

## Research Submission

# Rizatriptan 10-mg ODT for Early Treatment of Migraine and Impact of Migraine Education on Treatment Response

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**Objective.**—To examine the efficacy of rizatriptan 10-mg orally disintegrating tablet (ODT) for treating migraines of mild intensity soon after onset, with or without patient-specific migraine education.

**Background.**—Studies have shown rizatriptan tablet efficacy in early migraine treatment.

**Methods.**—In this randomized, placebo-controlled, double-blind, factorial design study, adults with a history of migraine were assigned to rizatriptan 10-mg ODT ± patient education (personalized summary of early migraine signs and symptoms) or placebo ± patient education in a 1 : 1 : 1 : 1 ratio. Patients were instructed to treat 1 attack at the earliest time they knew that their headache was a migraine, while pain was mild. During the next 24 hours, patients assessed pain severity, associated symptoms, functional disability, use of rescue medication, and treatment satisfaction. The primary endpoint was pain freedom at 2 hours; a key secondary endpoint was 24-hour sustained pain freedom.

**Results.**—Of 207 patients randomized to treatment, 188 (91%) treated a study migraine. Significantly more patients taking rizatriptan reported pain freedom at 2 hours compared with placebo (66.3% vs 28.1%,  $P < .001$ ). Similarly, significantly more patients taking rizatriptan reported 24-hour sustained pain freedom (52.2% vs 17.7%,  $P < .001$ ). A greater proportion of patients in the rizatriptan + education group reported pain freedom at 2 hours compared with those in the rizatriptan + no education group (71.7% vs 60.9%,  $P = .430$ ). Few adverse events were reported.

**Conclusion.**—Rizatriptan 10-mg ODT, when taken early, while headache pain is mild, was superior to placebo at providing pain freedom at 2 hours and 24-hour sustained pain freedom (NCT00516737).

**Key words:** rizatriptan, migraine, efficacy, early treatment, education

**Abbreviations:** AE adverse experience, CI confidence interval, HCP healthcare provider, IVRS Interactive Voice Response System, ODT orally disintegrating tablet, TAME Treat A Migraine Early

(*Headache* 2009;49:687-696)

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Funding support: This study was funded by Merck & Co., Inc.

Accepted for publication December 20, 2008.

Studies of triptan efficacy conducted for regulatory approvals required that study medications be administered only after the migraine headache pain became moderate or severe in intensity. Clinical observations and post-hoc analyses of protocol violators have suggested that administration of medication

*Conflict of Interest:* Drs. Cady and Martin have received research grants and honoraria from Merck & Co., Inc. Dr. Geraud has received research grants and honoraria from Merck & Co., Inc. Mr. Rodgers, Ms. Ramsey, and Drs. Ho, Hustad, Zhang, Connor, and Ho are employed by Merck & Co., Inc. and may own stock or hold stock options in the company.

when the migraine headache was mild significantly improved the pain-free response of triptan medications.<sup>1-3</sup> These observations led to double-blind, placebo-controlled studies of several triptan medications for the early treatment of migraine when the pain is mild that confirmed this finding.<sup>4-9</sup> A plausible explanation for the improved efficacy of early intervention with triptans was provided by Burstein et al, when they demonstrated that triptan efficacy markedly diminished after central sensitization was established.<sup>10</sup>

Despite numerous clinical studies supporting the treatment of migraine during the mild headache phase, other studies demonstrated that patients have difficulty using this treatment strategy. For example, Foley et al confirmed that many patients would frequently “wait and see” if a headache was going to be a migraine or wait until the migraine headache had become severe enough to be worthy of treatment.<sup>11</sup>

Both retrospective analyses and prospective clinical trials of the tablet formulation of rizatriptan demonstrated a trend toward increased efficacy for pain freedom at 2 hours when treatment is initiated early in the evolution of a migraine attack, specifically when the headache pain was mild.<sup>12-14</sup> In addition, in the rizatriptan Treat A Migraine Early (TAME) studies, it was observed that patients had numerous nonheadache symptoms associated with mild headache, and many were experiencing mild to moderate functional impairment before the onset of headache and before treatment was initiated.<sup>14</sup> To date, few studies have prospectively examined the symptoms occurring in the preheadache and early phase of a migraine.<sup>15</sup> Further, no studies have evaluated the effect on treatment efficacy of adding patient-specific migraine education, which emphasized awareness of these symptoms as a harbinger of their migraine, to pharmacologic interventions for migraine within the early acute treatment paradigm.

The primary purpose of the current study was to evaluate the efficacy and tolerability of rizatriptan 10-mg orally disintegrating tablet/oral lyophilisate (ODT) in the early acute treatment of migraine attack, while the pain is mild. As an exploratory objective, this study also evaluated the impact of patient-specific migraine education for early treat-

ment of migraine on medication efficacy. It was anticipated that by implementing a standardized approach to patient-specific migraine education, the participants who received the education intervention would be able to detect the onset of a migraine headache earlier and thereby treat a migraine attack earlier, while the pain is mild.

## PATIENTS AND METHODS

**Participants.**—Participants were at least 18 years of age with at least a 1-year history of migraine with or without aura by International Headache Society criteria.<sup>16</sup> Participants had a history of 1 to 4 migraine attacks per month with attacks that were typically mild at onset and recognizable as migraine. Women of childbearing potential agreed to use adequate contraception during the study. Participants with a history of coexisting migraine and episodic tension-type headache had to be able to clearly distinguish migraine attacks from tension-type headache to be eligible; those with chronic tension-type headache or with >15 headache days per month or who had taken medication for >10 days per month in any of the previous 3 months were excluded. Participants with a history of cerebrovascular accident, transient ischemic attack, ischemic heart disease, uncontrolled hypertension, coronary artery vasospasm (including Prinzmetal’s variant angina), or other significant underlying cardiovascular or peripheral vascular disease were excluded. Participants agreed to discontinue use of the following: monoamine oxidase inhibitors and propranolol 1 month before randomization; any 5HT<sub>1B/1D</sub> agonist, ergot-type medication, opiates, or barbiturates 24 hours before treatment with study medication; and nonopiate analgesics and antiemetics 6 hours before treatment with study medication. In addition, daily analgesics taken for any reason were not permitted (except for aspirin ≤325 mg/day). Continuation of standard anti-migraine prophylactic medication and selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors was permitted as long as the daily dose had been stable for 3 months and would not change during the study.

**Study Design.**—This was a multicenter, randomized, double-blind (with in-house blinding), placebo-

controlled, 2×2 factorial design, parallel-group, study conducted in the United States (10 sites) and Germany (3 sites) from October 2007 through April 2008 (protocol 081). The study was funded by Merck & Co., Inc. A Scientific Advisory Committee composed of headache experts and Merck Research Laboratories scientists developed the protocol, formulated the statistical analysis plan, analyzed and interpreted the data, and authored this report. The protocol was approved by a central Institutional Review Board (Schulman Associates IRB, Cincinnati, OH, USA), and all participants were required to give written informed consent before undergoing any study procedures.

The study used a central randomization scheme, utilizing an Interactive Voice Response System (IVRS). The IVRS assigned an allocation number, which allocated a participant to a particular group and identified the participant for data collection purposes. Eligible participants were randomly assigned to 1 of 4 groups: rizatriptan 10-mg ODT ± patient-specific migraine education or matching placebo ± patient-specific migraine education in a 1 : 1 : 1 : 1 ratio. Participants also were stratified via IVRS according to current triptan use (use within the last 30 days preceding randomization vs >30 days or triptan naive). All study personnel, participants, and the sponsor remained blinded to treatment allocation throughout the study. Investigators provided all participants with standardized instructions for administration of study treatment asking them to initiate treatment when the headache intensity was mild and within 2 hours of headache onset. In addition, in the diary, all participants received a printed reminder that they may be receiving a placebo. Participants treated a single migraine attack at the earliest time they knew that their headache was a migraine and when the headache pain was mild. Participants were allowed to treat a nonresponding headache or headache recurrence with any nonstudy rescue medication between 2 and 24 hours post-dose, consistent with the local rizatriptan prescribing information. Participants had 2 months from the first visit to treat a qualifying migraine attack.

A standardized patient-specific migraine education format was utilized in this study. Education was

divided into a 3-part discussion between the study participant and the healthcare provider (HCP). In part 1, the HCP asked an open-ended question to the participant to determine their awareness of the onset of their own migraine symptoms before the onset of headache as well as during the mild headache phase of a migraine that would evolve into a fully developed migraine. The answers were recorded on the standard worksheet. In part 2, the HCP read from a predefined list of frequent migraine-associated symptoms that can occur during the premonitory or early headache phase of migraine and discussed with the participant whether or not each symptom was present before their typical migraine started, during the mild headache only, or both; all responses were recorded. In part 3, the HCP summarized, with the subject's participation, the information learned during parts 1 and 2 on a card that also contained instructions for treating a study migraine. The summary card was provided to the participant for future reference for treatment of a qualifying migraine. At the end of the session, the HCP recorded the time it took to administer the education. Subjects in the no-education group were given a card containing only the printed treatment instructions for a study migraine at the end of the first study visit.

**Efficacy and Safety Endpoints.**—Efficacy measurements were recorded in the patient diary at baseline (immediately before dosing with study medication) and 30, 60, 90, and 120 minutes post-dose. The 120-minute (2-hour) time-point was the primary time-point of interest. Immediately after taking study medication, the participant recorded the date and time study medication was administered and whether liquid was taken with the medication. All participants recorded their use of concomitant therapies, time and date of headache onset, assessment of headache intensity (measured on the following scale: 0 = no headache; 1 = mild pain; 2 = moderate pain; 3 = severe pain), absence or presence of migraine-associated symptoms (photophobia, phonophobia, nausea, and vomiting), absence or presence of other migraine-associated symptoms, ability to perform daily activities (rated on a scale from grade 0 to 3: grade 0 – normal [able to perform daily activities]; grade 1 – daily activities mildly impaired;

grade 2 – daily activities severely impaired; grade 3 – unable to carry out daily activities, requires bed rest), and use of rescue medication. Total migraine freedom (pain freedom and absence of photophobia, phonophobia, nausea, and vomiting) was also assessed. Sustained pain freedom, defined as pain freedom at 2 hours and no use of rescue medication, with no return of pain in the 2 to 24 hours post-dose, and patient's overall satisfaction with study medication (rated on a 7-point scale ranging from 1 – completely satisfied, couldn't be better to 7 – completely dissatisfied, couldn't be worse) were assessed at 24 hours post-dose. Participants recorded any adverse experiences (AEs) that occurred any time after taking their dose of study medication until the post-treatment visit.

**Statistical Methods.—Objectives and Hypothesis.—**

The primary hypothesis was that rizatriptan 10-mg ODT would be superior to placebo, as measured by the percentage of patients who have pain freedom at 2 hours post-dose. An additional objective was to determine whether treatment effects were consistent across migraine education vs no migraine education subgroups with respect to pain freedom at 2 hours.

**Efficacy.—**A Full Analysis Set population including all randomized participants who had at least 1 assessment within 2 hours post-dose (ie, after baseline evaluation) was used for the primary efficacy analysis. Participants were counted in the treatment group to which they were randomized. Nonbaseline missing data were imputed using a last-observation-carried forward approach.

A logistic regression model with factors for treatment group, country (USA vs ex-USA), current triptan use (yes, no), and administration of the patient-specific migraine education (yes, no) was used to compare the treatment groups with respect to the primary endpoint of pain freedom at 2 hours post-dose. Assuming a true underlying active vs placebo difference of 24 percentage points (58% vs 34%) for pain-free status at 2 hours, 176 (88 rizatriptan 10-mg ODT/88 placebo) randomized patients would be needed to have 90% power to demonstrate the primary efficacy hypothesis. The expected failure-to-treat rate was 10%.

The same logistic regression model was used to evaluate key secondary endpoints: 24-hour sustained pain freedom, pain freedom at time-points other than 2 hours, elimination of associated symptoms, use of rescue medication, and satisfaction with treatment. A logistic regression model with factors for treatment group, current triptan use, patient education, country, and baseline presence/absence was used to compare treatment groups with respect to absence of associated symptoms (photophobia, phonophobia, and nausea), and absence of functional disability. A logistic regression model with factors for treatment group, current triptan use, patient education, country, and 3 separate factors for the baseline presence/absence of photophobia, phonophobia, and nausea was used to compare treatment groups with respect to migraine freedom.

**Safety.—**Data from all participants who received at least 1 dose of study medication were included in the safety analysis. Safety was assessed by statistical and clinical review of the incidence of AEs and vital signs. The primary safety measurement was incidence of AEs (overall, drug-related, and serious) reported by participants after administration of study treatment and before taking any rescue medication up to 14 days post-treatment. A participant's treatment group was determined by the actual treatment received during the study. The difference between treatment groups, with associated 95% confidence intervals (CIs), was provided based on Wilson's score method.

## RESULTS

**Participant Accounting.—**Of 207 participants randomly assigned to treatment, 188 (91%) treated with the study medication, completed the study, and were included in the Full Analysis Set population for the primary efficacy analysis (Fig. 1). The most common reason for discontinuation in both treatment groups was lack of a qualifying migraine.

**Demographics and Baseline Characteristics.—**Treatment groups were similar with respect to participant demographic and most baseline characteristics (Table 1). The majority of participants were female and white. The median age was 42 years, and ages ranged from 18 to 69 years. More than half of partici-

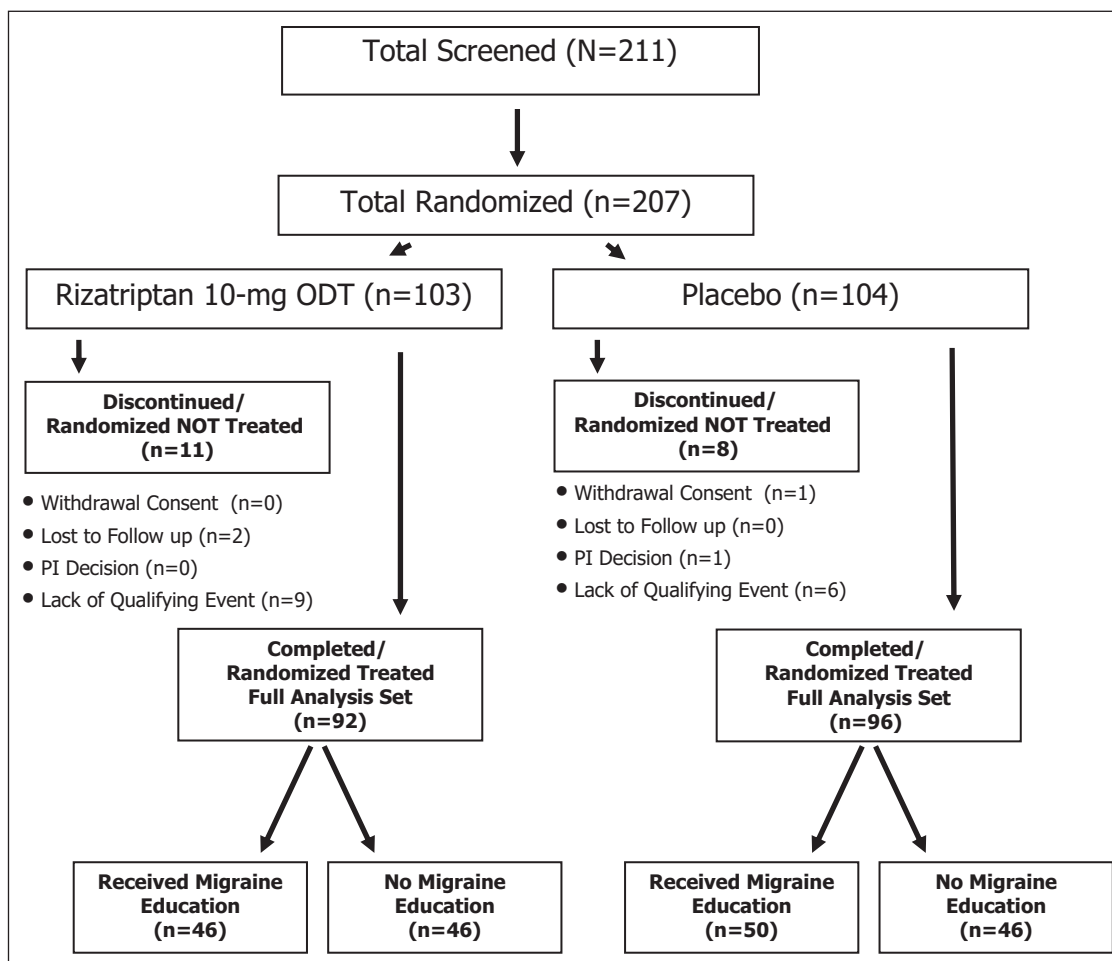


Fig 1.—Participant accounting. ODT = orally disintegrating tablet.

participants in both treatment groups were current triptan users, and 51% of those had used triptans for >24 months. Of the triptan users, 8% had no active prescription, 35% used sumatriptan, 22% used rizatriptan, 8% used zolmitriptan, 4% used eletriptan, 3% used frovatriptan or naratriptan, and 2% used almotriptan. More participants in the placebo group reported having associated symptoms and mild impairment in functional abilities at baseline than in the rizatriptan ODT group.

**Efficacy.—Primary and Key Secondary Endpoints.**—All participants treated when their headache was mild. The majority of participants treated within 2 hours of pain onset (>2 hours, rizatriptan: 9%, placebo: 11%), and most (rizatriptan: 49%, placebo: 58%) treated within 30 minutes of pain onset. The percentage of participants reporting pain

freedom at 2 hours after taking study drug was significantly greater for rizatriptan ODT (66%) compared with placebo (28%; odds ratio = 5.20, 95% CI: [2.75, 9.80],  $P < .001$ ; Fig. 2). The percentage of participants reporting sustained pain freedom between 2 and 24 hours post-dose also was significantly greater for rizatriptan ODT (52%) compared with placebo (18%; odds ratio = 5.40, 95% CI: [2.71, 10.79],  $P < .001$ ), as it was for total migraine freedom (Fig. 2). All other efficacy endpoints, as well as no use of rescue medication, favored rizatriptan ODT (Table 2).

**Educational Intervention.**—A greater proportion of participants receiving rizatriptan + patient-specific migraine education reported pain freedom at 2 hours compared with those receiving rizatriptan + no education (Fig. 3,  $P = .430$ ). The proportion of partici-

Table 1.—Participant Demographics and Baseline Characteristics

			Education Yes		Education No	
	Riza ODT N = 92	Pbo N = 96	Riza ODT N = 46	Pbo N = 50	Riza ODT N = 46	Pbo N = 46
<b>Demographics</b>						
Women, %	87	93	93	92	80	93
Median age, years	40	42	43	41	39	43
White, %	91	96	91	96	91	96
<b>Current triptan user, %</b>						
Yes	67	65	70	64	65	65
<b>Ability to perform activities, %</b>						
Normal	40	26	39	20	41	33
Mildly impaired	60	73	61	80	59	65
Severely impaired	0	1	0	0	0	2
Unable to perform activities, bedrest	0	0	0	0	0	0
<b>Associated symptoms, %</b>						
Photophobia	53	70	54	76	52	63
Phonophobia	46	60	48	64	43	56
Nausea	18	34	20	30	17	39
Vomiting	0	2	0	4	0	0

ODT = orally disintegrating tablet.

pants reporting 2-hour pain freedom in the placebo groups was similar regardless of education (yes: 28.0%; no: 28.3%). Results were similar for the other efficacy endpoints (Fig. 3, Table 2). More participants in the rizatriptan + education group reported satisfaction with their treatment at 24 hours (Fig. 4).

**Safety.**—Overall, few AEs were reported, and none were serious. The incidence of AEs (rizatriptan 6.5%, n = 6; placebo 3%, n = 3) was greater in the rizatriptan ODT treatment group compared with the placebo group, and these were consistent with the existing safety profile for rizatriptan. Specific AEs in the rizatriptan group and not in the placebo group (a single participant may appear in more than 1 AE group) were hyperchlorhydria (n = 2), nausea (n = 1), feeling jittery (n = 1), pain (n = 1), myalgia (n = 1), balance disorder (n = 1), and throat tightness (n = 1). Dizziness was reported in both treatment groups (rizatriptan n = 2; placebo n = 1).

## DISCUSSION

This study provides further insight into the use of rizatriptan for acute treatment of a migraine. The

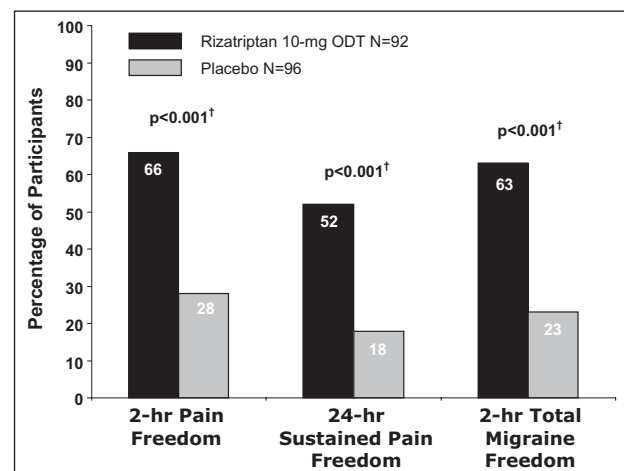


Fig 2.—Efficacy endpoints. Bar graph showing the percentage of participants who reported pain freedom at 2 hours (left), sustained pain freedom from 2-24 hours (middle), and total migraine freedom (no pain and no associated symptoms) at 2 hours (right) after taking rizatriptan 10-mg ODT (black bars) or placebo (gray bars). †Rizatriptan 10 mg vs placebo, *P* value based on a logistic regression model adjusting for treatment group, current triptan use, administration of the standard education component, and country. ODT = orally disintegrating tablet.

Table 2.—Secondary Endpoints

	Riza ODT N = 92	Pbo N = 96	P value†	Education Yes		Education No	
				Riza ODT N = 46	Pbo N = 50	Riza ODT N = 46	Pbo N = 46
Absence at 2 hours (%)							
Photophobia	75	45	<.001	76	38	74	52
Phonophobia	78	57	.009	78	50	78	65
Nausea	89	76	.112	91	76	87	76
Functional disability	72	44	<.001	76	46	67	41
Elimination at 2 hours (%)							
Photophobia	61	31	.002	60	26	62	38
Phonophobia	62	48	.110	73	41	50	58
Nausea	76	48	.090	89	40	62	56
Functional disability	65	37	.001	68	42	63	29
No rescue use up to 24 hours	66	33	<.001	72	32	61	35

†Based on a logistic regression model with factors for treatment group, current triptan use (yes, no), administration of the standard patient migraine education component (yes, no), and country (USA vs ex-USA). The respective baseline presence/absence was included in the model for absence of photophobia, phonophobia, nausea, and functional disability. ODT = orally disintegrating tablet.

efficacy of rizatriptan 10-mg ODT in treatment of migraine while the headache is mild in intensity is significantly increased over placebo. Of note is the fact that all participants treated their headache while the pain was mild, and most treated within 2 hours of

pain onset. Previous treat early/treat mild trials have been confounded by the number of protocol violators who waited to treat their migraines or treated a moderate-to-severe headache.<sup>4-8</sup> The primary endpoint of superiority of rizatriptan 10-mg ODT for

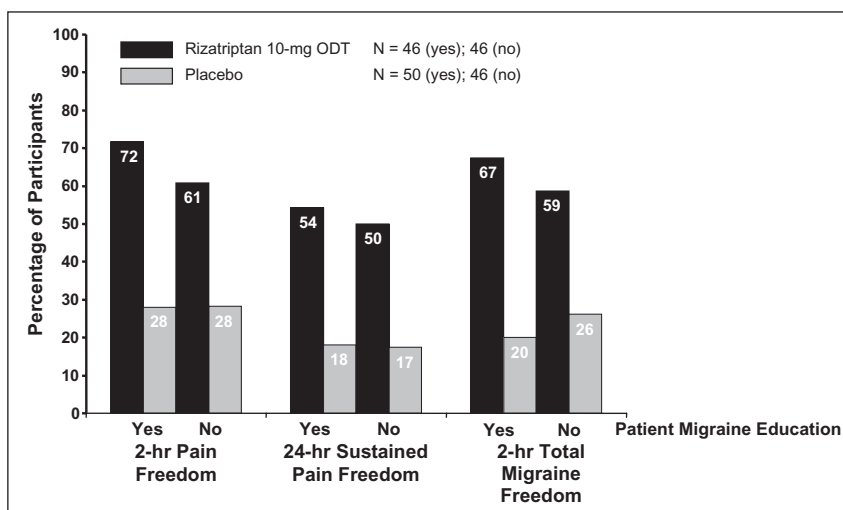
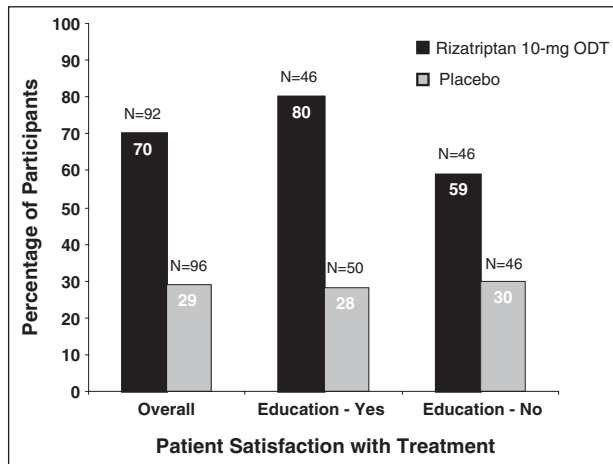


Fig 3.—Efficacy by patient-specific migraine education status. Bar graph showing the percentage of participants who received patient-specific migraine education (yes) or who received treatment instructions only (no) who reported pain freedom at 2 hours (left), sustained pain freedom from 2-24 hours (middle), and total migraine freedom (no pain and no associated symptoms) at 2 hours (right) after taking rizatriptan 10-mg ODT (black bars) or placebo (gray bars). ODT = orally disintegrating tablet.



**Fig 4.—Participant satisfaction with treatment.** Bar graph showing the percentage of participants who reported being satisfied with treatment at 24 hours in the overall population (left) and in the subgroups who did (middle) or did not (right) receive patient-specific migraine education. Rizatriptan 10-mg ODT (black); placebo (gray). ODT = orally disintegrating tablet.

achieving pain freedom at 2 hours compared with placebo was met. In addition, the rizatriptan ODT group experienced a greater sustained pain-free response 2-24 hours post-dose and required less rescue medication than did the placebo group. The greater efficacy of rizatriptan ODT compared with placebo is reflected in the significantly higher satisfaction ratings by those receiving rizatriptan vs placebo. This outcome was achieved with few subjects reporting adverse events in the rizatriptan ODT group, and no serious AEs were reported by either group. These data are clearly consistent with desired attributes of therapy for acute migraine as reported by patients.<sup>17</sup>

Results from the current study are comparable to those seen with the tablet formulation of rizatriptan in the TAME studies.<sup>14</sup> Placebo response was less in this study compared with the TAME studies, perhaps because participants were stratified by current triptan use: 66% of participants in this study used a triptan within the past 30 days, and the amount of experience with triptan therapy has been shown to influence placebo response rate, with lower placebo response for current triptan users.<sup>18</sup> The balanced allocation ratios used in this study (1 : 1 vs 2 : 1 in TAME) also may have led to lower placebo rates, as well as the

reminder in the diary that the possibility existed that they might receive placebo as the study medication. Also, more patients in the placebo group reported associated symptoms and functional disability at baseline than in the rizatriptan ODT group, so this may account for lower placebo response rates for at least these endpoints. Whether these differences represent an effect of education resulting in perceptual changes of symptoms or are truly a difference in the study population cannot be fully ascertained.

This study provides a unique integration of therapeutic efficacy of rizatriptan 10-mg ODT and patient-specific migraine education in early treatment of migraine while the headache pain is mild in intensity. Of note is that the population of subjects receiving rizatriptan plus education reported greater efficacy and satisfaction over subjects receiving rizatriptan or placebo without education. As described earlier, for participants randomized to receive education, a standardized procedure and script was used to elicit the participant's individual migraine characteristics when their headache is mild. This discussion and education presumably improved the ability of the participant to know what a qualifying study migraine attack may feel like. The educational intervention took approximately 15 minutes to administer.

The group receiving the educational intervention reported numerically greater pain-free efficacy at 2 hours than those in the no-education group. In addition, there was improved efficacy of all associated symptoms with education compared with no education, as well as a reduction of the need for rescue medications and greater satisfaction with treatment. None of these results reached statistical significance, however, because the study was not powered sufficiently to detect a difference in a population of this size. Nonetheless, the fact that numerical superiority was observed with several of our outcome measures increases the probability that a true difference exists between the education and noneducation groups. Further studies with larger sample sizes will need to be performed to confirm these preliminary findings.

Of interest is the observation that the patient-specific migraine education did not increase placebo response despite the fact that subjects received a

significant amount of attention and extra time from the HCP to administer the intervention. This lack of nonspecific therapeutic effect may be due to the focused and highly structured nature of the migraine educational interaction in addition to the reminder of the potential of receiving placebo in the randomized clinical trial. Participants were engaged in a manner that considered them “partners” in the research study, and making objective observations about their migraine and treatment response was encouraged. It is the authors’ hope that the positive benefits observed in this study without elevation of placebo rates will encourage inclusion of patient-specific migraine education in future pharmacologic treatment studies.

## CONCLUSION

Rizatriptan 10-mg ODT, when taken early during a migraine attack, while pain is mild, was superior to placebo at providing pain freedom at 2 hours and sustained pain freedom from 2 to 24 hours post-dose. Rizatriptan 10-mg ODT also effectively reduced migraine-associated symptoms and functional disability compared with placebo. Patient-specific migraine education appears to enhance pharmacologic treatment and may increase both efficacy and subject satisfaction.

*Acknowledgments: The following investigators participated in the MAXALT Protocol 081 study: Hartmut Goebel (Kiel, Germany), Volker Pfaffenrath (Muenchen, Germany), Guenther Schumann (Bochum, Germany), Tanya Bilchik (East Hartford, CT, USA), Roger Cady (Springfield, MO, USA), Daniel Groblewski (Jacksonville, FL, USA), Steven Herzog (Dallas, TX, USA), David Morin (Bristol, TN, USA), Lawrence Robbins (Northbrook, IL, USA), Noah Rosen (Manhasset, NY, USA), Vernon Rowe (Overland Park, KS, USA), Sara Sacco (Charlotte, NC, USA), and Stuart Stark (Alexandria, VA, USA).*

*The authors thank the following for their contributions to the conduct of the study: Eleanor Schaefer, Cristin Byrne, Benjamin Lanning, Ines Klaudius, Li Liu, Richard Mayewski, Casey McDermott, Amanda Murakami, and Makenzie Newman. The authors also thank Sheila Erespe and Jennifer Pawlowski for assistance with manuscript formatting and submission.*

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