

Research Submission

Elimination of Migraine-Associated Nausea in Patients Treated with Rizatriptan Orally Disintegrating Tablet (ODT): A Randomized, Double-Blind, Placebo-Controlled Study

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Objective.—To confirm the efficacy of rizatriptan 10 mg orally disintegrating tablet (ODT) for the elimination of migraine-associated nausea.

Background.—Pooled studies of rizatriptan analyzing elimination of nausea as a secondary endpoint showed that 65% of rizatriptan patients reported elimination of nausea at 2 hours compared with 41% of patients taking placebo.

Methods.—This was a multicenter, randomized, double-blind, placebo-controlled single-attack trial enrolling adult patients with at least a 6-month history of migraine who typically experience migraine-associated nausea. Patients treated a moderate or severe migraine headache at the earliest sign of nausea with either rizatriptan 10 mg ODT or placebo (2 : 1). The primary endpoint was elimination of nausea at 2 hours postdose, and the secondary endpoint was pain relief at 2 hours postdose.

Results.—Although not statistically significant, a greater percentage of patients had elimination of nausea at 2 hours with rizatriptan compared with placebo (70.3% vs 62.0%, $P = .165$, odds ratio [95% CI] = 1.45 [0.86, 2.46]). When patients were grouped by baseline headache severity, rizatriptan showed a greater advantage than placebo for patients with moderate pain (rizatriptan 72.8% vs placebo 57.4%), but no difference for patients with severe pain (rizatriptan 67.7% vs placebo 66.7%). There were significantly more patients who achieved 2-hour pain relief with rizatriptan (69.7% vs 54.3%, $P = .012$, odds ratio [95% CI] = 1.94 [1.16, 3.25]).

Conclusion.—Although the efficacy of rizatriptan 10 mg ODT for the elimination of migraine-associated nausea was comparable to that seen in previous rizatriptan trials, the higher-than-usual placebo response prevented a finding of a statistically significant difference. There was a sizable difference in placebo response between patients who treated moderate vs severe migraine. Rizatriptan was effective for 2-hour pain relief.

Key words: rizatriptan, nausea, migraine, triptan, placebo, headache

Abbreviations: AEs adverse experiences, IRB Institutional Review Board, ODT orally disintegrating tablet

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INTRODUCTION

Migraine headaches are debilitating not only because of pain, but also because of other associated symptoms such as sensitivity to light, sensitivity to sound, nausea, and vomiting. Of these associated symptoms, nausea has been reported to be the most bothersome.^{1,2} A telephone survey of 500 self-reported migraineurs found that more than 90% of migraineurs reported experiencing nausea during attacks, and one third of these reported experiencing nausea with every attack.¹ The American Migraine Study II, a national survey of 20,000 households in the United States, found that 73% of respondents reported experiencing nausea during an attack.² Thus, treatments that relieve nausea as well as migraine headache pain are optimal.

Although most migraine trials of the various triptans have examined the effectiveness of the drug on relieving headache pain as well as other commonly associated symptoms, none that we are aware of have examined effectiveness specifically for nausea as the primary endpoint. A meta-analysis of 5 phase III rizatriptan trials, which included 3 trials with the 10-mg tablet and 2 trials with the 10-mg orally disintegrating tablet (ODT), showed that rizatriptan was significantly better than placebo for the secondary endpoint of elimination of nausea at 2 hours (65% vs 41%, $P < .001$).³ A retrospective analysis of 5 clinical trials of rizatriptan 10-mg tablet compared with other triptans and placebo also found that rizatriptan was significantly better than placebo for elimination of nausea at 2 hours (59-68% vs 30-54%, $P \leq .001$ for all comparisons).⁴ A retrospective analysis of the 2 trials of rizatriptan 10-mg ODT vs placebo showed that more patients taking rizatriptan experienced relief of migraine-associated nausea than with placebo, but the result was significant for only one of the 2 trials (64% vs 48%, $P = .07$; 62% vs 39%, $P \leq .05$, data on file, Merck & Co., Inc.). The purpose of this current prospective study was to confirm the efficacy of rizatriptan 10-mg ODT for the elimination of migraine-associated nausea. This is the first trial, to our knowledge, to specifically require all patients to have nausea at baseline and to measure elimination of nausea as the primary hypothesized endpoint.

METHODS

Patients.—The study enrolled adults with at least a 6-month history of migraine with or without aura who typically experienced migraine-associated nausea by the time their headache became moderate or severe. Patients had to be able to distinguish between migraine and other types of headache. Women were required to use adequate contraception. Antimigraine prophylactic medications other than propranolol were permitted. No prohibited medications were allowed, including non-opiate analgesics and antiemetics 6 hours before treatment. Patients had to be in generally good health, with no cardiovascular disease and no other confounding health conditions.

Study Design.—A Scientific Advisory Committee composed of headache medicine physicians and Merck scientists developed the protocol, formulated the statistical analysis plan, analyzed and interpreted the data, and authored this report. Protocol 074 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted at 23 sites in the United States from March 2006 to October 2006. The protocol was approved by a centralized Institutional Review Board (IRB) (Schulman Associates IRB, Inc., Cincinnati, OH, USA) and local IRBs for site-specific requirements. Written informed consent was obtained from each patient before enrollment into the study. Patients were randomly assigned in a 2 : 1 ratio to either rizatriptan 10-mg ODT or placebo according to a computer-generated allocation schedule generated by the study sponsor. Numbered containers were used to implement allocation, and each patient was assigned the next number in the sequence upon being enrolled. All study personnel, including investigators, study site personnel, patients, and monitors, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers once the recruitment and data collection were complete. Patients were instructed to treat a single migraine attack at the earliest sign of nausea accompanied by moderate or severe pain. Patients were given 3 months to treat a qualifying attack. Rescue medication was permitted after 2 hours, including antiemetics, if needed. This study used an electronic diary (e-Diary, etrials,

Morrisville, NC, USA), rather than a traditional paper diary, to record efficacy observations. Adverse experiences (AEs) were recorded in a paper diary.

Efficacy and Tolerability Endpoints.—Efficacy and tolerability endpoints were recorded in an electronic patient diary. The presence of nausea was required at baseline and was self-assessed at 15, 30, 45, 60, 90 minutes, and 2 hours postdose. Headache severity (rated on a 4-point scale from grade 0 [no pain] to grade 3 [severe pain]), associated symptoms (phonophobia, photophobia, vomiting), and functional disability (rated on a 4-point scale from grade 0 [able to perform daily activities] to grade 3 [unable to carry out daily activities, requires bed rest]) were recorded at baseline, 15, 30, 45, 60, 90 minutes, and 2 hours postdose. Patients also noted satisfaction with medication at 2 hours postdose using a 7-point Likert scale ranging from 1 = *completely satisfied, couldn't be better* to 7 = *completely dissatisfied, couldn't be worse*. The time to elimination of nausea and the time to pain relief (from grade 2/3 to grade 1/0) were also recorded. Patients also noted use of any rescue medication between 2 and 24 hours postdose. Patients recorded any AEs occurring between enrolling in the study and the end-of-study visit.

Statistical Methods.—The hypotheses of the study were that rizatriptan 10-mg ODT would be superior to placebo, as measured by the percentage of patients with elimination of migraine-associated nausea at 2 hours postdose (primary) and that rizatriptan 10-mg ODT would be superior to placebo, as measured by the percentage of patients with pain relief at 2 hours postdose.

The primary endpoint for the efficacy analysis was no migraine-associated nausea at 2 hours. The primary efficacy analysis used a Full Analysis Set approach. The analysis included all randomized patients who had at least one assessment within 2 hours postdose (ie, after baseline evaluation). Patients were counted in the treatment group to which they were randomized. Missing values in the treatment phase (ie, after the baseline phase) were imputed by carrying forward the preceding values in the same phase. 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 the first post-baseline assessment. A logistic regression model with a factor for treatment group was used to compare the groups with respect to elimination of migraine-associated nausea at 2 hours. For analyzing all other binary outcome measures, a logistic regression model with factors for treatment group and the baseline binary outcome measure was used to compare the groups. For pain relief and pain freedom, the baseline severity of moderate (and mild if any) or severe was used as the baseline measure. The absence or presence of functional disability and associated symptoms (except for nausea) was used as the baseline measure. For the analysis of time-to-event endpoints, a proportional hazards regression model with the same covariate structure as in the logistic regression model was used. Kaplan-Meier estimates were used graphically to display the time-to-event endpoints.

Assuming an observed difference between treatments (rizatriptan 10-mg ODT vs placebo) for the percentage of patients with elimination of nausea at 2 hours to be 65% vs 45% and with pain relief at 2 hours to be 71% vs 40%, a projected sample size of 287 patients would provide 90% power to demonstrate superiority of rizatriptan 10-mg ODT compared with placebo with respect to 2-hour elimination of nausea and >99% power to demonstrate superiority of rizatriptan with respect to 2-hour pain relief, based on a 2-sided alpha level of 0.05.

All patients treated in the study were included in the safety analysis. Patients were counted in the treatment group for the drug they actually received, in the event that it was different from the treatment group to which they were randomized. The primary safety analysis compared the incidence of AEs (overall, drug-related, and serious) reported before taking any additional analgesia/antiemetics in patients initially treated with rizatriptan 10-mg ODT vs patients initially treated with placebo. Pairwise comparisons were analyzed using Fisher's exact test. No multiplicity adjustment was used for the safety analysis. In addition to the incidence of AEs, the difference between treatment groups and 95% confidence intervals are also provided. Wilson's score method was used to compute the confidence intervals.

RESULTS

Patient Accounting and Baseline Characteristics.—Of the 359 patients screened, 346 patients were enrolled in the study and randomly assigned to treatment, and 297 patients treated a qualifying migraine (Fig. 1). The most common reason for not treating was lack of a qualifying migraine (8.4%). Twenty patients did not record a post-baseline nausea assessment because of diary failure (frozen screen, incorrect operation, etc.); without post-baseline data, these patients were necessarily excluded from the efficacy analysis.

The treatment groups were generally similar and typical of other rizatriptan trials (Table 1). The majority of patients were white women. The median age was 40 years, and ages ranged from 18 to 65 years. Eighty percent of patients reported experience with triptans. Nearly half of the patients treated a severe migraine, and the majority of patients reported

having associated symptoms in addition to nausea. Of note, nearly 21% of patients reported inability to perform activities because of their migraine, and 11.4% of patients reported vomiting as an associated symptom at baseline.

Efficacy.—Although not statistically significant, there was a greater percentage of patients with elimination of nausea at 2 hours (primary efficacy endpoint) in the rizatriptan ODT group compared with the placebo group (70.3% vs 62.0%), $P = .165$, odds ratio (95% CI) = 1.45 (0.86, 2.46) (Fig. 2). There was a significantly greater percentage of patients who achieved 2-hour pain relief (secondary efficacy endpoint) with rizatriptan ODT compared with placebo (69.7% vs 54.3%), $P = .012$, odds ratio (95% CI) = 1.94 (1.16, 3.25). Treatment differences between rizatriptan and placebo became apparent by 15 minutes after treatment for both elimination of nausea and pain relief (Fig. 3).

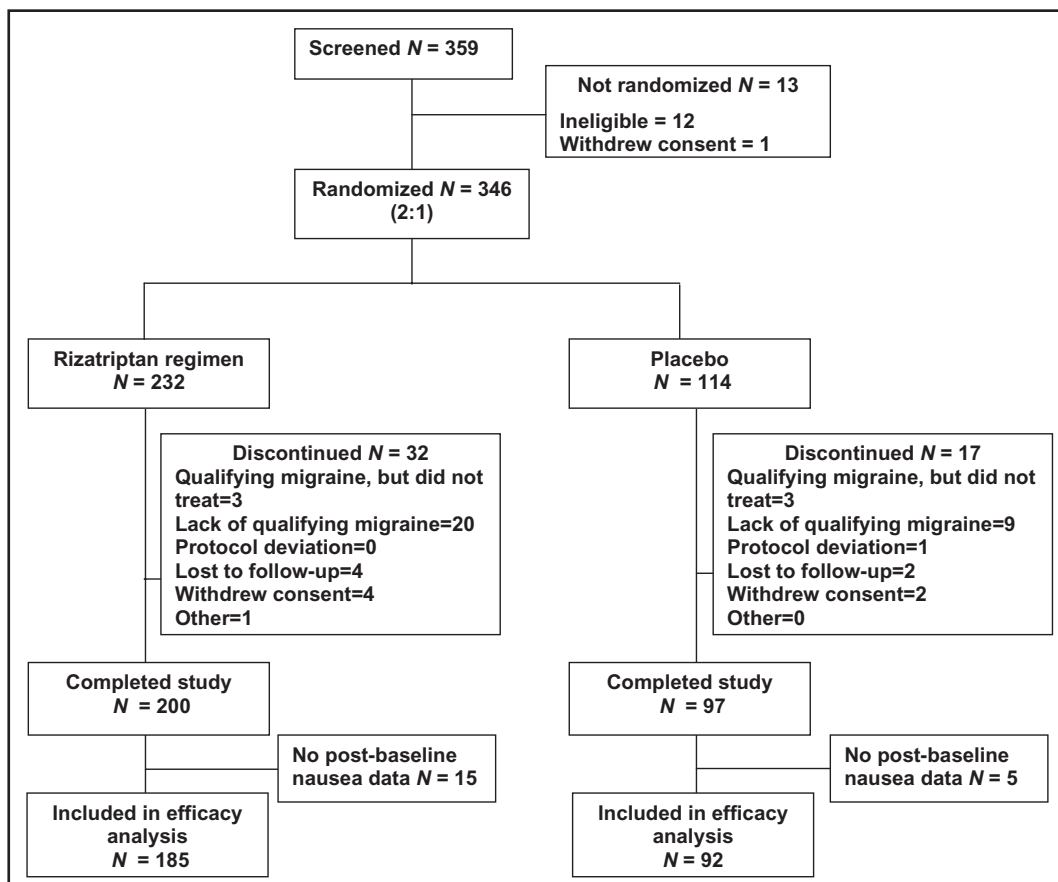


Fig 1.—Patient accounting.

Table 1.—Baseline Characteristics

	Rizatriptan 10 mg N = 200	Placebo N = 97
Patient demographics		
Female, %	89.5	89.7
Median age, years	40.0	41.0
White, %	81.5	78.4
Prior triptan use, %		
At any time in the past	77.0	86.6
At study entry	50.5	58.8
Pain severity at baseline, %		
Moderate	46.5	53.6
Severe	49.5	46.4
Unknown	4.0	0
Ability to perform activities, %		
Normal	0.5	3.1
Mildly impaired	42.5	47.4
Severely impaired	32.0	28.9
Unable to perform activities, bed rest	21.0	20.6
Unknown	4.0	0
Associated symptoms, %		
Photophobia	88.5	86.6
Phonophobia	73.0	82.5
Vomiting	10.0	14.4

A per-protocol analysis was performed for the primary endpoint of elimination of nausea at 2 hours. Of the 277 patients included in the primary efficacy analysis, 67 patients (24%) were excluded from the per-protocol analysis because of the absence of a nausea assessment at the 2-hour time point (53 patients) or use of prohibited medication (14 patients). The results of the per-protocol analysis revealed a slightly larger treatment advantage for rizatriptan ODT compared with placebo than what was seen in the primary analysis: rizatriptan 72.7% vs placebo 60.6%, $P = .075$, odds ratio (95% CI) = 1.73 (0.95, 3.17).

Other efficacy endpoints at 2 hours (absence of photophobia, absence of phonophobia, and functional disability), with the exception of vomiting, also favored rizatriptan ODT compared with placebo (Fig. 4). Similarly, rizatriptan ODT demonstrated significantly greater efficacy for the elimination of photophobia (53% vs 36%, $P = .016$), phonophobia (55% vs 40%, $P = .034$), and functional disability (42% vs 22%, $P = .002$) at 2 hours in those who had these symptoms at baseline. Significantly more patients in the rizatriptan ODT group were satisfied (completely, very, or somewhat) with their treatment at 2 hours

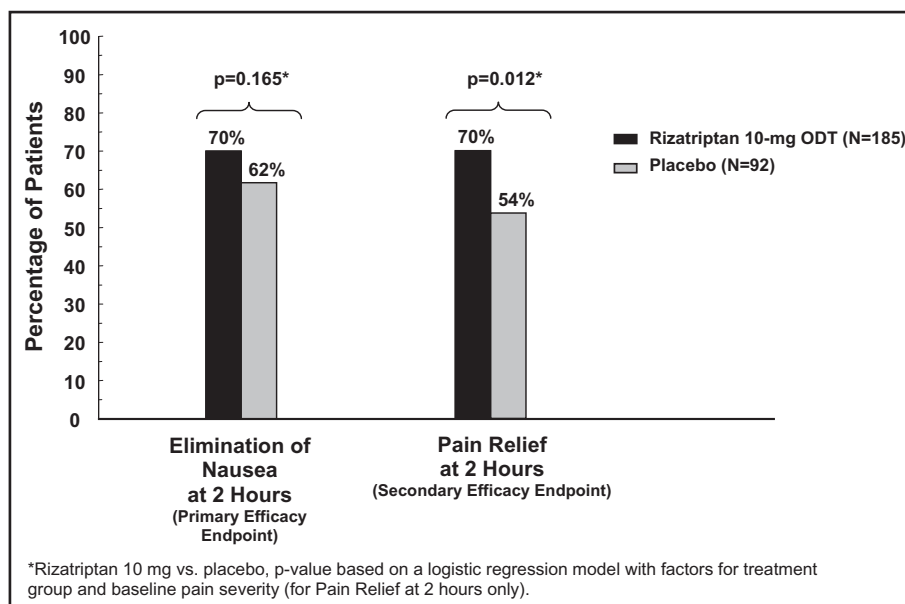


Fig 2.—Elimination of nausea and pain relief at 2 hours. Bar graph showing the percentage of patients who reported elimination of nausea (left) and pain relief (right) 2 hours after taking rizatriptan 10-mg orally disintegrating tablet (ODT) (black bars) or placebo (gray bars).

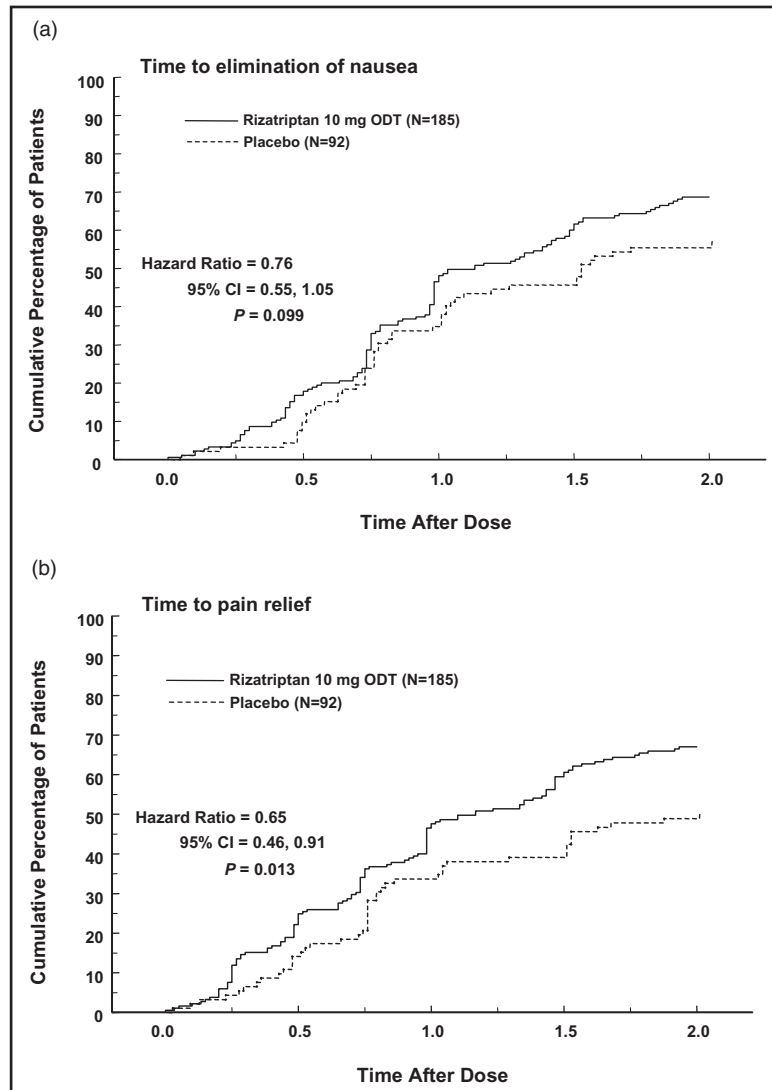


Fig 3.—Time to elimination of nausea and time to pain relief. Kaplan-Meier graphs depicting time to elimination of nausea (a) and time to pain relief (b) after treatment with rizatriptan (solid line) or placebo (dotted line). CI = confidence interval; ODT = orally disintegrating tablet.

(rizatriptan 63% vs placebo 43%, $P = .005$). Fewer patients in the rizatriptan ODT group required rescue medication within 24 hours post-treatment (rizatriptan 27% vs placebo 47%).

To further investigate the unusually high observed placebo response rate for both nausea and pain relief endpoints, patient data were subsequently divided into subgroups based on baseline headache severity (Table 2). For the nausea endpoint, rizatriptan 10-mg ODT showed a greater treatment advantage than placebo among patients with moderate pain, but showed no difference for patients with

severe pain (Fig. 5). In contrast, for the pain relief endpoint, the treatment difference between rizatriptan and placebo was preserved in both baseline pain severity subgroups (Fig. 5). Other subsequent analyses were consistent with the pain relief endpoint and contrast with the nausea endpoint: treatment differences between rizatriptan and placebo were seen in both moderate and severe pain baseline subgroups for both photophobia and phonophobia (data not shown).

Tolerability.—Tolerability was evaluated in each treatment group by summarizing the number of AEs

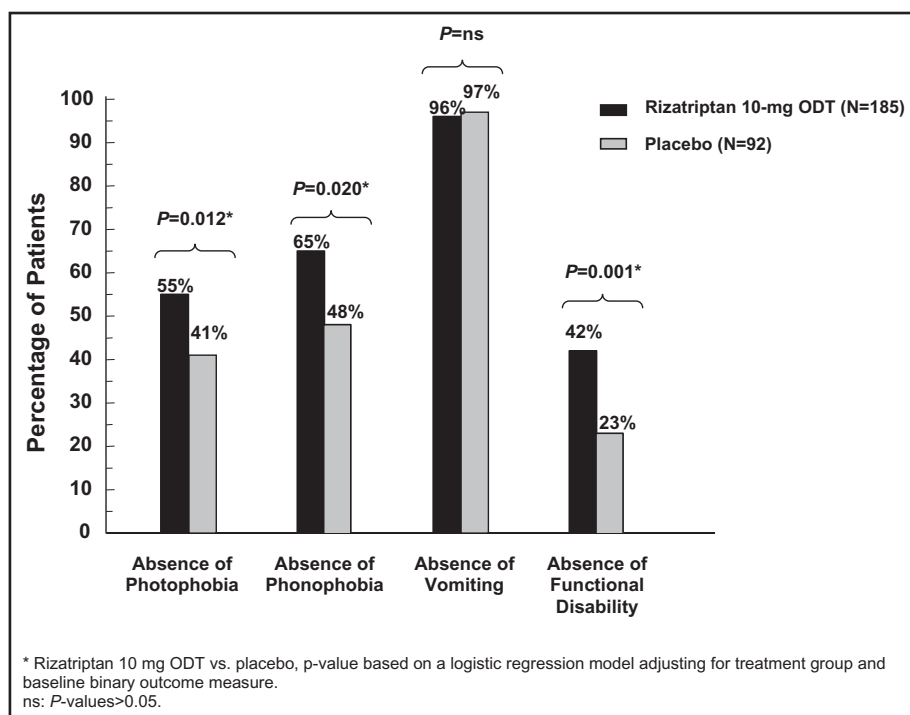


Fig 4.—Associated symptoms at 2 hours. Bar graph showing the percentage of patients who reported absence of the specified associated symptoms at 2 hours after taking rizatriptan 10-mg orally disintegrating tablet (ODT; black) or placebo (gray). * $P < .05$ vs placebo based on a logistic regression model. CI = confidence interval.

Table 2.—Baseline Characteristics of Patients With Moderate or Severe Pain at Baseline

	Moderate pain		Severe pain	
	Rizatriptan 10 mg N = 93	Placebo N = 52	Rizatriptan 10 mg N = 99	Placebo N = 45
Ability to perform activities, %				
Normal	1.1	5.8	0	0
Mildly impaired	72.0	67.3	18.2	24.4
Severely impaired	22.6	23.1	43.4	35.6
Unable to perform activities, bed rest	4.3	3.8	38.4	40.0
Unknown	1.1	0	0	0
Associated symptoms, %				
Photophobia	89.2	78.8	94.9	95.6
Phonophobia	65.6	73.1	85.9	93.3
Vomiting	3.2	3.8	17.2	26.7
Duration from pain onset to treatment, %				
<0.5 hours	14.0	11.5	8.1	13.3
0.5 to <1 hour	15.1	5.8	10.1	8.9
1 to <1.5 hours	14.0	13.5	13.1	15.6
1.5 to <2 hours	1.1	7.7	2.0	6.7
≥2 hours	28.0	28.8	36.4	33.3
Unknown	29.0	32.7	30.3	22.2

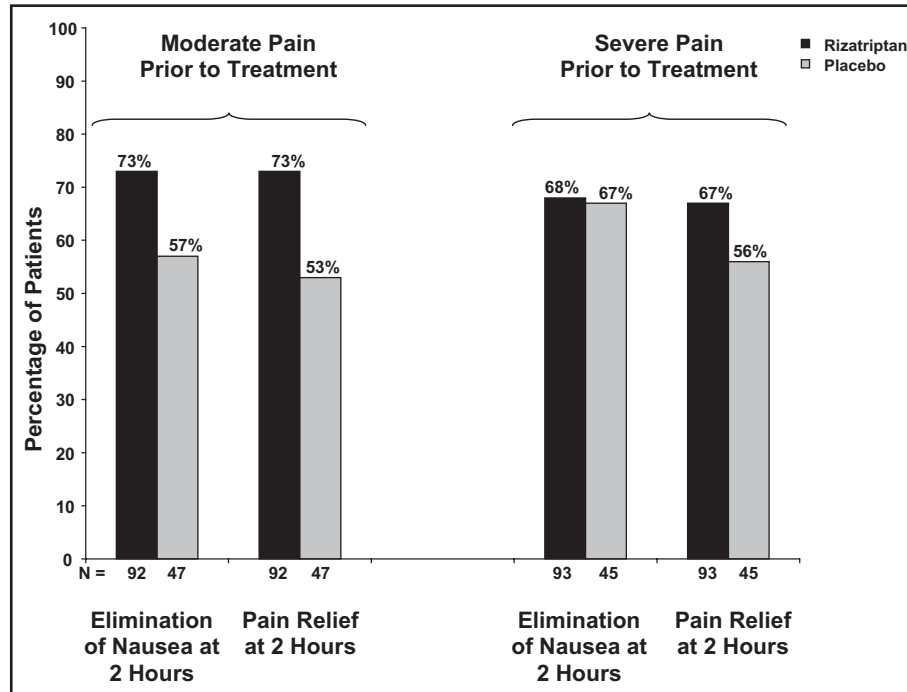


Figure 5.—Elimination of nausea and pain relief at 2 hours in patients treating moderate vs severe migraine pain. Bar graph showing the percentage of patients with either moderate (left) or severe (right) pain at baseline who reported elimination of nausea and pain relief 2 hours after taking rizatriptan 10-mg orally disintegrating tablet (ODT; black bars) or placebo (gray bars).

reported after treatment but before use of any rescue medication. The incidence of AEs (15% vs 4%) and investigator-determined drug-related AEs (13% vs 3%) was greater in the rizatriptan ODT treatment group than in the placebo group. There were no serious AEs reported. The most common ($\geq 2\%$) clinical AEs were dizziness (rizatriptan 2% vs placebo 1%) and somnolence (rizatriptan 2% vs placebo 0%). These results are consistent with the safety profile previously reported for rizatriptan.

DISCUSSION

Nausea is reported to be the most common and most bothersome migraine-associated symptom.^{1,2} Recent studies have examined the evolution of a migraine attack to understand when nausea and other associated symptoms appear in relation to headache pain. Linde et al⁵ observed that nausea typically followed the same time-intensity profile as headache pain, although some patients could experience severe pain and severe photophobia and phonophobia without experiencing any nausea. Pryse-Phillips et al⁶ asked 253 headache patients to characterize how

quickly a typical migraine developed, whether nausea was associated with it, and what the consequences of the nausea were, if present. They found that nausea was common (91.7%), but it appeared earlier and lasted longer in those patients experiencing migraine with aura. Consequently, approximately 20% of the respondents noted that nausea prevented self-administration of acute oral antimigraine medication. Thus, migraine medications that eliminate nausea as well as headache pain are most desirable; migraine therapies that potentiate nausea, whether as a pharmacologic effect or due to the route of administration, such as administration of a tablet with water, may adversely impact overall medication effectiveness.⁷

A retrospective analysis of 5 clinical trials of rizatriptan 10-mg tablet compared with other triptans found that approximately 60% of patients in each treatment group had nausea at baseline.⁴ The purpose of the current prospective study was to confirm the efficacy of rizatriptan 10-mg ODT for the elimination of migraine-associated nausea. Large prospective analyses of the elimination of nausea as a secondary

endpoint in two rizatriptan ODT trials demonstrated the efficacy of rizatriptan. In the current trial, elimination of nausea was elevated to the level of a primary hypothesized endpoint. Although the efficacy of rizatriptan 10-mg ODT for the elimination of migraine-associated nausea was comparable to that seen in previous rizatriptan trials, the higher-than-usual placebo rate seen when elimination of nausea was elevated to a primary endpoint contributed to the failure to achieve statistical significance. Given this, multiple potential explanations for the elevated placebo response seen in this study require exploration.

Placebo response rates have been increasing since the era of the triptan registration trials. A proposed explanation for this observation is the ratio of active- to placebo-treated subjects (eg, 2:1 in the current study); however, this has not been borne out across the range of studies with the triptans.⁸ A second explanation that has been postulated is that patients have an increased expectation of success in later migraine trials compared with early registration trials, leading to a higher placebo response rate, but this was also not apparent in the study by Loder et al.⁸

The high placebo response for the elimination of nausea endpoint in the current trial may reflect differences in patient instruction, symptom perception, and subsequent patient behavior. In this study, patients were required to have nausea as well as moderate or severe pain to treat a migraine attack, whereas patients in previous rizatriptan trials treated when migraine pain was moderate or severe without attention to the presence of nausea. In the current study, almost half the patients (vs 20-25% in typical rizatriptan trials) treated with severe pain at baseline, which would more likely be associated with a decreased, not an increased, placebo response rate. Prospectively planned subgroup analyses, however, showed that the patients treating a migraine attack with a baseline pain intensity of moderate were different from those treating a severe attack, in that those in the severe group had a placebo response that was not different from the rizatriptan response for elimination of nausea, whereas those in the moderate group showed a difference in treatment response favoring rizatriptan, with a placebo response that was

more aligned with what was observed in the most recent rizatriptan trials.⁹ However, the same trend was not seen for the pain relief endpoint or for the other associated symptoms of photophobia and phonophobia, where there was an advantage for rizatriptan over placebo regardless of baseline pain severity.

Another potential explanation for the high placebo response rate is that the degree of nausea necessary for patients to report it as a migraine-associated symptom may be greater than that necessary to treat at the earliest sign of nausea once the headache pain was moderate or severe, as was required in the current study. This may have led more patients, especially those with severe pain, to treat their migraine when nausea was mild, which may, in turn, have increased the likelihood that both the pharmacologically active agent and placebo would perform similarly. This could explain why all other associated symptoms as well as pain relief and pain freedom revealed a treatment advantage for rizatriptan over placebo regardless of baseline pain severity and why only elimination of nausea among the patients with severe baseline pain showed no treatment advantage for rizatriptan. Rather than requiring a binary decision of nausea or no nausea when deciding when to treat a migraine attack, it may have been more meaningful to ask patients to rate their degree of nausea before treatment or to treat when nausea was moderate or severe and record if it improved to mild or no nausea at the 2-hour endpoint.

The U.S. Food and Drug Administration recently elevated the efficacy standards for new antimigraine agents: the quaternary endpoint of relief of migraine pain, nausea, photophobia, and phonophobia must be demonstrated. In this new construct, relief of nausea is perhaps the most difficult to achieve with currently available treatments. The triptans are designed to modulate the serotonin receptors that are responsible for the pain associated with migraine. The mechanisms responsible for the other associated symptoms of migraine are not proven. The pathophysiologic basis for photophobia and phonophobia are not yet entirely known. The mechanism of nausea is complex and may involve both central and peripheral effects and may be modulated by different serotonin

receptor subtypes or non-serotonin systems. Therefore, although relief of the head pain of migraine is clinically associated with relief of associated symptoms, the expectation that a specific medication would necessarily adequately alleviate the range of associated symptoms of migraine when a given symptom is the focus of intense study may be unrealistic. Those patients who experience nausea (or any other significantly disruptive associated symptom) as a prominent component of migraine may benefit from the use of adjunctive medications better targeted to the relief of that symptom.

In this trial, we believe the first of its kind, study subjects focused attention on treating the migraine-associated symptom of nausea at its earliest appearance with moderate or severe headache pain. The result was the inability to distinguish between active drug and placebo due to an unexpected high placebo response rate. A number of possible explanations exist, with perhaps additional possibilities to those we have considered. In the future, we recommend very careful consideration in picking any migraine-associated symptom as a primary treatment study endpoint given what little is currently known about associated symptom mechanisms. Furthermore, a binary all or none presence and absence of that symptom may not be optimal to distinguish active from placebo treatments.

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