on anticoagulants. The investigator concluded the event was unrelated and I agree, given the long interval between dosing and the event.

Syncope: A **54 y/o F (022-031)** with a history of syncope associated with migraine was hospitalized for dehydration and syncope, which occurred during a severe migraine attack and approximately 11 hours after taking rizatriptan 5mg x 2. The investigator felt the adverse experience was not related to therapy as these events had been a regular feature of her migraine episodes for many years.

Several patients were admitted with severe migraines requiring inpatient intensive intravenous analgesia or other therapy. These represent treatment failures and not drug related SAE's.

8.4 Dropouts

8.4.1 Overall Profile of Dropouts

In phase 1 studies, five out of 313 subjects (2%) discontinued due to an adverse experience while on rizatriptan. Another 2 out of 134 (1%) discontinued due to an

AE while on placebo. In addition, one subject out of 313 discontinued due to a protocol deviation (0.3%). Five other subjects discontinued while on other control agents (*e.g.*, paroxetine, nadolol, propranolol, and clonidine).

In phase 2 studies, 97% completed the study. Five patients (0.5%) discontinued due to AE's while on rizatriptan. An additional eight (0.8%) discontinued due to protocol deviation, and 17 (2%) discontinued for other reasons while on rizatriptan. Other possible reasons for discontinuation included lost to follow-up, withdrew from study, patient uncooperative, lack of therapeutic response, lack of migraine to treat, pregnancy.

In phase 3 controlled studies, 96% complete the phase 3 single attack studies. Seventy-nine percent (79%) completed the extension studies. The lower completion rate is not unexpected since there was a greater opportunity to discontinue. Sponsor Table 67 (ISS Table D-93, page D-304) summarizes the disposition of patients in phase 3 controlled trials.

Table 67: Disposition of Patients in Phase 3 Controlled Trials

	Riza 5 mg Single-Attack Studies (N= 1012)	Riza 10 mg Single-Attack Studies (N= 889)	Riza 10 mg Multiple-Attack Study (N= 323)	PBO (N= 547)	Suma 50 mg (N= 357)	Suma 100 mg (N= 388)
Completed	999 (98.7)	875 (98.4)	256 (79.3)	518 (94.7)	356 (99.7)	383 (98.7)
Lack of effect	1 (0.1)	1 (0.1)	2 (0.6)	6 (1)	0	0
AE	1 (0.1)	1 (0.1)	5 (1.5)	3 (0.5)	0	1 (0.3)
Protocol deviation	8 (0.8)	5 (0.6)	5 (1.5)	0	0	2 (0.5)
Other	3 (0.3)	7 (0.8)	55 (17)	20 (3.7)	1 (0.3)	2 (0.5)

In phase 3 extension studies, 673 out of 1854 (36%) had completed treatment at the time of data cutoff (9/30/96), whereas 33%, 42%, and 39% were ongoing in the rizatriptan 5mg, 10mg, and standard care groups, respectively. These are summarized in sponsor Table 68 (ISS Table D-94, page D-305). Seven percent (7%, or 113 patients) on rizatriptan discontinued due to lack of an effect. This was higher in patients taking rizatriptan 5mg (11%) compared to those taking 10mg (4%) consistent with the greater efficacy of the 10mg tablet. There were 7 patients (2%) on standard care who discontinued for lack of an effect. However, such patients could change their medication rather than discontinue treatment—an option not available to those taking rizatriptan. Twenty-seven patients (27 or 2%) on rizatriptan and 1 patient (0.3%) on standard care discontinued for protocol deviation. There were 212 patients (14%) on rizatriptan and 50 patients (15%) on standard care who discontinued for other reasons.

Table 68: Disposition of Patients in Phase 3 Extension Studies

	Rizatriptan 5 mg (N= 700) †	Rizatriptan 10 mg (N= 825) ‡	Standard Care (N= 329)
Ongoing	232 (33)	344 (42)	128 (39)
Completed	238 (34)	298 (36)	137 (42)

Discontinued:			
Lack of effect	80 (11)	33 (4)	7 (2)
AE (clinical or laboratory)	25 (4)	36 (4)	6 (2)
Protocol deviation	16 (2)	11 (1)	1 (0.3)
Other	109 (16)	103 (12)	50 (15)

8.4.2 Adverse Events Associated with Dropouts

Sponsor Table 69 (ISS Table D-89, page D-299) lists the number of patients who discontinued due to clinical adverse experiences (adverse dropouts, ADO's). The incidence of adverse dropouts across all groups is very low. However, many of the studies were single dose studies where the opportunity to drop out was limited. The highest adverse dropout rates were seen in the extension studies, but even in these studies, the incidence of ADO's was low: 3% and 4% for rizatriptan 5mg and 10mg, respectively, vs. 2% for "standard care."

Table 69: Adverse Dropouts

	Rizatriptan 5mg		Rizatriptan 10mg		Rizatriptan > 10mg		PBO		Suma		Standard Care	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Phase 1	80	0 (0)	234	3 (1)	162	2 (1)	134	1 (0.7)	ND	0 (0)		
Phase 2	153	1 (0.6)	253	3 (1)	492	0 (0)	214	1 (0.5)	89	0 (0)		
Phase 3 Single Attack	1012	1 (0.1)	889	1 (0.1)			547	0 (0)	745	1 (0.1)		
Mult. Attacks			395	5 (1)			289	3 (1)				
Exten-sions	700	24 (3)	825	35 (4)							329	5 (2)

In phase 3 trials, seven (7) patients discontinued from the controlled trials, most of them (n=5) coming from the multiple attack study 025 where there was a greater opportunity to discontinue. The most common reasons for discontinuation among the seven were dizziness and somnolence. These two symptoms occurred alone or in combination in 5 of the 7 patients in this group.

Sixty-four (64) patients discontinued from phase 3 extensions due to one or more adverse event. Patients on standard care could be switched to any alternative migraine treatment, so discontinuation could have been avoided by switching medications in this group. This is likely a factor to explain the lower rate of discontinuation in the "standard care" group (2%) vs. the two rizatriptan groups (3% and 4%).

The only AE that resulted in discontinuation in ≥1% of patients in any treatment group in the extensions studies was nausea, which was also the most common

AE reported overall. All 13 patients discontinuing due to nausea were taking rizatriptan (7, or 1.1% were on 5mg and 6, or 0.7% were on 10mg).

The second most common AE resulting in discontinuation was dizziness. Four patients (0.6%) on rizatriptan 5mg, 6 patients (0.7%) on rizatriptan 10mg and 1 patient on standard care (0.3%) dropped out due to dizziness. In 10 out of the 11 patients, the AE was considered drug related. None was serious.

The incidence of other AE's resulting in discontinuations were all less than 1%. All adverse dropouts are listed individually in Appendix D, page 143.

8.5 Adverse Events Incidence Tables

The sponsor tabulated clinical adverse events for phase 1, phase 2, phase 3 (controlled) and phase 3 (extensions) studies separately.

8.5.1 Phase 1 AE's

A total of 313 healthy subjects received rizatriptan and 134 received placebo in phase 1 studies. Because many of these studies were crossover in design, many patients are counted twice depending upon whether they received rizatriptan or placebo.

Of the 313 subjects on rizatriptan, 155 (50%) reported one or more AE. Of the 134 on placebo, 65 (49%) reported one or more AE. The most common clinical AE's on rizatriptan or placebo were headache (19% vs. 17%, respectively), somnolence (16% vs. 12%), dizziness (12% vs. 8%), asthenia/fatigue (9% vs. 4%), and nausea (9% vs. 16%).

Several episodes of syncope or vasovagal reaction were seen with rizatriptan, placebo, or during pre-treatment. These were generally associated with painful venipuncture.

8.5.2 Phase 2 AE's

Nine hundred seventy-four (974) patients were exposed to rizatriptan in phase 2 studies, in addition to 214 placebo patients and 89 sumatriptan 100mg patients. The percentages of patients with one or more clinical AE were 30% placebo, 30% rizatriptan 2.5mg, 24% rizatriptan 5mg, 44% rizatriptan 10mg, 57% rizatriptan 20mg, and 70% rizatriptan 40mg. The incidence of any AE in the sumatriptan 100mg group was 43%, which was similar to that reported by patients taking 5mg or 10mg.

The most common AE's in patients on rizatriptan during phase 2 studies were typical of $5HT_{1B/1D}$ agonists: dizziness, somnolence, asthenia/fatigue, paresthesia, dry mouth, hypesthesia, nausea, regional heaviness (arms, legs and head), and vomiting. Paresthesia and nausea occurred at incidences less than or equal to those on placebo in patients on rizatriptan 5mg or 10mg.

In patients taking sumatriptan 100mg, the most common AE were asthenia/fatigue, regional heaviness, paresthesia, chest pain, headache, and nausea.

The incidence of chest pain and regional heaviness were higher in patients on sumatriptan than on any dose of rizatriptan. For example, the incidence of chest pain for rizatriptan 5mg was <1%, and for rizatriptan 10mg was 2%, reaching a high of 4% on the rizatriptan 40mg group. The incidence of chest pain for sumatriptan 100mg was 5%.

8.5.3 Phase 3 (Acute) AE's

The ≥1% AE incidence table are summarized when the AE occurred [1] after a single dose in a single attack, [2] after up to 3 doses for a single attack and up to 2 recurrences within 24 hours, and [3] after multiple doses for a series of discrete multiple attacks (including recurrences).

8.5.3.1 AE's After Single Dose for Single Attack

Sponsor Table 70 (ISS Table D-74, page D-229) summarizes the incidence of adverse events experienced in phase 3 controlled trials after a single dose of study medication. Only those occurring with an incidence of ≥1% are displayed.

One or more clinical AE's were observed in 33% of patients on rizatriptan 5mg, and in 42% of patients taking rizatriptan 10mg, compared to 25% on placebo. In the pooled data, as well as in the individual studies using sumatriptan as a control (029, and 030), the incidence of AE's in sumatriptan 50mg patients was higher than in rizatriptan 5mg patients (38% vs. 33%) and was also greater for patients taking sumatriptan 100mg vs. rizatriptan 10mg (52% vs. 42%).

It is notable that chest pain does occur in patients with rizatriptan, although the incidence appears to be less than that seen with sumatriptan in these studies. The AE's are similar to those seen in phase 1 and phase 2 trials, and are typical of those seen with other $5HT_{1B/1D}$ receptor agonists, *i.e.* dizziness, asthenia, chest pain, nausea, paresthesia, heaviness, somnolence.

Table 70: Adverse Events (≥1%) in Phase 3 Controlled Trials, After a Single Dose

	Riza 5 mg (N= 977)	Riza 10 mg (N= 1167)	PBO (N= 627)	Suma 50 mg (N= 357)	Suma 100 mg (N= 388)
% with any clinical AE	33	42	25	38	52
Body as a Whole	***9***	***13***	***7***	***12***	***20***
Asthenia / fatigue	4	7	2	5	8
Pain, chest	2	3	1	5	6
Pain, abdominal	2	2	1	<1	1
Chills	<1	<1	<1	0	2
Cold sensation	<1	<1	<1	<1	1
Cardiovascular System	***2***	***2***	***1***	***3***	***3***
Palpitation	<1	1	<1	2	<1
Tachycardia	<1	<1	<1	<1	2
Digestive System	***9***	***13***	***8***	***11***	***14***

Nausea	4	6	4	6	9
Dry mouth	3	3	1	3	2
Dyspepsia	<1	<1	<1	<1	2
Musculoskeletal System	***3***	***5***	***2***	***8***	***8***
Heaviness, regional	<1	2	0	1	2
Stiffness	<1	<1	<1	1	1
Myalgia	<1	<1	<1	<1	1
Pain, back	0	<1	0	1	<1
Pain, neck	<1	<1	<1	2	1
Hypesthesia	<1	<1	1	2	2
Flushing	<1	1	1	<1	1
Nervous System	***16***	***23***	***13***	***18***	***30***
Dizziness	4	9	5	5	9
Somnolence	4	8	4	5	7
Paresthesia	3	4	2	3	4
Headache	2	2	<1	2	3
Mental acuity decreased	<1	<1	<1	1	1
Anxiety	<1	<1	<1	<1	2
Nervousness	<1	<1	<1	<1	1
Insomnia	1	<1	<1	<1	2
Respiratory System	***4***	***6***	***3***	***6***	***6***
Discomfort, pharyngeal	1	2	0	1	3
Dyspnea	<1	<1	<1	<1	1
Pharyngitis	<1	<1	<1	<1	1
Skin and Skin Appendage	***2***	***3***	***2***	***3***	***6***
Sweating	<1	<1	<1	1	3
Special Senses	***3***	***4***	***3***	***3***	***6***
Blurred vision	<1	<1	<1	<1	1
Perversion, taste	<1	<1	<1	<1	1
Urogenital System	***2***	***3***	***1***	***<1***	***3***
Hot flashes	<1	<1	<1	<1	2

Most AE's were mild and transient (Table 71, adapted from ISS Table D-76, page D-233).

Table 71: Intensity of AE's in Phase 3 Controlled Trials (Percent of Patients)

Adverse Experience	Riza 5 mg (N= 977)				Riza 10 mg (N= 1167)				Placebo (N= 627)			
	Mild	Mod	Sev	Any	Mild	Mod	Sev	Any	Mild	Mod	Sev	Any
Somnolence	1.7	1.9	0.5	4.2	4.3	3.2	0.9	8.4	1.6	1.6	0.3	3.5
Dizziness	3.0	1.2	0	4.2	5.7	2.7	0.5	8.9	2.6	1.8	0.2	4.5
Asthenia/ fatigue	2.0	1.3	0.8	4.2	3.3	2.5	1.1	6.9	0.3	1.1	0.6	2.1
Nausea	1.5	1.7	0.8	4.1	2.6	2.0	1.2	5.7	0.6	2.4	0.5	3.5
Pain, chest	1.1	0.5	0.1	1.7	2.0	1.0	0.1	3.1	0.6	0.5	0	1.1

The sponsor also summarizes AE's according to those that are "drug-related" in the opinion of the investigators. The conclusions drawn from this table are the same as those seen for all AE's reported. Since "drug-related" is a subjective term, I only display the "all AE's" table.