

# Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies

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## Cephalalgia

Mannix LK, Loder E, Nett R, Mueller L, Rodgers A, Hustad CM, Ramsey KE & Skobieranda F. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies. *Cephalalgia* 2007; 27:414–421. London. ISSN 0333-1024

These are the first prospective studies to use criteria for menstrual migraine proposed in the 2004 revision of the International Classification of Headache Disorders (ICHD-II) to examine the efficacy of rizatriptan for treatment of a menstrual attack. Two identical protocols (MM1 and MM2) were randomized, parallel, placebo-controlled, double-blind studies. Adult women with ICHD-II menstrual migraine were assigned to either rizatriptan 10-mg tablet or placebo in a 2:1 ratio. Patients treated a single menstrual migraine attack of moderate or severe pain intensity. The primary end-point was 2-h pain relief and the secondary end-point was 24-h sustained pain relief. A total of 707 patients (MM1 357, MM2 350) treated a menstrual migraine attack. The percentage of patients reporting 2-h pain relief was significantly greater for rizatriptan than for placebo (MM1 70% vs. 53%, MM2 73% vs. 50%), as was the percentage of patients reporting 24-h sustained pain relief (MM1 46% vs. 33%; MM2 46% vs. 33%). Rizatriptan 10 mg was effective for the treatment of ICHD-II menstrual migraine, as measured by 2-h pain relief and 24-h sustained pain relief. □ *Clinical trial, menstrual migraine, migraine, rizatriptan*

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## Introduction

Migraine attacks occur as acute, intermittent events with many well-recognized trigger factors. Menses is frequently cited as a trigger factor for female migraineurs (1, 2) and, in consulting populations, it is commonly believed that migraine attacks that occur during the perimenstrual period may be more refractory to treatment. Until recently, there has been no consistently applied definition of menstrual migraine (MM) in clinical trials; in previous studies, the perimenstrual window ranged from beginning within one to several days before the onset of menses

and up to several days after onset of menses (3). In 2004, the International Headache Society (IHS) revised the International Classification of Headache Disorders (ICHD-II) guidelines to include proposed research criteria for MM in the Appendix (4). According to this definition, MM refers to attacks of migraine without aura that occur on day  $1 \pm 2$  (i.e. days  $-2$  to  $+3$ ) of menstruation in at least two of three menstrual cycles. Two subtypes are described. In pure menstrual migraine (PMM), attacks occur exclusively with menstruation and at no other times of the cycle. In menstrually related migraine (MRM), attacks may also occur at other times of the cycle.

Few studies have looked specifically at treatment of menstrual migraine. Previous retrospective and prospective trials with sumatriptan (5, 6), zolmitriptan (7) and rizatriptan (8, 9) have studied treatment efficacy in MM subgroups; results of these studies have shown that these triptans were effective at treating MM, as measured by pain relief at 2 or 4 h. The retrospective studies, however, examined MM attacks that were merely coincidental to the menstrual period; the antecedent history of migraine attacks as a prevalent feature of the menstrual period, as suggested in the 2004 ICHD-II research criteria, was not reported. Recent prospective studies of sumatriptan (10, 11), zolmitriptan (7) and naratriptan (12) for the treatment of MM (using different definitions of the perimenstrual period) have also demonstrated efficacy. A prospective subgroup analysis of the rizatriptan Treat A Migraine Early (TAME) studies, in which patients were instructed to treat a migraine attack within 1 h of onset, while the pain was still mild, demonstrated efficacy in the subgroup of patients who (i) had a history of ICHD-II MM and (ii) elected to treat a menstrual attack as the study attack (13, 14). The studies reported here—the first prospective studies to use the 2004 ICHD-II diagnostic criteria for MM—were performed to compare the efficacy of rizatriptan 10 mg with placebo in the treatment of MM, as defined by the newly proposed ICHD-II criteria. The results of each trial are presented separately; the data were not pooled for these analyses.

## Methods

### *Patients*

Women aged  $\geq 18$  years who had both a  $\geq 6$ -month history of ICHD-II migraine and a  $\geq 6$ -month history of MM as proposed in the 2004 update of ICHD-II guidelines were eligible for the studies. Additionally, a history of monthly menses and a recent history of MM occurrence in at least two of the most recent three menstrual periods were required. If MM typically preceded menstrual flow, the patient attested to her ability to predict the onset of menstrual flow within 1 day. Patients had to agree to use adequate contraception during the study. Patients with other headache disorders were required to be able to distinguish clearly migraine attacks from other headaches. Patients with ischaemic heart disease, uncontrolled hypertension, coronary artery vasospasm (including Prinzmetal's variant angina) or other significant underlying cardiovascular disease were excluded. Patients agreed

to discontinue using monoamine oxidase inhibitors and propranolol 2 weeks before receiving study medication; any 5-HT<sub>1B/1D</sub> agonist, ergot-type medication (e.g. methysergide, dihydroergotamine), opiates or barbiturates 24 h before receiving study medication; and non-opiate analgesics and antiemetics 6 h before receiving study medication. Patients using agents for perimenstrual migraine prophylaxis were excluded. In addition, daily analgesics taken for any reason were not permitted (except for aspirin  $\leq 325$  mg/day for cardioprotection). Patients were not eligible to participate in both studies.

### *Study design*

A Scientific Advisory Committee comprising headache medicine physicians and Merck & Co., Inc. clinical research professionals developed the protocols, formulated the statistical analysis plan, analysed and interpreted the data and authored this report. Protocols 071 (MM1) and 072 (MM2) were identical, randomized, parallel, placebo-controlled, double-blind studies. MM1 was conducted at 22 centres in the USA from June 2005 to February 2006. MM2 was conducted at 28 centres in the USA from June 2005 to March 2006. The protocols were approved by a central Institutional Review Board and all patients gave written informed consent to participate. Patients were randomly assigned to either rizatriptan 10-mg tablet or matching placebo in a 2:1 ratio using a computer-generated allocation schedule with a block size of six that was supplied by the sponsor. Patients were instructed to take the study medication to treat a single MM attack when the pain was moderate (Grade 2) or severe (Grade 3). Patients were allowed three menstrual cycles after randomization to treat a qualifying MM attack. Rescue medication was allowed for a non-responsive headache or a headache recurrence 2 h postdose.

### *Efficacy and safety end-points*

Patients rated baseline headache severity and functional disability immediately before taking study medication and at 30, 45, 60 and 90 min and at 2 and 4 h postdose and recorded that information in a diary. Headache severity was rated on a scale from 0 to 3: 0, no headache; 1, mild pain; 2, moderate pain; 3, severe pain. Functional disability was also rated on a scale from 0 to 3 (0, able to perform daily activities; 1, daily activities mildly impaired; 2, daily activities severely impaired; 3, unable to

carry out daily activities, requires bed rest). Patients recorded the presence of migraine-associated symptoms (photophobia, phonophobia, nausea and vomiting) at baseline and at all post-baseline time intervals. For the analysis of 24-h sustained pain relief, defined as pain relief at 2 h with no recurrence between 2 and 24 h and no use of any additional abortive migraine medications during that period, patients recorded the presence of headache between 2 and 24 h postdose and any medication taken for migraine headache up to 24 h after initial treatment. Patients recorded any adverse experiences occurring between enrolling in the study and the end-of-study visit.

### Statistical methods

#### Hypotheses

The primary hypothesis of these studies was that, in patients with MM, rizatriptan 10 mg would be superior to placebo, as measured by the percentage of patients with 2-h pain relief. A secondary hypothesis was that, in patients with MM, rizatriptan 10 mg would be superior to placebo, as measured by the percentage of patients with 24-h sustained pain relief.

#### Efficacy

The primary end-point for efficacy analysis was pain relief, defined as a reduction in headache severity from moderate or severe pain (Grade 2 or 3) at baseline to no pain or mild pain (Grade 0 or 1) at 2 h. The primary efficacy analysis used a modified intention-to-treat (mITT) approach, which included all randomized patients who had at least one pain severity rating within 2 h after taking the study medication. Missing values in the treatment phase were imputed by carrying forward the preceding on-treatment values, except that no imputations were made to missing values at baseline or at 30 min. A logistic regression model with factors for treatment group and baseline pain severity (moderate or severe) was used to compare treatment groups with respect to 2-h pain relief, as well as all other binary efficacy outcome measures. All treatment group comparison *P*-values based on the logistic regression model were summarized with the corresponding odds ratio (OR) and associated 95% confidence interval (CI).

With a projected 315 patients (210 for rizatriptan and 105 for placebo) satisfying criteria from both studies and assuming 2-h pain-relief rates of 68% and 56% for rizatriptan and placebo, respectively, there was 98% power to demonstrate superiority of

rizatriptan 10 mg compared with placebo with respect to 2-h pain relief and 92% power to demonstrate superiority of rizatriptan with respect to 24-h sustained pain relief, based on a two-sided  $\alpha$  level of 0.05.

### Tolerability and adverse events

All patients treated in the studies were included in the tolerability analysis. Tolerability was assessed by statistical and clinical review of the incidence of adverse events (AEs) and vital signs. The primary tolerability measurement was the incidence of AEs (overall, drug-related, serious and those causing discontinuation) reported by patients before taking any rescue medication. Pairwise comparisons of the incidence of AEs were conducted using Fisher's exact test. No multiplicity adjustment was used for the tolerability analysis.

## Results

### Patient accounting

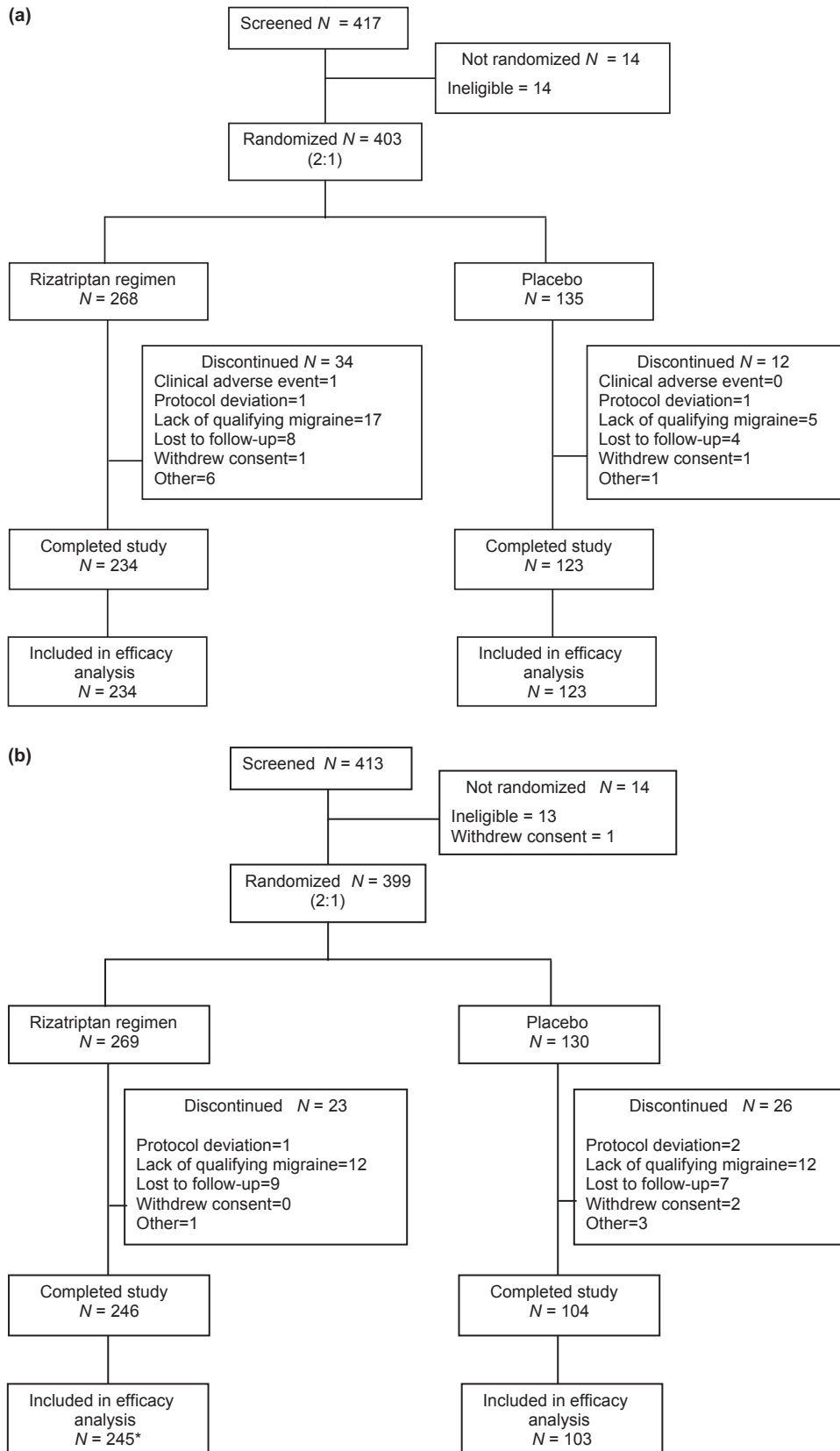
In MM1, 417 patients were screened, 403 patients were randomly assigned to treatment and 357 patients (89%) treated a qualifying migraine (Fig. 1a). In MM2, 413 patients were screened, 399 patients were randomly assigned to treatment and 350 (88%) treated a qualifying migraine (Fig. 1b). The most common reason cited for not treating was the lack of a qualifying migraine during the treatment period. All but two randomized patients who treated a migraine had at least one post-treatment diary headache severity assessment and were included in the primary efficacy analysis of 2-h pain relief (MM1 357 patients; MM2 348 patients).

### Demographics and baseline characteristics

The treatment groups were generally similar with respect to demographic characteristics (Table 1). The majority of patients were White. The median age was 37 years in both studies and ages ranged from 18 to 54 years.

### Efficacy

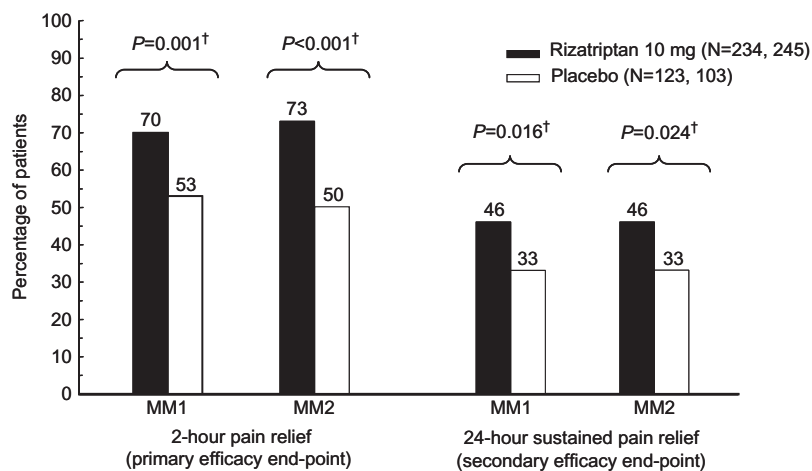
The results of both studies are presented separately; the data were not pooled for these analyses. The percentage of patients reporting pain relief at 2 h after taking study drug was significantly higher in the rizatriptan group compared with the placebo group, based on a logistic regression



**Figure 1** Patient accounting. (a) MM1. (b) MM2. \*One rizatriptan patient and one placebo patient completed the study but had no diary data.

**Table 1** Patient demographics and baseline characteristics

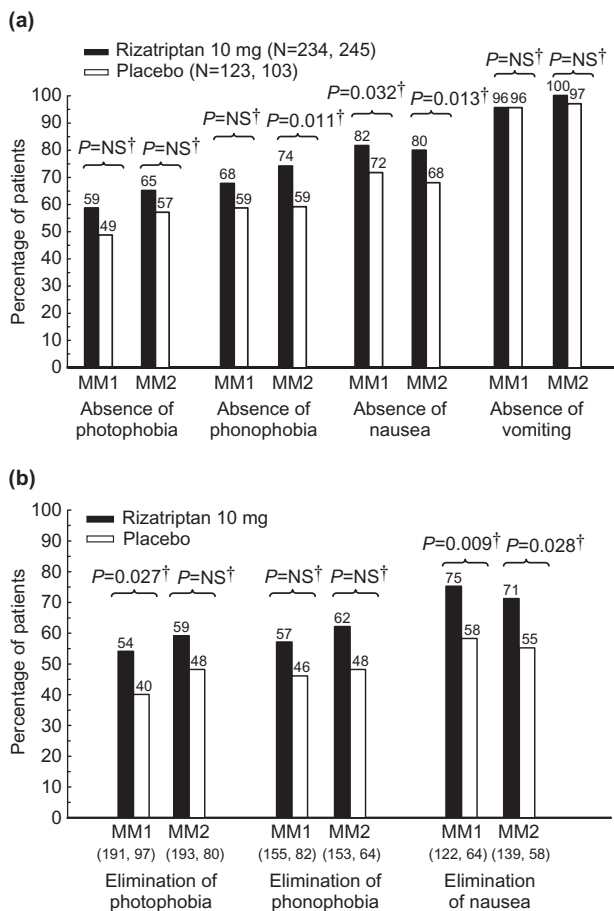
	MM1		MM2	
	Riza 10 mg N = 234	Placebo N = 123	Riza 10 mg N = 246	Placebo N = 104
Patient demographics				
Median age, years	38.0	37.0	37.0	37.5
Age >45 years, %	14.5	11.4	16.3	21.2
White, %	73.1	74.0	81.3	75.0
Prior triptan use, %				
At any time in the past	76.9	72.4	76.4	76.9
At study entry	43.6	40.7	54.5	49.0
Hormonal contraceptive/HRT	35.0	34.1	33.3	36.5
Pain severity at baseline, %				
Mild	3.0	4.1	2.8	3.8
Moderate	72.2	78.0	76.0	71.2
Severe	24.8	17.9	20.7	24.0
Functional disability, %				
Normal	6.4	4.9	6.9	8.7
Mildly impaired	57.3	63.4	61.0	51.9
Severely impaired	26.9	21.1	24.0	28.8
Unable to perform activities, bedrest	9.4	10.6	7.7	9.6
Associated symptoms, %				
Photophobia	81.6	78.9	78.5	76.9
Phonophobia	66.2	66.7	62.2	61.5
Nausea	52.1	52.0	56.5	55.8
Vomiting	3.8	2.4	3.7	2.9



**Figure 2** Two-hour pain relief and 24-h sustained pain relief in both MM1 and MM2. Bar graph showing the percentage of MM patients who reported 2-h pain relief (left) and the percentage of patients who reported 24-h sustained pain relief (right) after taking rizatriptan 10 mg (■) or placebo (□). †Rizatriptan 10 mg vs. placebo, *P*-value based on a logistic regression model including factors for treatment group and baseline pain severity (moderate or severe).

model including factors for treatment group and baseline pain severity (moderate or severe; Fig. 2; OR 2.11, 95% CI 1.34, 3.32,  $P=0.001$  in MM1; OR 2.69, 95% CI 1.66, 4.36,  $P<0.001$  in MM2). The percentage of patients reporting 24-h sustained

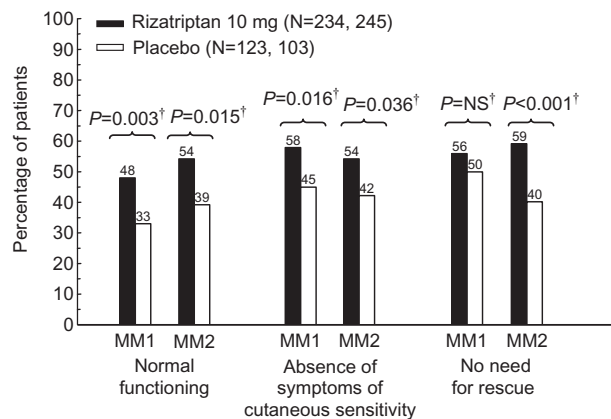
pain relief was also significantly higher in the rizatriptan group than in the placebo group (Fig. 2; OR 1.75, 95% CI 1.11, 2.77,  $P=0.016$  in MM1; OR 1.74, 95% CI 1.08, 2.82,  $P=0.024$  in MM2). Other efficacy end-points are shown in Figs 3a,3b and 4.



**Figure 3** (a) Associated symptoms at 2 h. Bar graph showing the percentage of MM patients who reported having the specified associated symptoms at 2 h after taking rizatriptan 10 mg (■) or placebo (□). †Rizatriptan 10 mg vs. placebo, *P*-value based on a logistic regression model including factors for treatment group and baseline pain severity (moderate or severe). NS, *P*-values >0.05. (b) Elimination of associated symptoms at 2 h. Bar graph showing the percentage of MM patients who reported having the specified associated symptoms at baseline, but not at 2 h after taking rizatriptan 10 mg (■) or placebo (□). †Rizatriptan 10 mg vs. placebo, *P*-value based on a logistic regression model including factors for treatment group and baseline pain severity (moderate or severe). NS, *P*-values >0.05.

**Tolerability**

Tolerability was evaluated in each treatment group by summarizing the number of AEs reported after treatment but before use of any rescue medication (primary approach for safety). The incidence of AEs [MM1: rizatriptan 18.8% (44 patients), placebo 11.4% (14 patients); MM2: rizatriptan 17.5% (43 patients), placebo 10.6% (11 patients)] and investigator-determined drug-related AEs [MM1: rizatriptan 15.0% (35 patients), placebo 5.7% (seven



**Figure 4** Supportive efficacy end-points at 2 h. Bar graph showing the percentage of MM patients who reported not needing rescue medication, not having any functional disability, or not having symptoms of cutaneous sensitivity at 2 h after taking rizatriptan (■) or placebo (□). †Rizatriptan 10 mg vs. placebo, *P*-value based on a logistic regression model including factors for treatment group and baseline pain severity (moderate or severe). NS, *P*-values >0.05.

patients); MM2: rizatriptan 13.0% (32 patients), placebo 5.8% (six patients)] was greater in the rizatriptan treatment group compared with the placebo group for both studies. There were no serious AEs reported in either study. The most common clinical AEs are listed in Table 2.

**Discussion**

There is a perception that MM attacks are more painful, longer lasting and more difficult to manage than non-menstrual attacks. Recent studies in treatment-seeking women support this view, but this is less clearly true in the general population of women with migraine (15). In a study of 155 women in a specialized migraine clinic, MacGregor and Hackshaw (16) found that the risk of migraine was greater during the perimenstrual period and that women reported MM as more severe and more associated with nausea and vomiting. Granello et al. (17) studied women with menstrually related migraine who were referred to tertiary care centres and reported that attacks during the perimenstrual period were of longer duration and greater intensity. Martin and colleagues (18) found that abortive medication use was greater for treatment of migraine during the perimenstrual time period when compared with other periods of the menstrual cycle. Dowson et al. (19) found a trend for migraine headaches concurrent with menses to be more disabling than those occurring at other times

**Table 2** Clinical adverse events  $\geq 2\%$  in any treatment group

	MM1		MM2	
	Rizatriptan %	Placebo %	Rizatriptan %	Placebo %
Dry mouth	2.1	1.6	2.4	3.8
Fatigue	1.7	1.6	2.4	0
Dizziness	3.8	0.8	2.0	0
Paraesthesia	0.4	0.8	2.0	0
Somnolence	3.0	0	2.0	1.9

of the menstrual cycle. Although the findings cited did not involve all menstrual migraineurs as defined by the new ICHD-II criteria, it is commonly believed that, for some women, MM is more severe, disabling and refractory to abortive treatment than non-MM.

To our knowledge, these are the first studies to use the newly proposed ICHD-II MM research criteria. These criteria, by convention, exclude patients with aura. Applying these criteria did not appear to affect the recruitment of patients for these trials, which was not more difficult than for trials in the general migraine population. The current studies examined the efficacy of rizatriptan 10 mg for the treatment of MM and demonstrated that rizatriptan was superior to placebo, as measured by 2-h and 24-h pain relief. Other efficacy end-points were consistent with the hypothesized 2-h and 24-h efficacy end-points. Across the two studies, the difference between rizatriptan and placebo reached statistical significance for some end-points and revealed a non-significant trend in others.

The efficacy of rizatriptan for the treatment of MM in these studies was similar to that seen for the treatment of migraine demonstrated in the rizatriptan pivotal registration trials (20), although it is important to note that we did not directly compare menstrual and non-menstrual efficacy in the current studies. These studies are consistent with the existing retrospective data for rizatriptan, in which efficacy was unaffected by relationship to menses. Although not intended as a validation study for the proposed MM criteria, this study may serve as a frame of reference for future studies of ICHD-II MM.

It is interesting to note that a large placebo effect rate was seen in both of these trials. There are several possible explanations. One explanation, which has been seen in other triptan trials (21), may be a higher placebo response rate with younger age. A posthoc exploratory analysis revealed a treatment-by-age interaction driven primarily by a

lower response among older (age >45 years) vs. younger patients in the placebo group; the current trials enrolled a substantially smaller proportion (13% in MM1 and 18% in MM2) of older patients (age >45 years) than were enrolled, for example, in the pivotal trials (~31%). A second explanation may be that patients in the current trials treated a greater proportion of moderate (and smaller proportion of severe) headache than that seen in the pivotal trials; the placebo effect was greater in those patients with moderate (and not severe) headache at baseline.

A limitation of this study is the perception that MM is a more severe and/or more difficult-to-treat form of migraine. Though ample evidence supports this belief in women who consult because of such headaches (22), the efficacy of rizatriptan in these studies of MM is consistent with the efficacy of rizatriptan in the pivotal trials in migraine, and this finding could support the hypothesis that treatment response of this subtype of migraine is not significantly different than that of non-MM attacks. Future studies that directly compare menstrual and non-menstrual attacks within the same patient, in both treatment-seeking and general population subgroups, would help address this unresolved issue.

## Acknowledgements

These studies were sponsored by Merck & Co., Inc., West Point, PA, USA. The lead author had free access to all data and analyses. Statistical analysis was provided by Merck & Co., Inc. The following investigators participated in the MAXALT Protocol 071 (MM1) and Protocol 072 (MM2) studies: JU Adelman, Greensboro, NC; SK Aurora, Seattle, WA; GD Berman, Plymouth, MN; JL Brandes, Nashville, TN; R Cady, Springfield, MO; AH Calhoun, Chapel Hill, NC; JR Couch, Oklahoma City, OK; JW Dean, Tulsa, OK; SE DeRossett, Decatur, GA; ML Diamond, Chicago, IL; CA Foster, Phoenix, AZ; BM Frishberg, Oceanside, CA; J Goldstein, San Francisco, CA; G Ishkanian, Mt Vernon, NY; RG Kaniecki, Pittsburgh, PA; LC Kirby, II, Peoria, AZ; SF Knox, Sacramento, CA; DB Kudrow, Santa Monica, CA;

RS Kunkel, Cleveland, OH; HA Leonard, Portland, OR; SM Lucas, Seattle, WA; LK Mannix, West Chester, OH; DA Marcus, Pittsburgh, PA; VT Martin, Cincinnati, OH; NT Mathew, Houston, TX; A Mauskop, New York, NY; L Mueller, Stratford, NJ; P Nikpey, Charlottesville, VA; CP O'Carroll, Newport Beach, CA; FJ O'Donnell, Westerville, OH; N Ramadan, North Chicago, IL; AM Rapoport, Stamford, CT; LD Robbins, Northbrook, IL; JF Rothrock, Mobile, AL; GE Ruoff, Kalamazoo, MI; JR Saper, Ann Arbor, MI; TR Smith, Chesterfield, MO; ELH Spierings, Wellesley Hills, MA; SR Stark, Alexandria, VA; RM Stewart, Dallas, TX; CB Strout, Mt Pleasant, SC; FR Taylor, Minneapolis, MN; GE Tietjen, Toledo, OH; JJ Tomasovic, San Antonio, TX; MM Tuchman, Palm Beach Gardens, FL; RD Verson, Columbus, GA; TN Ward, Lebanon, NH; SD Wheeler, Hialeah, FL; M-C. Wilson, Tampa, FL; WB Young, Philadelphia, PA. The authors thank Susan Macera for assistance with the execution of the study.

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