Evaluating the clinical utility of the patient-identified most bothersome symptom measure from PROMISE-2 for research in migraine prevention

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Funding information
This study was funded by H. Lundbeck A/S, Copenhagen, Denmark

Abstract

Objective: To assess the utility of the novel patient-identified (PI) most bothersome symptom (MBS) measure from PROMISE-2, a phase 3 trial of eptinezumab for the preventive treatment of chronic migraine.

Background: Relief of bothersome migraine symptoms can influence satisfaction with treatment and therapeutic persistence. Understanding the impact of preventive treatment on a PI-MBS could improve clinical decision-making.

Methods: In PROMISE-2, patients with chronic migraine received eptinezumab 100, 300 mg, or placebo administered intravenously every 12 weeks for up to 2 doses (n = 1072). PI-MBS was an exploratory outcome requiring each patient to self-report their MBS in response to an open-ended question. At baseline and week 12, patients rated overall improvement in PI-MBS. The relationships among PI-MBS at week 12 and change in monthly migraine days (MMDs) from baseline to month 3 (weeks 9–12), Patient Global Impression of Change at week 12, and changes from baseline to week 12 in the 6-item Headache Impact Test total, EuroQol 5-dimensions 5-levels visual analog scale, and 36-item Short-Form Health Survey component scores were assessed.

Results: Treatment groups had similar baseline characteristics and reported a total of 23 unique PI-MBS, most commonly light sensitivity (200/1072, 18.7%), nausea/vomiting (162/1072, 15.1%), and pain with activity (147/1072, 13.7%). Improvements in PI-MBS at week 12 correlated with changes in MMDs (ρ = −0.49; p < 0.0001) and other patient-reported outcomes. Controlling for changes in MMDs, PI-MBS improvement predicted other patient-reported outcomes in expected directions. The magnitude of

Abbreviations: CM, chronic migraine; EQ-SD-5L, EuroQol 5-Dimensions 5-Levels; HIT-6, 6-Item Headache Impact Test; MBS, most bothersome symptom; MCS, mental component summary; MMDs, monthly migraine days; PCS, physical component summary; PGIC, Patient Global Impression of Change; PI-MBS, patient-identified most bothersome symptom; PROMs, patient-reported outcome measures; SF-36, 36-Item Short-Form Health Survey; SMDs, standardized mean differences; VAS, visual analog scale.

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INTRODUCTION

Migraine attacks are characterized by pain features (e.g., exacerbation of pain by activity), canonical associated symptoms (nausea, phonophobia, and photophobia), and other symptoms (e.g., cognitive disruption, fatigue, changes in mood, sensitivity to smell).\textsuperscript{1–10} Given this vast array of symptoms, establishing priorities for assessing endpoints in clinical trials is essential. One approach was to designate the same set of symptoms as primary endpoints for everyone. This approach was used in acute treatment trials which required statistically significant separation on four co-primary endpoints: pain, photophobia, phonophobia and nausea.\textsuperscript{11} This approach was viewed as problematic for several reasons. First, not everyone has every symptom so statistical power for nausea, present in perhaps 60% of patients, is lower than the power for pain, present in 100% of patients. Second, requiring significant differences on four co-primaries is a high bar which increases the risk of failure due to chance alone. Third, this approach does not incorporate patient priorities regarding their symptoms. Regulator guidance was modified in 2018; the number of co-primary endpoints was reduced from four to two. Pain was retained but the associated symptoms were replaced with freedom from the patient-designated most bothersome symptom (MBS), selected from among nausea, photophobia, and phonophobia.\textsuperscript{12–14} Allowing the patient to select their MBS from a circumscribed list has some advantages: It reduces the number of statistical comparisons required if pain, nausea, photophobia, and phonophobia were all co-primary endpoints in migraine trials, and it prioritizes the symptoms that generally are considered the most bothersome to the patient, providing a more patient-centered measure. However, this approach also has a major disadvantage: For some patients, their MBS is not nausea, photophobia, or phonophobia, and limiting the available choices renders the measure less patient-centered. An alternative approach to the limited MBS selection is an open-ended question to identify, without restriction, the migraine-related symptom each patient finds most bothersome, which was used in the PROMISE-2 study.\textsuperscript{15,16} We refer to this measure as the patient-identified most bothersome symptom (PI-MBS).

In the PROMISE-2 migraine prevention study in chronic migraine (CM), patients described their PI-MBS at screening and were asked to rate overall improvement in the PI-MBS using a 7-point ordinal scale after treatment with eptinezumab or placebo. These exploratory analyses were designed to determine the potential research and clinical utility of the PI-MBS measure for future trials and clinical practice. It was hypothesized that PI-MBS would correlate with changes on other related patient-reported outcome measures (PROMs), add unique clinical information above and beyond change in monthly migraine days (MMDs), and be sensitive to differences across treatment groups.

METHODS

Study and data source

PROMISE-2 (NCT02974153)\textsuperscript{15} was a randomized, double-blind, placebo-controlled, parallel-group trial that evaluated the preventive efficacy, tolerability, and safety of eptinezumab in adults with CM. Migraine diagnosis was based on the International Classification of Headache Disorders, 3rd edition (beta version).\textsuperscript{17} The planned sample size for this study was 1050 randomized and treated patients: 350 patients per group provided at least 90% power to detect the primary endpoint for each comparison assuming a treatment effect of at least 1 day and a common standard deviation of 4 days or less. For the key secondary 75% migraine responder rate endpoints 90% power was achieved for the pairwise comparisons, assuming a placebo responder rate of 20% and an eptinezumab responder rate of 31%. These sample size calculations were performed as previously described.\textsuperscript{15} As MBS was an exploratory endpoint, it was not included in power calculations.

Eligible patients were randomized to receive eptinezumab 100, 300 mg, or placebo, administered intravenously every 12 weeks for up to 2 doses (24 weeks of treatment). Detailed methodology for PROMISE-2 has been published.\textsuperscript{15,16} This study was approved by the independent ethics committee or institutional review board at each study site; all clinical work was conducted in compliance with current Good Clinical Practices per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, local regulatory requirements, and the principles of the Declaration of Helsinki. All patients enrolled in the study provided written informed consent prior to participation.
Outcome measures

Patient-identified most bothersome symptom

Patients were asked to verbally describe the MBS that they associated with CM at the screening visit. This question was open-ended and there were no limits regarding the type of migraine-associated symptom, the specific migraine attack, or the phase of migraine attack (e.g., premonitory/prodrome). Prior to analysis, the study investigator categorized the PI-MBS into 1 of 9 predefined categories: nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, or other/specific. The other/specific option was used for PI-MBS responses not readily classified into a predefined category, reports of multiple symptoms, and cases in which the investigator chose to include specific details of the patient’s description. The verbatim descriptions included in the other/specific category were reviewed and then classified into a predefined symptom group (when possible) or were assigned to a new symptom category.

The open-ended symptom categories constructed by investigators were reduced into 3 broad symptom classes by clinical (R.B.L.) and methodological experts (J.S.M., R.J.W.). These 3 classes were as follows.

1. Pain related to migraine symptoms (pain-related): eye pain, headache, non-anatomical/extracranial pain, pain-anatomical, pain with activity, and throbbing/pulsation
2. Canonical/traditional symptoms (canonical): nausea/vomiting, sensitivity to light, and sensitivity to sound
3. Other symptoms (other): allodynia, aura manifestations, cognitive disruption, dizziness, fatigue, inactivity, mood changes, neck pain, pressure/tightness, sensitivity to smell, sensory disturbance, sleep disturbance, speech difficulty, vision impacts, multiple, and other. Neck pain was included in the “other” category because it is unique from a clinical standpoint relative to the other pain responses.

PI-MBS was identified at screening and reaffirmed at Day 0. [new sentence]: At weeks 4, 8, 12, 16, 20, 24, and 32, patients were asked to rate the overall improvement in the PI-MBS they felt that their overall condition has changed from the start of the study. Patients were asked to respond to the question, “Since first receiving study drug in this study, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life, as related to your migraine?” using a 7-point ordinal scale identical to the one used for PI-MBS (1 = very much worse, 2 = much worse, 3 = minimally worse, 4 = no change, 5 = minimally improved, 6 = much improved, and 7 = very much improved). PGIC scores were evaluated every 4 weeks; this analysis focused on PGIC at week 12.

The SF-36 comprises 36 questions that cover 8 domains of health; 2 component scores can also be calculated, a physical component summary (PCS) and a mental component summary (MCS) score.19 During the PROMISE-2 study, PCS and MCS scores were computed at weeks 4, 12, 16, 24, and 32. The change in SF-36 scores from baseline to week 12 was evaluated for this analysis.

In addition to five individual dimensions of health-related quality of life, the EQ-5D-5L20 includes a visual analog scale (VAS) on which patients rate their overall health from 0 (the worst health imaginable) to 100 (the best health imaginable). VAS scores were collected at weeks 4, 12, 16, 24, and 32. The change in the EQ-5D-5L VAS from baseline to week 12 was evaluated in the current analysis.

The HIT-621 is a 6-item PROM used to assess the impact of headache on daily life; it comprises six questions and a total summed score is calculated. During PROMISE-2, total scores were calculated at weeks 4, 12, 16, 24, and 32. For this analysis, change in HIT-6 total scores from baseline to week 12 was evaluated.

Statistical analyses

All of the following post hoc analyses were conducted using SAS v9.4 (SAS Institute, Inc., Cary, NC, USA). The standard significance threshold of 0.05, with no correction for multiple comparisons, was used to determine statistical significance (i.e., differences between groups). With the exception of MMDs, missing PROM data were not imputed, and all available non-missing data were used for analyses.
PROM analyses largely focused on pooled treatment groups, an approach that has been previously utilized.22,23

Assessing the ability to pool individual PI-MBS into a single measure

One-way analysis of variance (ANOVA) models and chi-squared tests were used to evaluate demographic variables across PI-MBS classes. One-way ANOVA (treating PI-MBS improvement scores as continuous) and ordinal proportional odds regression (treating PI-MBS improvement scores as ordinal) models were used to compare PI-MBS improvement across PI-MBS classes, with 2-sided p values presented. To assess if the different classes of PI-MBS functioned uniquely, invariance of the relations among PI-MBS and PROM scores were evaluated using Pearson (when comparing with a continuous variable) and Spearman (when comparing with a categorical/or ordinal variable) correlations. The similarity of relationships among PI-MBS improvement and change in other PROMs was evaluated using Bartlett’s likelihood ratio test of the homogeneity of the within-group covariance matrices.24–26 A statistically non-significant value (i.e., p > 0.05) for the test for heterogeneity was pre-specified as the criterion for pooling over the PI-MBS classes.

Evaluating the unique effects of PI-MBS

Linear regression models were fit to test the unique effect of PI-MBS improvement, while controlling for change in MMDs. For each model, standardized regression coefficients were calculated to provide measures of effect size. Standardized regression coefficients were computed by dividing a parameter estimate by the ratio of the sample standard deviation of the dependent variable to the sample standard deviation of the regressor. Dependent variables were HIT-6 change, PGIC, EQ-5D-5L change, SF-36 MCS change, and SF-36 PCS change. For each model, SMDs were calculated by dividing the model-implied treatment group differences by the root mean square error from linear regression models treating PI-MBS improvement as continuous (scores ranged from 1 = very much worse to 7 = very much improved). Additionally, odds ratios were calculated from proportional odds models that treated PI-MBS improvement as ordinal.

Comparing treatment effect sizes

Linear regression models were fit to estimate the magnitude of treatment effects. The dependent variables were PI-MBS improvement, MMD change, HIT-6 change, PGIC, EQ-5D-5L change, SF-36 MCS change, and SF-36-PCS change. For each model, SMDs were calculated to compare the magnitude of treatment effects across PI-MBS classes. The SMDs were calculated by dividing the model-implied treatment group differences (e.g., 300 mg vs. placebo and 100 mg vs. placebo) by the root mean square error, which provides an effect size measure similar to Cohen's d.28,29

RESULTS

Patients and PI-MBS at baseline

A total of 1072 adults with CM participated in PROMISE-2. The mean age was 40.5 years; 88.2% of patients were female, and 91.0% were white.15 At baseline, the mean age at migraine diagnosis was 22.5 years, the mean duration of CM was 11.8 years, and the mean MMDs during screening was 16.1.

Patients reported a total of 23 unique PI-MBS, most commonly 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%; Table 1). More than 80% of patients identified a symptom that fell within either the pain-related or canonical PI-MBS classes (pain-related, 462/1072 [43.1%]; canonical, 440/1072 [41.0%]). The remaining 15.9% (170/1072) fell within the “other” PI-MBS class.

Pooling individual symptoms into a single PI-MBS measure

In this analysis, individual PI-MBS were first categorized into 3 classes (pain-related, canonical, and other) to determine if different classes of PI-MBS could be combined for subsequent analyses.
Demographics and baseline clinical characteristics stratified by PI-MBS class are shown in Table 2. PI-MBS classes did not differ with regard to sex ($p = 0.328$), age of migraine diagnosis ($p = 0.512$), or migraine days during screening ($p = 0.530$); between-group differences in age ($p = 0.016$), duration of migraine diagnosis ($p = 0.011$), and race ($p = 0.005$) could not be excluded, and their clinical meaningfulness remains unknown. Across PI-MBS classes, mean age differed by no more than 2 years (41.7, 39.7, and 39.8 years in the pain-related, canonical, and other classes, respectively) and mean duration of diagnosis by no more than 2.5 years (19.2 years, 16.9 years, and 18.0 years, respectively). In all PI-MBS classes, the majority of patients were white (94.8%, 88.2%, and 87.7% in the pain-related, canonical, and other classes, respectively).

Bartlett’s likelihood ratio test of the homogeneity of the within-group covariance matrices showed that the relationships among the PROMs did not differ across the 3 PI-MBS classes ($p = 0.052$). Furthermore, at week 12, a difference in reported improvement for PI-MBS classes was not found based on an ordinal proportional odds model ($\chi^2[2] = 3.12, p = 0.210$) or analysis of variance ($F[2$,
1022] = 1.91, \( p = 0.148 \)) models (Table 3). These results supported the use of a single PI-MBS variable (with patients identifying their MBS among the 3 classes) in subsequent analyses.

### Relationship and unique effects of PI-MBS on other PROMs and MMDs

Correlational analyses (to support convergent validity claims) were used to determine the relationship between PI-MBS classes and changes in theoretically related PROMs at week 12 (Table 4). PI-MBS improvement at week 12 showed a correlation with changes or improvement on all other PROMs evaluated (\( p < 0.0001 \)). Strong correlations were observed between PI-MBS improvement and changes in headache/migraine-specific outcomes, such as the HIT-6 total scores and MMDs (\( r \approx 0.5 \)). Moderate/weaker correlations were found between PI-MBS improvement and changes in non-headache/migraine-specific PROMs such as the SF-36 PCS, SF-36 MCS, and EQ-5D-5L VAS (\( r = 0.21–0.35 \)). Of note, the correlation between PI-MBS improvement and PGIC was very strong (\( r \approx 0.85 \)), which was expected given the similarity between both the item content and response options.

Regression analysis was used to determine the unique effects of PI-MBS in predicting reference measure scores, after controlling for MMD changes. Across all 5 PROMs, PI-MBS improvement predicted better outcomes above and beyond change in the MMDs (\( p < 0.003 \) for all). For 4 of the 5 PROMs (all but SF-36 MCS), PI-MBS had larger standardized effects compared with change in MMDs (Table 5).

### Known-groups analyses

In known-groups analyses, PI-MBS improvement ratings conformed to expectations, both in terms of reported descriptive values (mean, standard deviation, \( n \), %) and with respect to the outcome of tests of differences between the groups (Table 6). Both the \( \geq 50\% \) MMD responders and HIT-6 total score responders reported greater improvement in PI-MBS compared with the respective non-responding groups (Figure 1A,B). The effect size of each difference was large, indicating that the PI-MBS improvement rating can distinguish between clinically meaningful groups. Moreover, results aligned with the expected treatment results, with the eptinezumab 300 mg and 100 mg doses clearly differentiated from placebo according to PI-MBS improvement (Table 6; Figure 1C).

### Treatment effect sizes

The magnitude of treatment effects was generally greater for PI-MBS improvement at week 12 compared to changes in MMD from baseline to weeks 9–12. For patients receiving eptinezumab 300 mg, the overall effect size versus placebo was 0.54 (\( p < 0.0001 \)), and for those receiving 100 mg, the effect size versus placebo was slightly smaller (0.31; \( p < 0.0001 \); Table 6).

### Table 3

| Patients, n (%) | Pain-related | Canonical | Other |
|----------------|--------------|-----------|-------|
| Very much worse| 0            | 0         | 1(0.6)|
| Much worse     | 5 (1.1)      | 1 (0.2)   | 0     |
| Minimally worse| 12 (2.7)     | 7 (1.7)   | 7 (4.4)|
| No change      | 99 (22.3)    | 83 (19.7) | 32 (20.0)|
| Minimally improved | 118 (26.6) | 106 (25.2) | 46 (28.8)|
| Much improved  | 135 (30.4)   | 152 (36.1)| 47 (29.4)|
| Very much improved | 75 (16.9) | 72 (17.1) | 27 (16.9)|

Note: Due to missing data on PI-MBS at week 12, the total sample size for these analyses was \( n = 1025 \) (Pain-Related: \( n = 444 \); Canonical: \( n = 421 \); Other: \( n = 160 \)).

### Table 4

| PI-MBS    | ∆MMDs | ∆HIT-6 | PGIC | ∆EQ-5D-5L | ∆SF-36 MCS | ∆SF-36 PCS |
|-----------|-------|--------|------|-----------|------------|------------|
| PI-MBS    | 1.00  | -0.49  | -0.53| 0.85      | 0.25       | 0.35       | 0.22       |
| ∆MMDs     | -0.49 | 1.00   | 0.49 | -0.49     | -0.22      | -0.29      | -0.26      |
| ∆HIT-6    | -0.50 | 0.48   | 1.00 | -0.57     | -0.36      | -0.43      | -0.39      |
| PGIC      | 0.84  | -0.49  | -0.54| 1.00      | 0.28       | 0.34       | 0.28       |
| ∆EQ-5D-5L | 0.25  | -0.21  | -0.37| 0.28      | 1.00       | 0.38       | 0.31       |
| ∆SF-36 MCS| 0.34  | -0.29  | -0.45| 0.34      | 0.39       | 1.00       | 0.11       |
| ∆SF-36 PCS| 0.21  | -0.28  | -0.42| 0.27      | 0.35       | 0.13       | 1.00       |

Note: Pearson correlation coefficients are on the bottom diagonal (below 1 s) and Spearman correlation coefficients are on the top diagonal (above 1 s).

Abbreviations: ∆, change from baseline to week 12; EQ-5D-5L, EuroQol 5-dimension 5-level (visual analog scale); HIT-6, 6-Item Headache Impact Test; MCS, mental component summary score; MMDs, monthly migraine days; PCS, physical component summary score; PGIC, Patient Global Impression of Change; PI-MBS, patient-identified most bothersome symptom; PROMs, patient-reported outcomes measures; SF-36, 36-item Short-Form Health Survey.
In the pivotal phase 3 PROMISE-2 study of intravenous eptinezumab, the novel open-ended PI-MBS measure was used, and the effect of preventive treatment on the patients’ PI-MBS was measured during the trial. The resultant data were utilized in the current multifaceted post hoc analyses to empirically evaluate the appropriateness and clinical utility of the PI-MBS for preventive migraine research. The finding that PI-MBS improvement at week 12 consistently predicted improvement on PROMs, controlling for changes in MMDs, suggests that the PI-MBS may add clinically useful information reflecting patients’ symptom experience. Though we did not power the study for this exploratory endpoint, the statistically significant results suggest that power was adequate.

Known-groups analyses demonstrated that the PI-MBS improvement ratings were able to distinguish between clinically meaningful patient subgroups. Patients who were ≥50% MMD responders and patients who were HIT-6 total score responders reported greater improvement in PI-MBS compared with the respective non-responding groups, as did patients treated with eptinezumab compared with placebo. The magnitude of treatment effects for all PI-MBS appears to be in line with the eptinezumab dose (100 mg or 300 mg), with the 300 mg dose having a greater effect size (0.54 and 0.31, respectively; both \(p < 0.0001\) vs. placebo).

Advances in our understanding of the pathophysiologic mechanisms underlying migraine have resulted in the development of several new drugs and treatment classes for both preventive and acute migraine treatment. However, across the multitude of clinical trials of migraine preventive treatments undertaken to date, the outcomes and measures vary, particularly the inclusion of PROMs. Patient-centric measures that can identify and integrate the most bothersome aspects of the migraine experience...
with clinical efficacy data could inform and improve clinical decision-making and enhance the ability to prescribe appropriate treatment. Identification and understanding of how preventive treatment can impact PI-MBS has the potential to make future clinical trials more patient-centered and to provide support for the benefits of treatment.

A primary limitation of this study is the post hoc nature of the analysis, and additional studies will be necessary to confirm these findings.
findings. It is possible that interviewer bias confounded the identification of the PI-MBS as there was no standardized script at the baseline screening visit to elicit patient MBSs. Additionally, while the PI-MBS and PGIC correlate very highly, and the PI-MBS appears more specific in defining a migraine-related factor driving outcomes, the PGIC is conceptually and practically simpler. In this study, only changes in the PI-MBS identified at screening were evaluated, and it is not known if the PI-MBS for any given individual changed (to a different PI-MBS) over the course of the trial. Additionally, patients in this study were not asked when their PI-MBS occurred (ictal/interictal phase); thus, no analysis was done to investigate if this affected scores. This study also included headache pain as a PI-MBS, where traditionally studies of MBS have been of the cardinal symptoms other than headache pain (i.e., nausea, photophobia, and phonophobia). In future studies, it may be useful to explore a series of bothersome symptoms rather than a single PI-MBS, and to record which phase of migraine the symptoms occur for that patient.

CONCLUSION

These exploratory analyses of data from the PROMISE-2 study in patients with CM suggest that an open-ended question used to determine PI-MBS provides potential benefits for investigating patient-centric migraine treatment efficacy compared with other commonly evaluated PROMs. Correlations between PI-MBS and other migraine-specific PROMs were generally high, and improvement in PI-MBS at week 12 consistently predicted improvement on PROMs, even after controlling for MMDs. The data obtained in these analyses provide insights beyond the standard measure of reduction in MMDs; thus, clinicians, trialists, and policymakers should consider longitudinal monitoring of PI-MBS when evaluating the efficacy of preventive migraine treatments.

ACKNOWLEDGEMENTS

The authors thank the patients, their families, and the study sites that participated in PROMISE-2. The authors also thank Sally-Anne Mitchell, PhD, of The Medicine Group, LLC (New Hope, PA) for providing medical writing support, which was funded by H. Lundbeck A/S (Copenhagen, Denmark) in accordance with Good Publication Practice guidelines.

CONFLICT OF INTEREST

Dr. Lipton has been a consultant, advisory board member, and/or has received honoraria from Lundbeck Seattle BioPharmaceuticals, AER, Allergan/Abbvie, American Academy of Neurology, American Headache Society, Amgen, Biohaven Pharmaceuticals, BioVision, Boston Scientific, Dr. Reddy’s Laboratories, eNeura, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Impel Neuropharma, Merck, Pernix, Pfizer, Supernus, Teva, Trigemina, Vector, and Vedanta. In addition, he has received compensation from eNeura and Biohaven Pharmaceuticals, has stock or stock options in Biohaven Pharmaceuticals, Manistee, and has received research support from Amgen, Migraine Research Foundation, and National Headache Foundation. Dr. Goadsby has received grants and personal fees from Amgen and Eli Lilly, grants from Celgene, and personal fees from Aeon Biopharma, Alder Biopharmaceuticals, Allergan, Biohaven, Clexio, electroCore, eNeura, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, Novartis, Pfizer, Sanofi, Santara Therapeutics, Teva, Trigemina, as well as personal fees from Massachusetts Medical Society, MedicoLegal work, Oxford University Press, Up-to-Date, and Wolters Kluwer; and reports a patent magnetic stimulation for headache assigned to eNeura without fee. Dr. Dodick reports over the past 12 months consulting fees from Allergan, Biohaven, Amgen, Astra, Cerecin, Clexio, Cooltech, Ctrl M, GlaxoSmithKline, Impel, Lundbeck, Nocira, Novartis, Pfizer, Praxis, Revance, Axsome, Satsuma, Theranica, WL Gore. Honoraria: Speaking fees: Amgen, Eli Lilly, Lundbeck. Honoraria for CME activities: Academy for Continued Healthcare Learning, Cambridge University Press, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Majallin LLC, Medlogix Communications, Miller Medical Communications, MJH Lifesciences, Oxford University Press, Southern Headache Society (MAHEC), WebMD Health/Medscape, Wolters Kluwer. Research Support: American Migraine Foundation, Department of Defense, Henry Jackson Foundation, National Institutes of Health, Patient Centered Outcomes Research Institute (PCORI), Sperling Foundation. Stock Options/Shareholder/Patents/Board of Directors: Aural analytics (Options), Ctrl M (Options), ExSano (Options), Astra Institute (Options), Epalex (Options), Healint (Options), Palion (Options), Nocira (Options), Second Opinion/Mobile Health (Options), Theranica (Options), King-Devick Technologies (Options/Board), Matterhorn (Shares/Board), Ontologics (Shares/Board), Ayya Biosciences (options), Precon Health (Options/Board). Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Drs. McGinley, Houts, and Wirth are employees of Vector Psychometric Group, a company that received funding from H. Lundbeck A/S for time spent conducting this research. Dr. McGinley has also received research grants/sponsorship from Amgen and the National Headache Foundation and serves as the biostatistics editor for the journal Cephalalgia. Drs. Kymes, Ettrup, Østerberg, and Cady are employees of Lundbeck or one of its subsidiary companies and/or are stockholders in Lundbeck outside of the submitted work. Dr. Ashina is a principal investigator on clinical trials for AbbVie, Amgen, Eli Lilly, Lundbeck, and Novartis; has received personal fees from AbbVie, Amgen, Eli Lilly, Lundbeck, Novartis, Percept Corporation, and Teva; has received research grants from Lundbeck Foundation, Novo Nordisk Foundation, and Novartis; and serves as an Associate Editor of Cephalalgia. Associate Editor of The Journal of Headache and Pain, and Associate Editor of Brain. He has no ownership interest and does not own stocks of any pharmaceutical company. Dr. Buse is a part-time employee of Vector Psychometric Group, a company that received funding from H. Lundbeck A/S for time spent conducting this research; has received grant support from the National Headache Foundation; has received grant support and honoraria from Allergan, Amgen, Biohaven,
Eli Lilly, Lundbeck, and Teva; and serves on the editorial board of Current Pain and Headache Reports.

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**CLINICAL TRIALS REGISTRATION NUMBER**

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**How to cite this article:** Lipton RB, Goadsby PJ, Dodick DW, et al. Evaluating the clinical utility of the patient-identified most bothersome symptom measure from PROMISE-2 for research in migraine prevention. *Headache*. 2022;62:690-699. doi: [10.1111/head.14295](https://doi.org/10.1111/head.14295)