

# Erenumab in chronic migraine with medication overuse

## Subgroup analysis of a randomized trial

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## Abstract

### Objective

To determine the effect of erenumab, a human anti-calcitonin gene-related peptide receptor monoclonal antibody, in patients with chronic migraine and medication overuse.

### Methods

In this double-blind, placebo-controlled study, 667 adults with chronic migraine were randomized (3:2:2) to placebo or erenumab (70 or 140 mg), stratified by region and medication overuse status. Data from patients with baseline medication overuse at baseline were used to assess changes in monthly migraine days, acute migraine-specific medication treatment days, and proportion of patients achieving  $\geq 50\%$  reduction from baseline in monthly migraine days.

### Results

Of 667 patients randomized, 41% ( $n = 274$ ) met medication overuse criteria. In the medication overuse subgroup, erenumab 70 or 140 mg groups had greater reductions than the placebo group at month 3 in monthly migraine days (mean [95% confidence interval]  $-6.6$  [ $-8.0$  to  $-5.3$ ] and  $-6.6$  [ $-8.0$  to  $-5.3$ ] vs  $-3.5$  [ $-4.6$  to  $-2.4$ ]) and acute migraine-specific medication treatment days ( $-5.4$  [ $-6.5$  to  $-4.4$ ] and  $-4.9$  [ $-6.0$  to  $-3.8$ ] vs  $-2.1$  [ $-3.0$  to  $-1.2$ ]). In the placebo and 70 and 140 mg groups,  $\geq 50\%$  reductions in monthly migraine days were achieved by 18%, 36% (odds ratio [95% confidence interval] 2.67 [1.36–5.22]) and 35% (odds ratio 2.51 [1.28–4.94]). These clinical responses paralleled improvements in patient-reported outcomes with a consistent benefit of erenumab across multiple measures of impact, disability, and health-related quality of life. The observed treatment effects were similar in the non-medication overuse subgroup.

### Conclusions

Erenumab reduced migraine frequency and acute migraine-specific medication treatment days in patients with chronic migraine and medication overuse, improving disability and quality of life.

### Clinicaltrials.gov identifier

NCT02066415.

### Classification of evidence

This study provides Class II evidence that erenumab reduces monthly migraine days at 3 months in patients with chronic migraine and medication overuse.

### MORE ONLINE

#### → Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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## Glossary

**AE** = adverse event; **CGRP** = calcitonin gene-related peptide; **CI** = confidence interval; **CM** = chronic migraine; **eDiary** = electronic diary; **HIT-6** = Headache Impact Test; **HRQOL** = health-related quality of life; **MIDAS** = Migraine Disability Assessment; **MMD** = monthly migraine days; **MSQ** = Migraine-Specific Quality-of-Life Questionnaire; **PREEMPT** = Phase 3 Research Evaluating Migraine Prophylaxis Therapy; **PRO** = patient-reported outcome.

Patients with chronic migraine (CM) are a difficult-to-treat population.<sup>1</sup> In an attempt to manage their symptoms, patients with CM commonly overuse acute medications, including simple and combination analgesics, triptans, and opioids.<sup>2,3</sup> Such medication overuse is a risk factor for chronification<sup>4,5</sup> and can lead to medication overuse headache.<sup>6</sup> Medication overuse is defined by excessive use of medications to treat acute symptoms of migraine and is not based on a diagnosis of medication overuse headache, which is a secondary headache disorder.

Patients with CM and medication overuse represent a population with a high unmet need. Debated treatment approaches include withdrawal from the implicated acute treatment, initiation of a preventive treatment, or both.<sup>7-9</sup> It remains unclear whether migraine preventive treatments can reduce acute medication use or lower the risk of medication overuse headache.

Erenumab (in the United States, erenumab-aooe) is a fully human anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody approved for migraine prevention<sup>10</sup> with demonstrated clinically relevant efficacy in CM.<sup>11</sup> CGRP is implicated in migraine pathophysiology, and its levels are elevated in CM.<sup>12-14</sup> A 3-month pivotal trial in CM prevention demonstrated reduced monthly migraine days (MMD) for both 70- and 140-mg erenumab dose groups and reduced acute medication use, including migraine-specific medications (triptans, ergot derivatives).<sup>15</sup> Here, we report the results of a planned subgroup analysis of a hard-to-treat patient population, those with and without medication overuse (a study stratification factor), using data from a pivotal study of erenumab prevention in patients with CM.

## Methods

The objective of this subgroup analysis was to assess the efficacy of erenumab in patients with CM in the presence and absence of medication overuse. This study provided Class II evidence of efficacy as assessed by reduction in MMD, reduction in acute migraine-specific medication use, and improvements in patient-reported outcomes (PROs).

### Patients and data source

This was a preplanned exploratory analysis of a pivotal study that evaluated efficacy and safety of erenumab in patients with CM ( $\geq 15$  headache days per month, of which  $\geq 8$  were

migraine days). The eligibility criteria, design, and primary results of the parent study were previously published.<sup>15</sup> Patients with opioid overuse ( $>12$  days during the 3 months before screening or  $>4$  days during baseline) were excluded from the study, and migraine preventive drugs were prohibited during the study and 2 months before baseline. The study comprised 667 participants randomized at 69 study sites worldwide.

Patients were randomized to 1 of 3 treatment arms in a 3:2:2 ratio (subcutaneous placebo, erenumab 70 mg, or erenumab 140 mg monthly [daily]), stratified by region (North America vs other) and medication overuse (yes or no) for a 3-month double-blind treatment phase.

This analysis used data from patients with and without medication overuse based on frequency of acute headache medication intake during the baseline period, defined with strict criteria according to International Headache Society guidelines for CM clinical trials and similar to those previously used in a study of onabotulinumtoxinA.<sup>16,17</sup> Briefly, medication overuse was defined as use of simple analgesics (non-narcotic analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs) for  $\geq 15$  days ( $>3$  d/wk in each week with at least 5 diary days), triptans for  $\geq 10$  days ( $>2$  d/wk in each week with at least 5 diary days), or combination therapy (any combination of triptans, ergot derivatives, analgesics, or simple analgesics with opiates or butalbital) for  $\geq 10$  days ( $>3$  d/wk in each week with at least 5 diary days) per month. This classification of medication overuse should not be interpreted as confirming a secondary diagnosis of medication overuse headache.

### Standard protocol approvals, registrations, and patient consents

The study was approved by an independent ethics committee or local institutional review board at each participating site, and written informed consent was obtained from all enrolled patients. The study was conducted in accordance with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice. This study was registered at Clinicaltrials.gov (NCT02066415).

### Outcome measures

We conducted efficacy assessments throughout the baseline and double-blind phases of the study, with key assessments at month 3 (during the last month of double-blind treatment phase). Patients used a daily electronic diary (eDiary) to report information about their migraine and nonmigraine

headaches, acute medication use, and PROs (including Headache Impact Test [HIT-6],<sup>18,19</sup> Migraine Disability Assessment [MIDAS; measured as 4-week recall period vs 3-month recall of standard MIDAS],<sup>20</sup> and Migraine-Specific Quality-of-Life Questionnaire [MSQ]).<sup>21,22</sup> Efficacy endpoints for the subgroup analysis included changes in MMD, changes in acute migraine-specific medication days, proportion of patients achieving  $\geq 50\%$  reduction in MMD, PRO measures (MSQ, HIT-6, MIDAS), and proportion of patients changing status from medication overuse to nonoveruse status. We evaluated safety by monitoring adverse events (AEs) (with MedDRA version 19.0),<sup>23</sup> serious AEs,<sup>24</sup> laboratory assessments, vital signs, ECGs, and anti-erenumab antibodies.

## Statistical analysis

All patients who received at least 1 dose of study drug and completed at least 1 postbaseline monthly eDiary measurement were included in the intent-to-treat analysis. Descriptive summaries are provided for efficacy outcomes. Adjusted analyses of efficacy outcomes used a generalized linear mixed model including treatment, visit, treatment-by-visit interaction, region stratification factor, and baseline value as covariates and assuming a first-order autoregressive covariance structure. Values of  $p$  were not adjusted for multiple comparisons. Analyses of medication overuse by visit and patient reported outcome measures by medication overuse subgroup were post hoc.

## Data availability

Qualified researchers may request data from Amgen clinical studies. Complete details are available at [amgen.com/datasharing](http://amgen.com/datasharing).

# Results

## Patients

Of 667 patients randomized, 41% ( $n = 274$ ) met the criteria for medication overuse. At baseline, a few differences between the medication overuse and nonoveruse subgroups were observed (table 1). The percentage of patients with prior treatment failure with at least 1 preventive treatment was higher in the medication overuse subgroup (75% vs 63%; table 1). The mean (SD) baseline MMD was 19.0 (4.5) days in the medication overuse subgroup and 17.3 (4.6) days in the nonoveruse subgroup. Although there was almost no difference in the percentage of patients using acute headache medications, the percentage of patients using acute migraine-specific medications was higher in the medication overuse subgroup (92% vs 68%; table 1), as was the mean number of days of monthly acute migraine-specific medication use (table 1).

## Outcomes

### Mean MMD with and without medication overuse

At month 3, the reduction in MMD was greater in the erenumab groups than in the placebo group in both the

medication overuse and non-medication overuse subgroups (figure 1). The least-squares mean (95% confidence interval [CI]) change from baseline in MMD in the non-medication overuse placebo group was  $-4.7$  ( $-5.5$  to  $-3.8$ ) vs  $-6.7$  ( $-7.8$  to  $-5.7$ ) in both the erenumab 70 mg and 140 mg groups, representing treatment differences of  $-2.0$  ( $-3.4$  to  $-0.7$ ). Respective MMD changes in the medication over use subgroup were  $-3.5$  ( $-4.6$  to  $-2.4$ ) vs  $-6.6$  ( $-8.0$  to  $-5.3$ ) for both erenumab doses, with treatment differences of  $-3.1$  ( $-4.8$  to  $-1.4$ ).

### $\geq 50\%$ Responder rates with and without medication overuse

The percentage of patients achieving  $\geq 50\%$  reductions in MMD was greater in the erenumab groups than in the placebo group in both the medication overuse and non-medication overuse subgroups (figure 1). In the nonoveruse subgroup, the  $\geq 50\%$  responder rates were 27% (placebo) vs 42% (70 mg odds ratio [95% CI] 1.95 [1.17–3.23]) and 46% (140 mg OR 2.25 [1.36–3.74]). In the medication overuse subgroup, the respective  $\geq 50\%$  responder rates were 18% (placebo) vs 36% (70 mg OR 2.67 [1.36–5.22]) and 35% (140 mg OR 2.51 [1.28–4.94]).

### Acute migraine-specific medication use days with and without medication overuse

Reduction in acute migraine-specific medication use days was greater in the erenumab groups than in the placebo group in both the medication overuse and nonoveruse subgroups (figure 2). Compared with a least-squares mean (95% CI) change from baseline in acute migraine-specific medication use of  $-1.2$  ( $-1.7$  to  $-0.8$ ) days in the non-medication overuse placebo group, the change in acute migraine-specific medication use was  $-2.1$  ( $-2.7$  to  $-1.5$ ) days vs  $-3.6$  ( $-4.2$  to  $-3.0$ ) days in the erenumab 70 mg or 140 mg groups, respectively. The treatment differences were  $-0.9$  ( $-1.6$  to  $-0.1$ ) (70 mg) and  $-2.4$  ( $-3.2$  to  $-1.6$ ) (140 mg). The respective changes in acute migraine-specific medication use days in the medication overuse subgroup were  $-2.1$  ( $-3.0$  to  $-1.2$ ) vs  $-5.4$  ( $-6.5$  to  $-4.4$ ) and  $-4.9$  ( $-6.0$  to  $-3.8$ ) with treatment differences of  $-3.3$  ( $-4.7$  to  $-1.9$ ) (70 mg) and  $-2.8$  ( $-4.2$  to  $-1.4$ ) (140 mg).

### Transition from medication overuse to nonoveruse

Erenumab treatment reduced the number of patients with overuse of acute migraine medication intake (figure 3 and table 2). Of patients who overused simple analgesics at baseline, 60% (15 of 25) in the 70 mg group and 71% (24 of 34) in the 140 mg group transitioned to nonoveruse status at month 3, compared with 52% (23 of 44) of patients in the placebo group. Of patients who overused triptans at baseline, 65% (61 of 94) in the 70 mg group and 54% (52 of 96) in the 140 mg group changed to nonoveruse status at month 3, compared with 33% (42 of 127) of patients in the placebo group. Of patients who overused combination therapy at baseline, 45% (47 of 105) in the 70 mg group and 59% (66 of 112) in the 140 mg group changed to nonoveruse status at

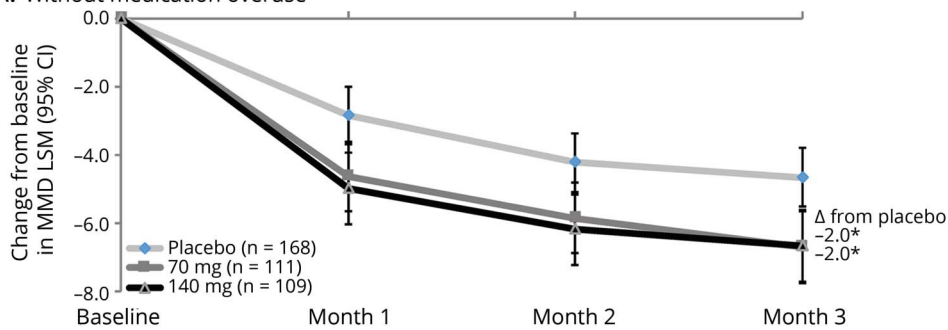
**Table 1** Demographics and baseline disease characteristics

	Without medication overuse				Medication overuse			
	Placebo (N = 169)	Erenumab 70 mg (N = 112)	Erenumab 140 mg (N = 112)	Total (N = 393)	Placebo (N = 117)	Erenumab 70 mg (N = 79)	Erenumab 140 mg (N = 78)	Total (N = 274)
<b>Age, y</b>	40.8 (11.8)	41.1 (11.5)	42.2 (11.1)	41.3 (11.5)	43.9 (10.4)	41.8 (11.2)	44.1 (10.3)	43.4 (10.8)
<b>Female, n (%)</b>	136 (81)	92 (82)	91 (81)	319 (81)	90 (77)	74 (94)	69 (89)	233 (85)
<b>White, n (%)</b>	156 (92)	100 (89)	108 (96)	364 (93)	112 (96)	76 (96)	76 (97)	264 (96)
<b>History of prior prophylactic failure,<sup>a</sup> n (%)</b>								
<b>Never failed preventive medication</b>	57 (34)	46 (41)	43 (38)	146 (37)	29 (25)	18 (23)	21 (27)	68 (25)
<b>Failed ≥1 preventive medications</b>	112 (66)	66 (59)	69 (62)	247 (63)	88 (75)	61 (77)	57 (73)	206 (75)
<b>Failed ≥2 preventive medications</b>	79 (47)	48 (43)	52 (46)	179 (46)	63 (54)	45 (57)	40 (51)	148 (54)
<b>Acute headache medication use at baseline, n (%)</b>								
<b>Migraine specific</b>	114 (68)	71 (63)	81 (72)	266 (68)	111 (95)	72 (91)	68 (87)	251 (92)
<b>Not migraine specific</b>	143 (85)	98 (88)	96 (86)	337 (86)	103 (88)	69 (87)	65 (83)	237 (87)
<b>Baseline period</b>								
<b>Monthly migraine days</b>	17.4 (4.7)	17.3 (4.2)	17.1 (4.7)	17.3 (4.6)	19.5 (4.5)	18.6 (4.6)	18.8 (4.5)	19.0 (4.5)
<b>Monthly migraine attacks</b>	4.5 (1.6)	4.6 (1.5)	4.4 (1.6)	4.5 (1.6)	3.9 (1.9)	4.5 (1.9)	4.2 (1.6)	4.1 (1.8)
<b>Monthly headache days</b>	20.4 (4.1)	19.9 (3.7)	20.2 (4.0)	20.2 (3.9)	22.1 (3.5)	21.3 (3.8)	21.5 (3.5)	21.7 (3.6)
<b>Monthly acute migraine-specific medication use days</b>	6.5 (6.3)	6.3 (6.4)	7.3 (6.1)	6.7 (6.3)	13.7 (7.3)	12.2 (6.7)	13.1 (6.9)	13.1 (7.0)

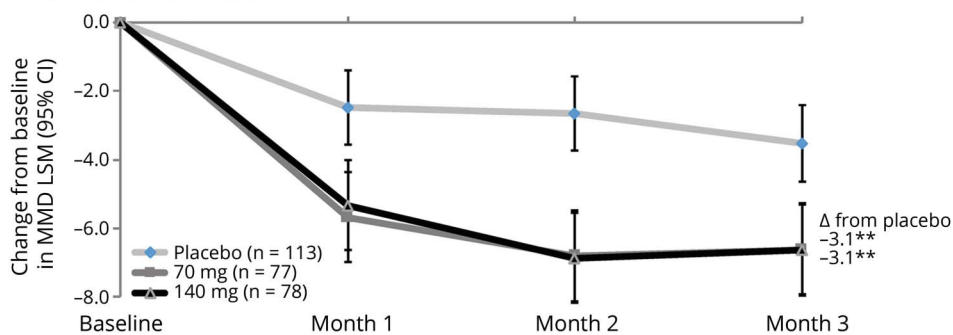
Abbreviation: N = number of patients randomized.  
 Data represent mean (SD) unless otherwise indicated.  
<sup>a</sup> Failure due to lack of efficacy or poor tolerability.

**Figure 1** Change from baseline in MMD over time

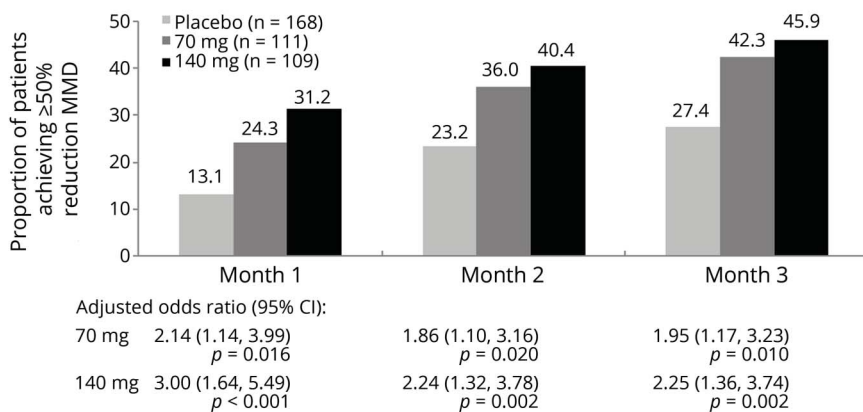
**A. Without medication overuse**



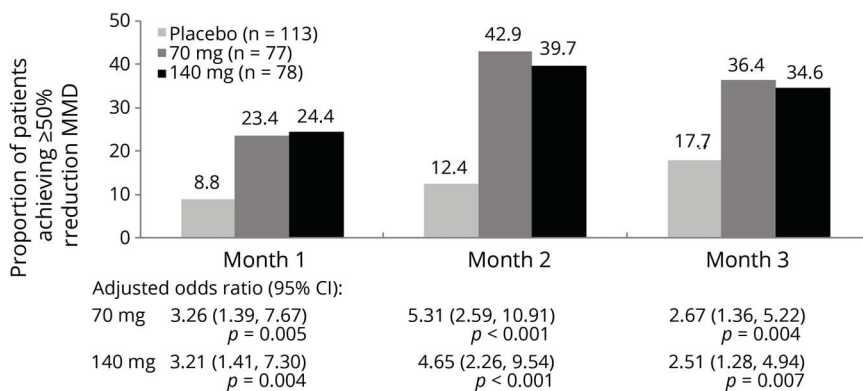
**B. With medication overuse**



**C. Without medication overuse**

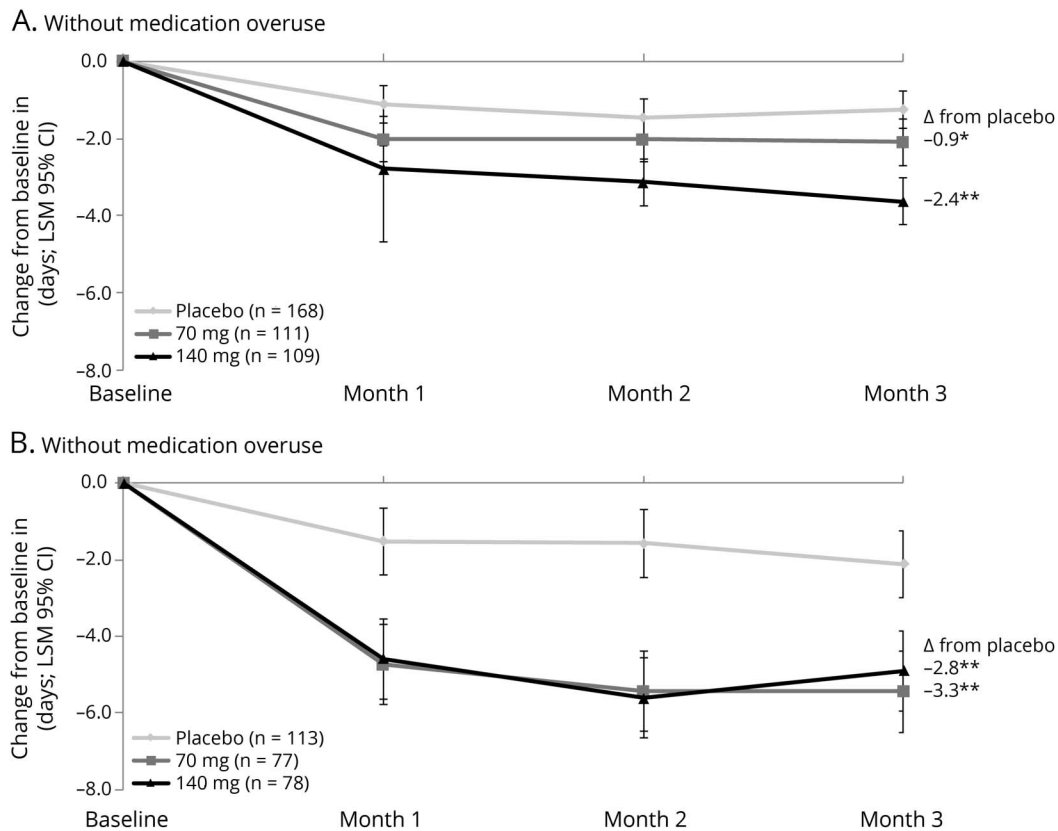


**D. With medication overuse**



Least-squares mean (LSM) changes from baseline in monthly migraine days (MMD) in patients (A) without and (B) with medication overuse among patients with chronic migraine (CM) who were assigned to receive placebo, erenumab 70 mg, or erenumab 140 mg every month. Error bars represent 95% confidence intervals (CIs). \* $p < 0.005$ , \*\* $p < 0.001$  for erenumab vs placebo. Proportion of patients (C) without and (D) with medication overuse who achieved  $\geq 50\%$  change from baseline in MMD among patients with CM who were assigned to receive placebo, erenumab 70 mg, or erenumab 140 mg every month.

**Figure 2** Change from baseline in acute migraine-specific medication treatment days over time



Least-squares mean (LSM) changes from baseline in acute migraine-specific medication treatment days in patients (A) without and (B) with medication overuse among patients with chronic migraine who were assigned to receive placebo, erenumab 70 mg, or erenumab 140 mg every month. Error bars represent 95% confidence intervals (CIs). \* $p < 0.05$ , \*\* $p < 0.001$  for erenumab vs placebo.

month 3, compared with 40% (70 of 176) of patients in the placebo group. Similar results were found when we assessed nonoveruse status over the full 3 months or over the last 2 months (table 2). More than half of the erenumab-treated patients who overused simple analgesics or triptans at baseline switched to nonoveruse status by month 1 (table 2). Of the 35 erenumab-treated patients who switched to nonoveruse of simple analgesics by month 1, 30 (86%) maintained nonoveruse status through all 3 months. Of the 112 erenumab-treated patients who switched to nonoveruse of triptans by month 1, 78 (70%) maintained nonoveruse status through all 3 months. Of the 78 erenumab-treated patients who switched to nonoveruse of combination therapy by month 1, 49 (63%) maintained nonoveruse status through all 3 months.

### Patient-reported outcomes

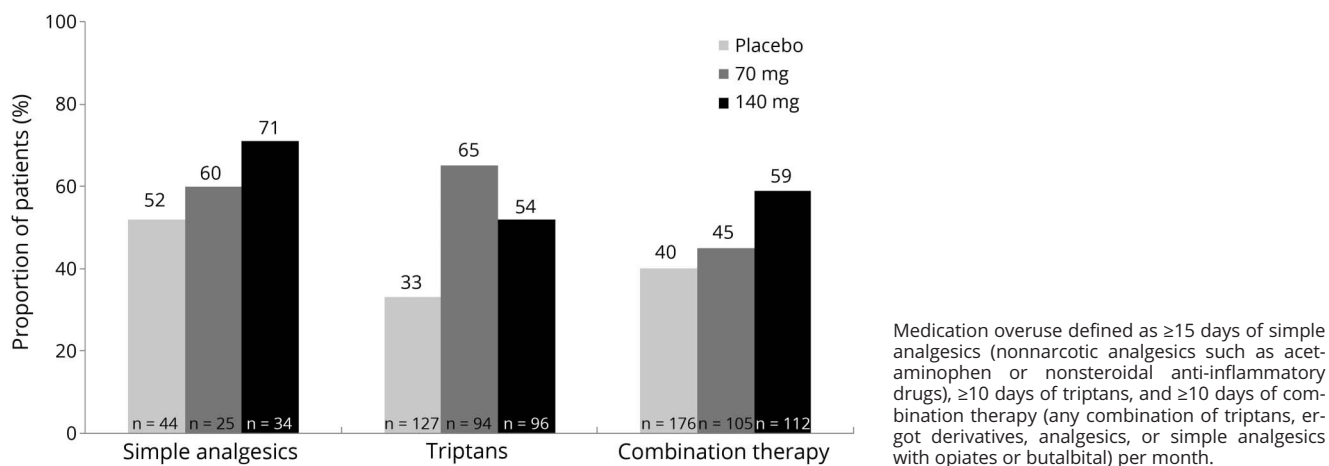
In the both subgroups, mean reduction (improvement) from baseline in total HIT-6 score was greater in the erenumab groups compared with the placebo group (table 3). Treatment difference for change in HIT-6 score at month 3 exceeded the established group-level minimally important difference for HIT-6 total score ( $\geq 2.3$ -point reduction). Reductions from baseline to month 3 in MIDAS total scores were greater in the erenumab groups compared with the

placebo group, indicating greater improvement. Differences from baseline in MIDAS total score were  $>5$  days, indicative of a clinically meaningful change.<sup>25</sup> Health-related quality of life (HRQOL) was measured by the change in MSQ scores from baseline. At month 3, changes from baseline were greater in the erenumab groups compared with the placebo group in each MSQ domain score in the non-medication overuse subgroup and in the medication overuse subgroup (table 3). The observed between-treatment-group differences exceeded the respective minimally important difference for the MSQ Role Function-Restrictive ( $\geq 3.2$ ) and MSQ Emotional Functioning ( $\geq 7.5$ ) domain scores in both the non-medication overuse and medication overuse subgroups.

### Adverse events

The safety profile and AE frequency in the full patient population were previously reported.<sup>15</sup> The frequency of AEs was similar among treatment groups and between the medication overuse and non-medication overuse subgroups, and most AEs reported were mild or moderate in severity (table 4). The most frequent AEs reported for the erenumab-treated patients ( $\geq 2\%$  of erenumab-treated patients) were injection site erythema, muscle spasms, migraine, injection site pain,

**Figure 3** Proportion of patients with medication overuse at baseline who changed status to non-medication overuse at month 3, by acute medication category



constipation, cough, oropharyngeal pain, upper respiratory tract infection, nausea, and nasopharyngitis.

## Discussion

Patients with CM who overuse acute headache medications are often difficult to treat and represent a large unmet need commonly encountered in clinical practice. Patients in this study were stratified by medication overuse on the basis of a daily eDiary completed over the 4-week baseline period in which frequency counts of acute medication intake were recorded (and should not be interpreted as having a confirmed secondary headache diagnosis of medication overuse headache). More than 40% of the patients in this study had medication overuse during the baseline period, lower than the estimated 68% to 75% of patients with CM as previously reported in a recent clinic-based study and the Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials of onabotulinumtoxinA for CM prevention and the European topiramate CM prevention study<sup>3,16,26,27</sup> but similar to 37% observed in the US topiramate CM prevention study.<sup>27,28</sup>

In both the medication overuse and non-medication overuse subgroups, erenumab treatment resulted in a significant clinical response with a larger reduction in MMD and acute migraine-specific medication treatment days and a larger percentage of patients achieving a  $\geq 50\%$  response rate compared with placebo. The treatment differences appeared to be greater in the medication overuse subgroup than in the non-medication overuse subgroup; however, the absolute treatment effect was the same between the 2 groups. The placebo response was lower in the medication overuse subgroup, resulting in an odds ratio of achieving a  $\geq 50\%$  response comparable to or slightly higher than that of the non-medication overuse group. Even

though all patients did not achieve this clinical endpoint, it is important to note that the  $\geq 50\%$  response, widely accepted by clinicians, is an arbitrary threshold and does not represent all patients who had a clinical improvement. In a separate analysis from this study, we showed that although  $\approx 40\%$  of patients achieved a  $\geq 50\%$  response,  $\approx 50\%$  to 60% achieved clinically meaningful changes in PRO scores.<sup>29</sup> This was similar to the PREEMPT studies with onabotulinumtoxinA in which 27% of treated participants had a  $\geq 5$ -point reduction in HIT-6 score and a  $\geq 50\%$  reduction in headache days.<sup>30</sup> Thus, a reduction in severity of a migraine may be sufficient to improve the quality of life for patients, which would not necessarily be reflected in the 50% responder rate data. However, even then not all patients may respond to treatments that are highly effective in other patients.

Regardless of the causal effect of medication overuse in migraine prevention, CM with medication overuse represents a severe form of migraine and can be difficult to treat.<sup>31</sup> In this study, the medication overuse subgroup had a higher use of preventive medications at baseline and a higher percentage who failed to respond to 1 or 2 prior preventive treatments, indicative of a more severe subgroup of patients.

To more completely understand the clinical meaningfulness of new therapeutics for a chronic disease, it is necessary to assess outcomes of measures of efficacy, safety, and HRQOL in patients with potentially different responses to therapy. The clinical responses observed in this subgroup analysis paralleled improvements in PROs with a consistent benefit of erenumab across multiple measures of impact (HIT-6), disability (MIDAS), and HRQOL (MSQ). These data demonstrate that the rapid reductions in migraine frequency are accompanied by early improvements in ability to perform daily activities and lessened feelings of hopelessness or frustration or impact of CM.

**Table 2** Proportion of patients transitioning from medication overuse to non-medication overuse status by medication category

	Medication overuse		
	Placebo (N = 113)	Erenumab 70 mg (N = 77)	Erenumab 140 mg (N = 78)
<b>Simple analgesics, N1</b>	44	25	34
<b>Month 1, n (%)</b>	22 (50.0)	13 (52.0)	22 (64.7)
<b>Month 2, n (%)</b>	24 (54.5)	15 (60.0)	25 (73.5)
<b>Month 3, n (%)</b>	23 (52.3)	15 (60.0)	24 (70.6)
<b>Over months 2-3, n (%)</b>	27 (61.4)	16 (64.0)	26 (76.5)
<b>Over months 1-3, n (%)</b>	25 (56.8)	17 (68.0)	27 (79.4)
<b>Odds ratio (95% CI)</b>		1.4 (0.5-3.9)	2.9 (1.1-7.9)
<b>p Value</b>		0.59	0.03
<b>All 3 mo,<sup>a</sup> n (%)</b>	16 (36.4)	11 (44.0)	19 (55.9)
<b>Odds ratio (95% CI)</b>		1.2 (0.4-3.3)	2.3 (0.9-5.7)
<b>p Value</b>		0.73	0.075
<b>Triptans, N1</b>	127	94	96
<b>Month 1, n (%)</b>	37 (29.1)	58 (61.7)	54 (56.3)
<b>Month 2, n (%)</b>	38 (29.9)	54 (57.4)	57 (59.4)
<b>Month 3, n (%)</b>	42 (33.1)	61 (64.9)	52 (54.2)
<b>Over months 2-3, n (%)</b>	43 (33.9)	60 (63.8)	57 (59.4)
<b>Over months 1-3, n (%)</b>	41 (32.3)	61 (64.9)	56 (58.3)
<b>Odds ratio (95% CI)</b>		3.9 (2.2-6.9)	2.9 (1.7-5.1)
<b>p Value</b>		<0.001	<0.001
<b>All 3 mo,<sup>a</sup> n (%)</b>	22 (17.3)	38 (40.4)	40 (41.7)
<b>Odds ratio (95% CI)</b>		3.2 (1.7-6.0)	3.3 (1.8-6.0)
<b>p Value</b>		<0.001	<0.001
<b>Combination, N1</b>	176	105	112
<b>Month 1, n (%)</b>	44 (25.0)	32 (30.5)	46 (41.1)
<b>Month 2, n (%)</b>	58 (33.0)	46 (43.8)	54 (48.2)
<b>Month 3, n (%)</b>	70 (39.8)	47 (44.8)	66 (58.9)
<b>Over months 2-3, n (%)</b>	58 (33.0)	49 (46.7)	67 (59.8)
<b>Over months 1-3, n (%)</b>	55 (31.3)	48 (45.7)	59 (52.7)
<b>Odds ratio (95% CI)</b>		1.8 (1.1-3.0)	2.5 (1.6-4.1)
<b>p Value</b>		0.02	<0.001
<b>All 3 mo,<sup>a</sup> n (%)</b>	32 (18.2)	17 (16.2)	32 (28.6)
<b>Odds ratio (95% CI)</b>		0.9 (0.5-1.7)	1.9 (1.1-3.3)
<b>p Value</b>		0.67	0.03

Abbreviations: CI = confidence interval; n, number of patients who converted to nonoveruser at postbaseline assessment; N = number of patients who received at least 1 dose of study drug and completed at least 1 postbaseline monthly electronic diary measurement; N1, number of patients who were medication overusers at baseline in the corresponding medication category; % = n/N1.

<sup>a</sup> Patients were nonoverusers in each of the 3 months of the double-blind treatment phase.



**Table 3** Patient-reported outcomes at month 3 in patients with chronic migraine by baseline medication overuse status

	Without medication overuse			Medication overuse		
	Placebo (N = 168)	Erenumab 70 mg (N = 111)	Erenumab 140 mg (N = 109)	Placebo (N = 113)	Erenumab 70 mg (N = 77)	Erenumab 140 mg (N = 78)
<b>HIT-6 total score (range: 36–78)</b>						
<b>Baseline score, mean (SD)</b>	63.0 (5.3)	63.0 (5.4)	62.2 (6.2)	63.8 (5.0)	63.9 (4.4)	63.3 (4.8)
<b>Change from baseline</b>	-3.4 (-4.4 to -2.3)	-6.0 (-7.2 to -4.6)	-5.8 (-7.1 to -4.6)	-2.9 (-4.1 to -1.7)	-5.2 (-6.7 to -3.7)	-5.4 (-6.9 to -3.9)
<b>Difference from placebo</b>		-2.6 (-4.2 to -1.0)	-2.5 (-4.1 to -0.8)		-2.3 (-4.2 to -0.3)	-2.5 (-4.4 to -0.6)
<b>p Value</b>		0.002	0.003		0.021	0.011
<b>MIDAS total score</b>						
<b>Baseline score, mean (SD)</b>	65.5 (58.2)	63.3 (47.5)	56.8 (49.4)	71.6 (52.7)	69.3 (43.4)	66.6 (55.7)
<b>Change from baseline</b>	-11.2 (-17.0 to -5.5)	-18.4 (-25.2 to 11.6)	-23.5 (-30.3 to -16.6)	-3.6 (-12.0 to 4.8)	-22.0 (-32.0 to -12.1)	-16.1 (-26.1 to -6.1)
<b>Difference from placebo</b>		-7.2 (-16.1 to 1.7)	-12.2 (-21.1 to -3.3)		-18.5 (-31.4 to -5.5)	-12.5 (-25.4 to 0.4)
<b>p Value</b>		0.11	0.007		0.005	0.058
<b>MSQ-RFR (range 0–100)</b>						
<b>Baseline score, mean (SD)</b>	43.8 (17.7)	46.0 (19.4)	46.8 (20.3)	41.3 (17.4)	42.9 (16.5)	43.7 (17.3)
<b>Change from baseline</b>	12.0 (9.0–15.1)	18.4 (14.7–22.1)	20.6 (16.8–24.3)	11.7 (8.0–15.4)	17.1 (12.6–21.5)	17.4 (13.0–21.9)
<b>Difference from placebo</b>		6.4 (1.6–11.2)	8.5 (3.7–13.3)		5.4 (-0.4 to 11.2)	5.7 (0.0–11.51)
<b>p Value</b>		0.009	<0.001		0.069	0.051
<b>MSQ-RFP (range 0–100)</b>						
<b>Baseline score, mean (SD)</b>	59.9 (1.6)	60.6 (2.1)	64.2 (2.1)	60.8 (19.5)	63.8 (21.6)	61.1 (20.0)
<b>Change from baseline</b>	10.0 (7.3–12.7)	14.2 (11.0–17.5)	16.7 (13.4–20.0)	7.7 (4.4–11.1)	11.6 (7.6–15.6)	10.5 (6.5–14.4)
<b>Difference from placebo</b>		4.3 (0.0–8.5)	6.8 (2.5–11.0)		3.9 (-1.3 to 9.0)	2.7 (-2.4 to 7.9)
<b>p Value</b>		0.048	0.002		0.14	0.30
<b>MSQ-EF (range 0–100)</b>						
<b>Baseline score, mean (SD)</b>	52.4 (26.7)	55.6 (26.1)	57.7 (27.9)	53.8 (24.3)	50.8 (23.9)	55.4 (24.8)
<b>Change from baseline</b>	11.3 (7.9–14.8)	19.4 (15.3–23.5)	21.2 (17.1–25.4)	8.2 (4.2–12.2)	17.1 (12.3–21.9)	15.9 (11.1–20.7)

Continued

**Table 3** Patient-reported outcomes at month 3 in patients with chronic migraine by baseline medication overuse status (continued)

	Without medication overuse		Medication overuse	
	Placebo (N = 168)	Erenumab 70 mg (N = 111)	Placebo (N = 113)	Erenumab 140 mg (N = 78)
Difference from placebo		8.1 (2.7–13.4)	8.9 (2.7–15.1)	7.7 (1.5–13.9)
p Value		0.03	0.005	0.015

Abbreviations: HIT-6 = Headache Impact Test (higher score indicates worse outcome); MIDAS = Migraine Disability Assessment (higher score indicates worse outcomes); MSQ = Migraine-Specific Quality-of-Life Questionnaire (higher scores indicate better outcomes); MSQ-EF = Migraine-Specific Quality-of-Life Questionnaire Emotional Functioning; MSQ-RFP = Migraine-Specific Quality-of-Life Questionnaire Role Function-Preventive; MSQ-RFR = Migraine-Specific Quality-of-Life Questionnaire Role Function-Restrictive; N = number of patients who received at least 1 dose of study drug and completed at least 1 postbaseline monthly electronic diary measurement. Data represent least-squares mean (95% confidence interval) unless otherwise indicated.

A substantial proportion of patients who overused acute medications at baseline transitioned to nonoveruse status, regardless of the type of acute medication used. There was no meaningful difference in the proportion of patients who changed status over the full course of 3 months or during the final 2 months of the double-blind phase, indicating an early reduction in acute medication use. This early switch to nonoveruse status was supported by the number of patients with nonoveruse status at month 1. It is not known whether this is due to a decrease in the frequency of migraine days and improved HRQOL or whether it was due to high patient expectations of a new preventive treatment and reduced acute medication intake in anticipation of clinical benefit. Although not all patients changed to nonoveruse status, data from a 1-year open-label extension study with erenumab demonstrated a sustained reduction in acute migraine-specific medication treatment days in the overall population.<sup>32</sup> However, longer-term studies may be required to confirm the durability of the effect on reduced medication overuse.

Similar to these results, previous studies have examined the effect of migraine treatments, including topiramate and onabotulinumtoxinA, in patients with CM and medication overuse. In the European topiramate CM trial, there was a significant reduction in the mean number of MMD from baseline compared with placebo within the medication overuse subgroup of patients.<sup>26,27</sup> In the onabotulinumtoxinA analysis of pooled data from the PREEMPT trials, the efficacy results in the medication overuse subgroup were similar to those of the overall population with a significant reduction in frequency of headache days and other headache symptom measures, including PROs.<sup>16</sup> However, the analysis of the PREEMPT data did not include an analysis of the subgroup of CM patients without medication overuse. These results, along with the current study of erenumab, support that, contrary to previous suggestions, headache preventive medications are not necessarily limited by acute headache medication overuse.<sup>2,33</sup>

The AE and tolerability profiles in the medication overuse subgroup mirrored those observed for the full study population and were consistent with the safety and tolerability profiles observed in multiple studies with erenumab in patients with episodic and CM.<sup>15,34,35</sup> Longer-term studies are needed not just to determine the durability of the treatment effect but also to assess long-term safety. Longer follow-up periods in large numbers of patients are necessary to detect rare AEs and to fully understand the safety profile of erenumab. Particularly for patients with medication overuse, any interactions with triptans are a concern. In vitro studies have demonstrated that erenumab did not have an additive effect on human coronary artery vasoconstriction induced by triptans.<sup>36</sup> Furthermore, there was no effect of combination erenumab and sumatriptan on blood pressure compared to sumatriptan alone in a phase 1 study.<sup>37</sup> These studies, in combination with the decrease in triptan use, indicate a lack of effect of erenumab on the effectiveness of triptans as acute

**Table 4** Adverse events through month 3 by baseline medication overuse status

	Without medication overuse, n (%)			Medication overuse, n (%)		
	Placebo (N = 168)	Erenumab 70 mg (N = 111)	Erenumab 140 mg (N = 109)	Placebo (N = 113)	Erenumab 70 mg (N = 77)	Erenumab 140 mg (N = 78)
<b>Adverse events</b>	71 (42.3)	47 (42.3)	50 (45.9)	39 (34.5)	36 (46.8)	38 (48.7)
<b>Common adverse events (reported in ≥2% of erenumab-treated patients)</b>						
Injection site erythema	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.3)	5 (6.4)
Muscle spasms	4 (2.4)	0 (0.0)	2 (1.8)	0 (0.0)	1 (1.3)	5 (6.4)
Migraine	3 (1.8)	1 (0.9)	1 (0.9)	0 (0.0)	2 (2.6)	4 (5.1)
Injection site pain	1 (0.6)	4 (3.6)	5 (4.6)	2 (1.8)	3 (3.9)	2 (2.6)
Constipation	1 (0.6)	0 (0.0)	4 (3.7)	0 (0.0)	0 (0.0)	4 (5.1)
Cough	2 (1.2)	0 (0.0)	2 (1.8)	0 (0.0)	1 (1.3)	3 (3.8)
Oropharyngeal pain	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)	2 (2.6)	2 (2.6)
Upper respiratory tract infection	3 (1.8)	5 (4.5)	4 (3.7)	1 (0.9)	0 (0.0)	2 (2.6)
Nausea	2 (1.2)	4 (3.6)	4 (3.7)	5 (4.4)	0 (0.0)	2 (2.6)
Nasopharyngitis	10 (6.0)	4 (3.6)	2 (1.8)	6 (5.3)	2 (2.6)	1 (1.3)

Abbreviation: N = number of patients who received at least 1 dose of investigational product.

migraine treatment, which one would expect triptan use to increase.

Overall, these results demonstrate that erenumab is effective in patients with CM and medication overuse with clinical improvements in reduction of the frequency of migraines and with improvements in PROs across multiple measures of HRQOL, social and psychological impact, and disability in patients with CM.

### Author contributions

S.J. Tepper, H.-C. Diener, M. Ashina, J.L. Brandes, D.I. Friedman, U. Reuter, S. Cheng, D.K. Leonardi, D.D. Mikol: interpreted the data and revised the manuscript for content. D.K. Leonardi: performed statistical analysis. R.A. Lenz: involved in design of the study, interpreted the data, and revised the manuscript for content. J. Nilsen: wrote the first draft of the manuscript based on an outline developed with all coauthors and revised the manuscript for content.

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