RESEARCH SUBMISSIONS

Patient-identified most bothersome symptom in preventive migraine treatment with eptinezumab: A novel patient-centered outcome

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Abstract

Objectives: To describe the methodology and implications of the patient-identified most bothersome symptom (PI-MBS) measure used in the phase 3, multicenter, randomized, double-blind, placebo-controlled, and parallel-group PROMISE-2 trial and to evaluate the contribution of this measure to the assessment of the preventive migraine benefits of treatment.

Background: Although freedom from MBS is a coprimary endpoint in acute migraine treatment trials, its evaluation in preventive migraine trials is limited. The PROMISE-2 study assessed a unique PI-MBS measure as a secondary endpoint.

Methods: This was a secondary analysis of data from the PROMISE-2 study. Adults with chronic migraine (CM) were randomized to receive intravenous (IV) eptinezumab 100 mg, eptinezumab 300 mg, or placebo, administered on day 0 and every 12 weeks. At the screening visit, patients were asked to verbally describe the MBS associated with their CM; the question format was open ended. At subsequent visits, patients were asked to rate the overall change in severity of their MBS from study inception to that time point, using a 7-point ordinal scale ranging from "very much worse" (−3) to "very much improved" (+3). Patients completed the Patient Global Impression of Change (PGIC) assessment during the same visits, using an identical rating scale and recall period. Endpoints were summarized descriptively; post hoc correlations using the methodologies of Pearson and Spearman were calculated to evaluate relationships between PGIC and PI-MBS and between PGIC and mean monthly migraine days (MMDs; primary efficacy endpoint in PROMISE-2).

Results: Altogether, 1072 patients received treatment (eptinezumab 100 mg, *n* = 356; eptinezumab 300 mg, *n* = 350; placebo, *n* = 366) and were included in the analysis. There were 23 unique MBS identified; those reported by ≥10 patients included light sensitivity (18.7%), nausea/vomiting (15.1%), pain with activity (13.7%), pain (12.4%),

headache (11.2%), sound sensitivity (7.3%), throbbing/pulsating pain (4.7%), cognitive disruption (4.1%), fatigue (2.4%), mood changes (1.5%), and sensitivity to smell (0.9%). Four weeks after the first dose (week 4), the rates of much or very much improvement in PI-MBS were higher with eptinezumab 100 mg (45%) and 300 mg (57%) than with placebo (29%). Four weeks after the second dose (week 16), the proportions with much or very much improvement in PI-MBS had increased to 58%, 65%, and 36%, respectively. At each time point, the percentages of patients with PGIC ratings of much or very much improved were similar to those for patient-reported improvement in PI-MBS. Patient ratings of changes in PI-MBS and PGIC correlated strongly across time points (Pearson, r range, 0.83–0.88; Spearman, r range, 0.83–0.89); the absolute value of the correlations was greater than the correlation among changes in MMDs and PGIC (Pearson, r range, −0.49 to −0.52; Spearman, r range, −0.49 to −0.52).

Conclusions: Among patients with CM in the PROMISE-2 study, a broad range of PI-MBS was reported at baseline. Throughout the study, patients treated with eptinezumab reported greater improvement in their PI-MBS severity compared with placebo recipients, and this improvement correlated strongly with PGIC findings. Collectively, these results indicate that PI-MBS is a promising and novel outcome measure for preventive trials of CM and thus may provide a unique patient-centered approach for identifying and measuring the burden of migraine symptoms that matter most to each patient, as well as the benefits of treatment.

INTRODUCTION

Migraine is a complex disorder characterized by paroxysmal attacks of disabling symptoms such as headache, sensory disruptions, gastrointestinal disturbances, and changes in cognition.[1] Although many clinical features are specified in the diagnostic criteria of the *International Classification of Headache Disorders*, third edition (ICHD-3), such as headache, throbbing/pulsation, pain, pain exacerbated by physical activity, nausea/vomiting, photophobia, phonophobia, and aura,[1] other symptoms also are common and contribute to the disease burden.[2-8] These include cognitive symptoms (e.g., memory, executive function, attention deficit), affective symptoms (e.g., mood changes, anxiety, irritability), non-ICHD-3 sensory symptoms (e.g., osmophobia, taste abnormalities, blurry vision, allodynia), cranial autonomic symptoms (e.g., nasal congestion, rhinorrhea, lacrimation, pallor, sweating, ptosis), non-ICHD-3 gastrointestinal symptoms (e.g., abdominal pain, diarrhea, tenesmus), and others (e.g., yawning, polyuria, dizziness, muscle pain [especially neck pain]).[2-8] Moreover, migraine symptoms vary from person to person, as well as within person, based on the duration of illness, the severity of illness in a particular time period and within an attack, and the time since attack onset.[1,9,10] Migraine-associated symptoms not included in ICHD-3 may persist between episodes of headache and contribute to interictal burden.[11-14] Bothersome or frequent symptoms have been linked

to decreased patient satisfaction with migraine treatment.[15] Thus, failure to account for the impact of these symptoms may partially explain why patients are often dissatisfied with treatment and why adherence to prescribed therapy remains low.[16,17]

The specific Food and Drug Administration guidelines for acute migraine trials recommend the use of the absence of the most bothersome symptom (MBS)—selected from among nausea, photophobia, and phonophobia—as a coprimary endpoint to "…better align the study outcome with the symptom(s) of primary importance to patients…."[18] Clinical studies of migraine preventives typically do not assess MBS, focusing instead on "reduction in mean monthly migraine days" (MMDs) or similar endpoints (e.g., change in the number of moderate/severe headache days) as the primary measure to establish clinical efficacy.[19-26] Such endpoints, although very useful, may not fully capture the burden of migraine or the benefits of treatment.

The PROMISE-2 trial adopted a broader and more patient-centered approach to assessing MBS rather than having the patient select from the three cardinal migraine symptoms (nausea, photophobia, and phonophobia). Participants were asked to identify their MBS in open-ended fashion, and investigators evaluated the effects of treatment on this symptom. The symptoms that could be reported as most bothersome were not constrained by the investigator as they are for trials of acute migraine treatment. We, therefore, refer to this measure as the patient-identified MBS (PI-MBS) to distinguish it from the patient-selected MBS used in acute trials. Herein, we report the novel

methodology for assessing PI-MBS, describe the symptoms that patients reported, and evaluate the impact of treatment on this outcome.

METHODS

Study design

Data for the current analysis are from the phase 3, randomized, double-blind, placebo-controlled, parallel-group PROMISE-2 clinical trial (*ClinicalTrials.gov* identifier: NCT02974153), the full details of which have been reported elsewhere.[20]

The PROMISE-2 study protocol was approved by the independent ethics committee or institutional review board at each study site, and all research was conducted in accordance with current Good Clinical Practice as specified in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, the Declaration of Helsinki, and local regulatory requirements. All study enrollees provided written informed consent prior to study participation.

The PROMISE-2 study included adults (18 through 65 years of age) with a diagnosis of migraine established at or before 50 years of age, a history of chronic migraine (CM) for ≥12 months before screening, and a report of ≥15 to ≤26 headache days, including ≥8 migraine days, during the 28-day screening period. The diagnosis of migraine was based on the ICHD-3 beta version (2013), Section 1.3.[27]

Eligible patients were randomized (1:1:1) to receive eptinezumab 100 mg, eptinezumab 300 mg, or placebo, administered intravenously on day 0 and at week 12. Participants were stratified by the number of migraine days reported during the screening period (≤17 vs. >17 days) and by use/nonuse of preventive migraine medication within 3 months before screening. The study included daily completion of an electronic diary (eDiary), as well as scheduled on-site visits at screening, day 0, and weeks 2, 4, 8, 12, 16, 20, 24, and 32.

Outcome measures

The primary efficacy outcome in PROMISE-2 was the change from baseline in MMDs during weeks 1–12; these results have been reported.[20] The key outcome for the present analysis was the PI-MBS, a secondary endpoint in PROMISE-2 that was captured at screening and evaluated at baseline and at weeks 4, 8, 12, 16, 20, 24, and 32. During the screening visit, patients were asked to verbally describe the MBS that they associated with CM. This question was open ended, and there were no limits regarding the type of migraine-associated MBS symptom, the specific migraine attack (e.g., the most recent), or the specific phase of a migraine attack (e.g., premonitory, prodrome). From the patient's description, the study investigator categorized the PI-MBS into one of nine predefined categories: nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, or other/specify. The "other, specify" option was used for patient-identified symptoms not readily classified into the predefined categories, for reports of

multiple symptoms, and for cases in which the investigator chose to include specific details of the patient's description. The verbatim descriptions included in the "other, specify" category were reviewed and then classified into one of the predefined symptom groups (when appropriate) or were assigned to a new symptom category. The PI-MBS from the screening visit was included on the assessment form for all subsequent visits, using the exact language from the patient to describe their MBS. At baseline (day 0) and at weeks 4, 8, 12, 16, 20, 24, and 32, patients were asked to rate the overall change in their PI-MBS severity since the start of the study. The rating scale for the overall change assessment included the following possible ordinal responses: very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse. The responses were grouped into four categories: much improved + very much improved; minimally improved; no change; and minimally worse + much worse + very much worse.

In addition to specifying changes in the PI-MBS, patients completed the Patient Global Impression of Change (PGIC) assessment[28] during the same scheduled visits (excluding baseline), using a rating scale identical to the one used for PI-MBS. The PGIC involves a single question about the patient's impression of the overall change in their disease status since the start of the study and encompasses multiple domains of health: activity limitations, symptoms, emotions, and overall quality of life. The same categorization scheme described for PI-MBS was used to classify responses to the PGIC.

Patients completed an eDiary daily, throughout the 28-day pretreatment screening period and then for the 24 weeks of active randomized treatment. The diary captured daily headache events, including migraine characteristics. Data from the diaries were used to determine days on which migraines occurred and days that were free of migraine. A migraine day was determined by eDiary information that fulfilled the definition of a migraine outlined in ICHD-3.[27] A "migraine" had to meet these three criteria: (1) lasting ≥4 h or lasting 30 min to 4 h and believed by the patient to be relieved by acute use of medication; (2) having ≥2 of the following: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity; and (3) having ≥1 of the following: nausea and/or vomiting, photophobia, or phonophobia. Individual migraine days were combined into "months" (28-day intervals) to create an MMD measure.

Statistical analysis

All patients who received at least one dose of study medication were included in the current analyses. Endpoints are summarized with descriptive statistics (alpha-controlled endpoints were presented previously[20]), and PI-MBS was designated as a tertiary endpoint in the protocol. All analyses are exploratory, and all test statistics were nominal. Analyses were conducted using SAS software (SAS Institute), version 9.2 or higher.

For the PI-MBS and PGIC measures, summary statistics were reported based on observed data, with no imputation for missing data.

Migraine frequency results for each 12-week dosing interval were based on the average number of MMDs occurring during each

associated 4-week period. If the headache diary was completed for ≥21 days in a 4-week period, the observed frequency was normalized to 28 days. If the diary was completed for <21 days in a 4-week period, the findings were a weighted function of the observed data for the current interval and the results for the previous interval, with the weight being proportional to the number of completed days.

Post hoc correlations using the Pearson[29] and Spearman[30] methodologies were calculated to evaluate the relationship between PGIC and PI-MBS and between PGIC and MMDs. PGIC and PI-MBS responses were ranked from −3 (very much worse) to +3 (very much improved) for correlation analyses. p-values were based on a test versus zero correlation using the Student's t distribution approximation method, with normal theory assumed.

RESULTS

Patients

Patient disposition, demographics, and baseline clinical characteristics were reported previously.[20] Briefly, 1072 patients received treatment and were included in these analyses (eptinezumab 100 mg, n = 356; eptinezumab 300 mg, n = 350; placebo, n = 366). Demographic and baseline clinical characteristics were generally balanced across treatment groups; the average age was 40.5 years and the average time since CM diagnosis was 11.8 years. Most patients were female (88.2%) and White (91.0%). During the 28-day screening period, the mean number of headache days was 20.5, and the mean number of migraine days was 16.1. At baseline, 34.5% of patients had aura in their migraine history, and 40.2% had a secondary diagnosis of medication-overuse headache.

Variety in PI-MBS

PI-MBS are summarized in Table 1. Overall, 23 unique events were identified. For 27 patients (2.5%), the MBS included more than one type of symptom type. Seven patients (0.7%) identified events that remained classified as "other." The most commonly identified MBS (n ≥ 10) were light sensitivity (n = 200 [18.7%]), nausea/vomiting (n = 162 [15.1%]), pain with activity (n = 147 [13.7%]), pain (n = 133 [12.4%]), headache (n = 120 [11.2%]), sound sensitivity (n = 78 [7.3%]), throbbing/pulsation (n = 50 [4.7%]), cognitive disruption (n = 44 [4.1%]), fatigue (n = 26 [2.4%]), mood changes (n = 16 [1.5%]), and sensitivity to smell (n = 10 [0.9%]).

Nausea/vomiting, light sensitivity, and sound sensitivity—the three symptoms traditionally included in MBS measures for acute migraine treatments[18]—were identified as the MBS by 41.0% of patients. An expanded symptom list, including these three traditional MBS symptoms, as well as aura and the cardinal pain features of migraine,[1] encompassed 83.7% of PI-MBS. Therefore, 16.3% of patients identified symptoms beyond this range, including 11.2% with prespecified symptoms (mental cloudiness, fatigue, mood changes)

and 5.1% with symptoms that were not prespecified (sensitivity to smell, visual impact, pressure/tightness, anatomical pain, eye pain, neck pain, dizziness, allodynia, inactivity, sensory disturbance, sleep disturbance, speech difficulty, multiple symptoms, or other symptoms).

When patients rated the level of change in severity of their MBS at the end of the 28-day screening period (i.e., before dosing at the baseline visit), >90% reported no change (eptinezumab 100 mg, 91.3%; eptinezumab 300 mg, 93.7%; placebo, 92.0%), indicating that the ranking of each PI-MBS was quite stable among this cohort prior to treatment. If a change in PI-MBS severity was indicated at baseline, it was primarily one of the "minimal" categories (i.e., minimally improved or minimally worse).

Impact of eptinezumab and placebo on PI-MBS and PGIC

At the 12-week time point, which was the primary time of assessment, much or very much improvement in PI-MBS was reported by 184/344 (53%; difference from placebo [95% CI], 19% [12.1%, 26.7%]) of the eptinezumab 100-mg group, by 207/338 (61%; difference from placebo [95% CI], 27% [19.9%, 34.4%]) of the eptinezumab 300-mg group, and by 117/343 (34%) of the placebo group (Figure 1; Table 2). Relative to placebo recipients, a greater percentage of eptinezumab-treated patients reported much or very much improvement in their MBS as early as week 4 (100 mg, 45%; 300 mg, 57%; placebo, 29%), and the rates increased for all treatment arms after the second dose. Within 4 weeks of the second dose (week 16), much or very much improvement was noted by 58% (100 mg), 65% (300 mg), and 36% (placebo). Interestingly, 20 weeks (five half-lives) after the second dose (i.e., week 32), the percentage of patients in each group indicating that their PI-MBS had improved much or very much was similar to that observed at the end of the second dosing interval (week 24).

Responses to the PGIC at the population level were very similar to responses for the PI-MBS at each time point (Figure 1; Table 3). At week 12, much or very much improvement in PGIC was reported by 180/344 (52%; difference from placebo [95% CI], 14% [7.1%, 21.8%]) patients who received eptinezumab 100 mg, by 215/337 (64%; difference from placebo [95% CI], 26% [18.6%, 33.2%]) patients treated with eptinezumab 300 mg, and by 130/343 (38%) patients who received placebo.

Correlation between PI-MBS and PGIC

At week 4, responses to the PGIC and PI-MBS measures were exactly the same for 75.1% of the entire study population. For 95.9% of patients, responses differed by no more than one category. (For example, "much improved" was reported for one measure, and "very much improved" or "minimally improved" was reported for the other.) Results were similar at weeks 12 and 24: 75.5% and 78.8% of

TABLE 1 Patient-identified MBS at baseline in PROMISE-2

Patients, n (%)	Eptinezumab		Placebo (n = 366)	Total (N = 1072)
	100 mg (n = 356)	300 mg (n = 350)		
Patient verbal reports assigned to prespecified MBS categories				
Nausea/vomiting[a]	55 (15.4)	46 (13.1)	61 (16.7)	162 (15.1)
Sensitivity to light[a]	67 (18.8)	64 (18.3)	69 (18.9)	200 (18.7)
Sensitivity to sound[a]	22 (6.2)	28 (8.0)	28 (7.7)	78 (7.3)
Fatigue	7 (2.0)	11 (3.1)	8 (2.2)	26 (2.4)
Pain exacerbation with activity[a]	53 (14.9)	45 (12.9)	49 (13.4)	147 (13.7)
Mood changes	8 (2.2)	4 (1.1)	4 (1.1)	16 (1.5)
Additional MBS categories created by study physician to fit patient verbal reports				
Pain[a,c]	35 (9.8)	45 (12.9)	53 (14.5)	133 (12.4)
Headache[a]	45 (12.6)	43 (12.3)	32 (8.7)	120 (11.2)
Throbbing/pulsation[a]	18 (5.1)	17 (4.9)	15 (4.1)	50 (4.7)
Cognitive disruption	17 (4.8)	14 (4.0)	13 (3.6)	44 (4.1)
Sensitivity to smell	1 (<1)	1 (<1)	8 (2.2)	10 (0.9)
Aura	4 (1.1)	1 (<1)	2 (<1)	7 (0.7)
Visual impact[b]	2 (<1)	3 (<1)	3 (<1)	8 (0.7)
Pressure/tightness	2 (<1)	2 (<1)	3 (<1)	7 (0.7)
Anatomical pain[c]	3 (<1)	3 (<1)	0	6 (0.6)
Eye pain	4 (1.1)	1 (<1)	1 (<1)	6 (0.6)
Neck pain	1 (<1)	1 (<1)	3 (<1)	5 (0.5)
Dizziness	2 (<1)	2 (<1)	1 (<1)	5 (0.5)
Allodynia	1 (<1)	1 (<1)	1 (<1)	3 (0.3)
Inactivity	0	1 (<1)	1 (<1)	2 (0.2)
Sensory disturbance[b]	1 (<1)	0	0	1 (0.1)
Sleep disturbance	0	0	1 (<1)	1 (0.1)
Speech difficult[b]	0	0	1 (<1)	1 (0.1)
Multiple[d]	7 (2.0)	12 (3.4)	8 (2.2)	27 (2.5)
Other	1 (<1)	5 (1.4)	1 (<1)	7 (0.7)

Abbreviation: MBS, most bothersome symptom.

[a]Included in the *International Classification of Headache Disorders*, 3rd edition (ICHD-3) diagnostic criteria.

[b]Could be related to ICHD-3 cardinal symptoms such as aura and photophobia or other visual impacts not considered migraine-defining, such as blurry vision.

[c]Extra-cephalic pain (patients were not limited in their description of MBS).

[d]Patient reported >1 type of MBS.

patients had the same response for PGIC and PI-MBS (respectively), and 97.2% and 96.6% had responses that differed by no more than one rating category.

PI-MBS severity scores and PGIC scores strongly correlated at each time point (Pearson correlation: week 4, $r = 0.83$; week 12, $r = 0.84$; week 24, $r = 0.88$; all $p < 0.0001$; Spearman correlation: week 4, $r = 0.83$; week 12, $r = 0.85$; week 24, $r = 0.89$; all $p < 0.0001$), with greater correlation coefficients than for the relationship between changes in MMDs and PGIC scores (Pearson correlation: week 4, $r = -0.50$; week 12, $r = -0.49$; week 24, $r = -0.52$; all $p < 0.0001$; Spearman correlation: week 4, $r = -0.51$; week 12, $r = -0.49$; week 24, $r = -0.52$; all $p < 0.0001$).

DISCUSSION

PROMISE-2 was the first trial for a migraine preventive treatment to capture PI-MBS in CM using a unique patient-centered measure that goes beyond the traditional triad of nausea, photophobia, and phonophobia provided as MBS options in acute migraine treatment trials. The current analysis not only illustrates the broad range of most bothersome migraine-associated symptoms identified by persons with CM during and/or between attacks but also demonstrates that preventive treatment with eptinezumab is associated with improvements in these PI-MBS relative to placebo. Patient-reported improvements in PI-MBS correlated strongly with PGIC, and these
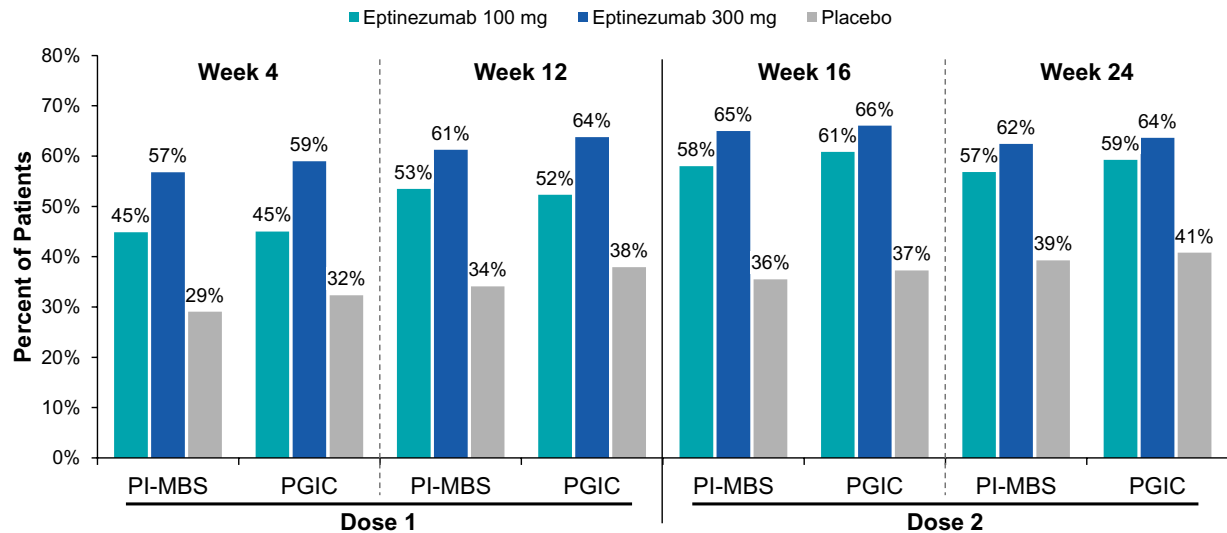
FIGURE 1 Improvements in PI-MBS and PGIC measures over time. Improvements defined as responses of "much improved" and "very much improved." At each visit, patients were asked to rate the change in their MBS or disease status since the start of the study, meaning that the recall period varied (and increased) over time. PI-MBS, patient-identified most bothersome symptom; PGIC, Patient Global Impression of Change [Color figure can be viewed at wileyonlinelibrary.com]

correlations—when analyzed using either the Pearson or Spearman methodologies—were higher than those demonstrated for MMD reduction and PGIC.

Importance of using a patient-focused measure

Patients with CM in PROMISE-2 described a total of 23 unique PI-MBS. This broad array likely reflects the method of collection; that is, patient self-identification of their MBS in response to an open-ended question. If patients mentioned a prespecified MBS, it was coded by study personnel; otherwise, the patient's verbatim report was recorded in writing and subsequently coded by a headache expert. This approach differs from that of large migraine surveys designed to identify the prevalence of common migraine symptoms, which typically relied on self-administered questionnaires or investigator-conducted interviews and prespecified lists of symptoms. Not surprisingly, these surveys showed a high prevalence of nausea (70%–90%), vomiting (30% to ~70%), and photophobia (20%–94%),[2-4] which are symptoms used to aid the diagnosis of migraine.[1] In PROMISE-2, nausea/vomiting, photophobia, and phonophobia accounted for only 41.1% of PI-MBS (15.1%, 18.7%, and 7.3%, respectively). Other ICHD-3 diagnostic symptoms (headache, aura, pain with activity, pain, and throbbing/pulsation) accounted for another 42.7%. Thus, nearly one-sixth of patients in PROMISE-2 reported a PI-MBS outside the cardinal and pain-related range of symptoms included in the ICHD-3 diagnostic criteria for migraine; unrecognized MBS may contribute to misdiagnosis and improper treatment. One example is the presence of sinus symptoms in patients with migraine, which may lead to misdiagnosis as sinus headache or rhinosinusitis.[31] In a prospective, open-label, observational study involving 2991 patients with a history of self-described or physician-diagnosed "sinus" headache, 80% fulfilled the International Headache Society criteria for migraine with or without aura; most reported prior treatment with nonnarcotic analgesics, nonsteroidal anti-inflammatory drugs, decongestants, and/or antihistamines; and a large proportion (67%) indicated at least some degree of dissatisfaction with prior therapy.[32]

Previous research suggests that MBS vary across sociodemographic and disease variables. In the observational Migraine in America Symptoms and Treatment study, nausea was more common as the MBS in women, patients with lower annual household income, and patients who were underweight.[33] Photophobia was more common in men, patients with higher annual household income, patients who were obese, and patients with aura; phonophobia was more common in patients with cutaneous allodynia.[33] In a 2006 single-center survey of 1025 patients with migraine, Kelman and Tanis identified relationships between headache intensity and MBS (nausea, vomiting, photophobia, phonophobia, dizziness, rhinorrhea/lacrimation, and osmophobia) and between headache duration and MBS (osmophobia and taste abnormality).[2] In both of these examples, patients selected their MBS from limited lists of traditional symptoms; thus, further research is needed to examine the impact of these and similar factors on the perceived "bothersomeness" of non-traditional migraine symptoms. Due to the sample size limitations, relationships between these variables and MBS were not assessed in PROMISE-2.

Migraine symptoms vary throughout the course of an attack; therefore, questions about MBS may solicit different answers depending on when and how the question is asked.[34] In the multi-center, prospective American Registry for Migraine Research study of 959 patients with headache treated in specialty care, patient

TABLE 2 Responses to the patient-identified most bothersome symptom measure over time

Patients, n (%)	Eptinezumab		Placebo
	100 mg	300 mg	
Week 4, N	350	345	361
Much or very much improved[a]	157 (44.9)	196 (56.8)	105 (29.1)
Minimally improved	106 (30.3)	77 (22.3)	107 (29.6)
No change	82 (23.4)	68 (19.7)	132 (36.6)
Minimally, much, or very much worse[b]	5 (1.4)	4 (1.2)	17 (4.7)
Week 8, N	350	342	354
Much or very much improved[a]	176 (50.3)	190 (55.6)	119 (33.6)
Minimally improved	90 (25.7)	82 (24.0)	104 (29.4)
No change	71 (20.3)	62 (18.1)	111 (31.4)
Minimally, much, or very much worse[b]	13 (3.7)	8 (2.3)	20 (5.6)
Week 12 (prior to infusion 2), N	344	338	343
Much or very much improved[a]	184 (53.5)	207 (61.2)	117 (34.1)
Minimally improved	84 (24.4)	75 (22.2)	111 (32.4)
No change	61 (17.7)	52 (15.4)	101 (29.4)
Minimally, much, or very much worse[b]	15 (4.4)	4 (1.2)	14 (4.1)
Week 16, N	338	334	338
Much or very much improved[a]	196 (58.0)	217 (65.0)	120 (35.5)
Minimally improved	82 (24.3)	62 (18.6)	95 (28.1)
No change	47 (13.9)	51 (15.3)	98 (29.0)
Minimally, much, or very much worse[b]	13 (3.8)	4 (1.2)	25 (7.4)
Week 20, N	333	333	335
Much or very much improved[a]	187 (56.2)	208 (62.5)	132 (39.4)
Minimally improved	78 (23.4)	64 (19.2)	95 (28.4)
No change	57 (17.1)	54 (16.2)	92 (27.5)
Minimally, much, or very much worse[b]	11 (3.3)	7 (2.1)	16 (4.8)
Week 24, N	329	330	331
Much or very much improved[a]	187 (56.8)	206 (62.4)	130 (39.3)
Minimally improved	71 (21.6)	61 (18.5)	76 (23.0)
No change	56 (17.0)	52 (15.8)	101 (30.5)
Minimally, much, or very much worse[b]	15 (4.6)	11 (3.3)	24 (7.3)
Week 32 (20 weeks after last infusion), N	324	320	322
Much or very much improved[a]	166 (51.2)	195 (60.9)	126 (39.1)
Minimally improved	71 (21.9)	56 (17.5)	78 (24.2)
No change	66 (20.4)	52 (16.3)	94 (29.2)
Minimally, much, or very much worse[b]	21 (6.5)	17 (5.3)	24 (7.5)

[a]Includes "very much improved" and "much improved" responses.
[b]Includes "minimally worse," "much worse," and "very much worse" responses.

responses to list-based MBS questions varied depending on the wording of the question.[35] When asked "Which of the following symptoms do you most frequently find to be the most bothersome during a headache?" (the list excluded headache), the most common responses were photophobia (26%), difficulty in thinking and understanding clearly (21%), nausea (13%), phonophobia (9%), and fatigue (9%). When the patients were asked "When present, which of the following symptoms do you find to be the most bothersome during a headache?" the order of responses changed slightly: difficulty in thinking and understanding clearly was the most common (20%), photophobia was next (18%), followed by nausea (15%), phonophobia (10%), and fatigue (8%). Considering that preventive medications are meant to be given long term and need to address MBS during the entire course of treatment, it is important to recognize that each patient's MBS may change during the course of an attack and over longer periods of time. Because PROMISE-2 was designed to assess

TABLE 3 Responses to the Patient Global Impression of Change measure over time

Patients, n (%)	Eptinezumab		Placebo
	100 mg	300 mg	
Week 4, N	351	346	362
Much or very much improved[a]	158 (45.0)	204 (59.0)	117 (32.3)
Minimally improved	111 (31.6)	77 (22.3)	87 (24.0)
No change	77 (21.9)	57 (16.5)	138 (38.1)
Minimally, much, or very much worse[b]	5 (1.4)	8 (2.3)	20 (5.5)
Week 8, N	349	342	354
Much or very much improved[a]	182 (52.1)	204 (59.6)	127 (35.9)
Minimally improved	91 (26.1)	67 (19.6)	90 (25.4)
No change	68 (19.5)	64 (18.7)	116 (32.8)
Minimally, much, or very much worse[b]	8 (2.3)	7 (2.0)	21 (5.9)
Week 12 (prior to infusion 2), N	344	337	343
Much or very much improved[a]	180 (52.3)	215 (63.8)	130 (37.9)
Minimally improved	82 (23.8)	68 (20.2)	85 (24.8)
No change	69 (20.1)	51 (15.1)	111 (32.4)
Minimally, much, or very much worse[b]	13 (3.8)	3 (0.9)	17 (5.0)
Week 16, N	337	333	338
Much or very much improved[a]	205 (60.8)	220 (66.1)	126 (37.3)
Minimally improved	74 (22.0)	60 (18.0)	91 (26.9)
No change	43 (12.8)	50 (15.0)	98 (29.0)
Minimally, much, or very much worse[b]	15 (4.5)	3 (0.9)	23 (6.8)
Week 20, N	332	333	335
Much or very much improved[a]	188 (56.6)	216 (64.9)	143 (42.7)
Minimally improved	69 (20.8)	55 (16.5)	74 (22.1)
No change	60 (18.1)	56 (16.8)	99 (29.6)
Minimally, much, or very much worse[b]	15 (4.5)	6 (1.8)	19 (5.7)
Week 24, N	329	330	331
Much or very much improved[a]	195 (59.3)	210 (63.6)	135 (40.8)
Minimally improved	71 (21.6)	56 (17.0)	72 (21.8)
No change	49 (14.9)	54 (16.4)	99 (29.9)
Minimally, much, or very much worse[b]	14 (4.3)	10 (3.0)	25 (7.6)
Week 32 (20 weeks after last infusion), N	324	320	322
Much or very much improved[a]	170 (52.5)	197 (61.6)	129 (40.1)
Minimally improved	75 (23.1)	52 (16.3)	75 (23.3)
No change	60 (18.5)	51 (15.9)	98 (30.4)
Minimally, much, or very much worse[b]	19 (5.9)	20 (6.3)	20 (6.2)

[a]Includes "very much improved" and "much improved" responses.
[b]Includes "minimally worse," "much worse," and "very much worse" responses.

the effect of treatment on baseline PI-MBS, changes in MBS related to disease course were not ascertained.

Ultimately, allowing a patient with migraine to self-identify an MBS as a part of routine management can foster collaborative, patient-centered care and communication for a disorder that varies from person to person. Patients may be more motivated to continue treatment if their MBS, or issue that is most interrupting their life, is addressed. Although assessing MBS and reducing its severity provide an important

insight into the burden of migraine and the benefits of treatment, results from a single study cannot establish whether this is an optimal strategy. The impact of allowing patients to identify more than one bothersome symptom remains unknown. Future research with larger patient populations is needed to determine if, and to what extent, sociodemographic factors influence traditional and nontraditional MBS in CM (such as in the Migraine in America Symptoms and Treatment study[33]); whether the question needs to be tailored or standardized

(such as in the American Registry for Migraine Research study[35]); and whether the MBS should be reidentified throughout the course of treatment (and if so, how often).

Impact of eptinezumab on PI-MBS

In the current study, rates of improvement in both PI-MBS severity and PGIC were apparent by week 4 following the first dose. The magnitude of the treatment effect was numerically greater after week 16 (4 weeks after the second dose of eptinezumab). Four weeks after the first dose, nearly 50% of patients treated with eptinezumab 100 mg and nearly 60% of those treated with eptinezumab 300 mg indicated that their MBS and/or PGIC was much or very much improved, compared with ~30% of patients who received placebo. The distribution of ratings for PI-MBS improvement and PGIC was similar across time points, suggesting that the two measures operate in parallel. This hypothesis is supported by the very high correlations of improvement in PI-MBS and PGIC (r range, ~0.8 to 0.9). It is possible that these correlations may be inflated by the use of identical rating scales to capture both PI-MBS and PGIC and by the temporal proximity of the ratings. Additional research is needed to determine whether there is a direct causal relationship between changes in PI-MBS severity and patient-reported outcomes, as well as how changes in MMDs impact those associations.

In general, the improvements in PI-MBS severity and PGIC were sustained through 8 weeks following the end of the 24-week treatment phase of PROMISE-2. Although eptinezumab provides most patients with improvement in their PI-MBS and PGIC, infrequent measurement prevents determination of the temporal sequence. Future work should be aimed at determining the timing of improvement in PI-MBS, migraine days, and PGIC. Perhaps improvement in the PI-MBS is predictive of improvement in PGIC. Unfortunately, due to the limited sample size for most symptom categories identified in PROMISE-2, it was not feasible to evaluate the impact of eptinezumab on specific symptoms. More research on the impact/mechanisms of eptinezumab and other migraine preventive treatments on a broader range of migraine-related symptoms is warranted, with the ultimate goal of tailoring preventive treatment strategies to each patient's specific needs.

Conclusion

Patients with CM in the PROMISE-2 study identified a broad range of MBS at baseline via use of a unique patient-focused measure. Throughout the study, patients treated with eptinezumab reported greater improvement in the severity of their PI-MBS than did patients who received placebo. Moreover, the changes in PI-MBS severity correlated strongly with changes in PGIC. These findings underscore the importance of evaluating outcomes beyond headache duration and frequency in patients with CM.

CONFLICT OF INTEREST

Richard B. Lipton serves as a consultant, advisory board member, and/or has received honoraria from AEON, Allergan, American Academy of Neurology, American Headache Society, Amgen, Biohaven, Dr. Reddy's Laboratories, electroCore Medical, Eli Lilly, GlaxoSmithKline, Lundbeck, Medscape, Pernix, Pfizer, Satsuma, Teva, Trigemina, Vector, and Vedanta. He has stock options in Biohaven and Cntrl M and receives research support from the NIH, Allergan/Abbvie, Amgen, Biohaven, and the National Headache Foundation. David W. Dodick reports the following conflicts within the past 12 months: Consulting: AEON, Amgen, Clexio, Cerecin, Cooltech, Ctrl M, Allergan, Alder, Biohaven, GSK, Linpharma, Lundbeck, Promius, Eli Lilly, eNeura, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, XoC, Zosano, Upjohn (Division of Pfizer), Pieris, Praxis, Revance, Equinox. Honoraria: CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, Southern Headache Society (MAHEC), WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient-Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), and Precon Health (Options/Board). Patent 17189376.1–1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Jessica Ailani has served as a consultant, advisory board member, and/or speaker for Allergan/Abbvie, Axsome, Amgen, Biohaven, Eli Lilly, Lundbeck, Impel, Satsuma, Teva, Medscape, and NeurologyLive. She has received honoraria from *Current Pain and Headache Reports* for editorial services and from *SELF* as a medical advisor. She has received clinical trial grants from Allergan, American Migraine Foundation, Biohaven, Eli Lilly, Satsuma, and Zosano. Lora McGill has served as a consultant, advisory board member, and/or speaker for Abbvie, Aevi, Alkermes, Allergan, Amgen, Aptinyx, Arbor, Axsome, AZTherapies, Bayer, Biogen, Biohaven, Bionomics, BlackThorn, CoLucid, Daiichi, Dr. Reddy's, Eli Lilly, Esperion, Intarcia, Intra-Cellular, Ironshore, Janssen, Labrys Biologic, Lundbeck, Mitsubishi, Mylan NLS Pharma, Nektar, Nestle Pamlab, Neuralstem, Neurocrine, Novartis, Novo Nordisk,

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INSTITUTIONAL REVIEW BOARD APPROVAL

Study approval was provided at each study site by the corresponding independent ethics committee or institutional review board.

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