# Improving to 4 or Fewer Monthly Headache Days per Month Provides a Clinically Meaningful Treatment Goal for Patients With Chronic Migraine

Robert G. Kaniecki,[1] Deborah I. Friedman,[2] Joe Hirman,[3] Roger Cady[4,5,6]

[1]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Departments of Neurology and Neurotherapeutics and Ophthalmology, University of Texas Southwestern Medical Center, Dallas, TX; [4]Pacific Northwest Statistical Consulting, Woodinville, WA; [4]Lundbeck LLC, Deerield, IL; [5]RK Consults, Ozark, MO; [6]Missouri State University, Springfield, MO

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## Introduction

- Chronic migraine (CM) is the most disabling and costly subpopulation of migraine[1]; however, treatment goals for CM have not been established.
  - The risk of migraine disease progression increases sharply at a frequency of ≥4 monthly headache days (MHDs).[2,3]
- Current therapeutic goals for migraine treatment include a ≥50% or ≥75% reduction in monthly migraine days (MMDs) compared to a patient-assessed baseline or a ≥50% or ≥75% responder rate.[2–5] This is achieved by fewer than 50% of patients treated with a preventive migraine treatment in clinical trials.[6]
  - Communication of these treatment goals is complex and has different implications for patients with different frequencies of migraine days.
  - Acute treatment goals are more clearly defined, i.e., for the patient to have <10 acute medicine days per month using ergot derivatives, triptans, opioids, and combination analgesics,[7] as well as freedom from headache pain and absence of the most bothersome symptom (MBS)[4,6]; however, preventive treatment goals are often difficult to assess and implement.
- In clinical practice, a headache diagnosis and frequency of migraine attacks is often expected to be relatively stable for an individual patient, despite evidence suggesting headache frequency changes significantly over time, where some individuals oscillate between CM and episodic migraine.[7]
- Similar to treatment numbers established in other therapeutic areas (e.g., diabetes HbA1c glycemic target), a migraine/headache "number" could establish an easily understandable and easily communicated treatment goal for prevention outcome for patients with CM and other high-risk populations.
- Eptinezumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that inhibits calcitonin gene-related peptide (CGRP) and is approved for the preventive treatment of migraine.[8]
  - Two pivotal phase 3 trials, PROMISE-1 in patients with episodic migraine and PROMISE-2 in patients with CM, determined that intravenous administration of 100 mg and of 300 mg achieved the primary efficacy endpoint by significantly decreasing mean MMDs over weeks 1–12 vs placebo.[9,10]

## Objective

- The purpose of this post hoc analysis of previously collected data from the PROMISE-2 clinical trial was to define a treatment goal for CM where treatment needs are met and the risk of chronification and acute medication overuse are minimized.

## Methods

### Study Design and Treatment Interventions

- PROMISE-2 was a phase 3, double-blind, randomized, placebo-controlled, parallel-group study that evaluated the efficacy and safety of eptinezumab in patients with CM over 24 weeks of treatment.[10]
- A total of 1,072 adults with CM were randomized to receive intravenous eptinezumab 100 mg, 300 mg, or placebo administered over 30 minutes on day 0 and week 12.

### Patients

- Patients were between the ages of 18–65 years, had a diagnosis of migraine at ≤50 years of age with history of CM for ≥12 months (ICHD-3β criteria).[11]
- Patients taking prescription or over-the-counter-medication for acute or preventive treatment of migraine were eligible only if the medications had been prescribed or recommended by a health care provider.
- Preventive migraine medication use had to be stable for ≥3 months prior to screening.
- Patients using barbiturates or prescription opioids ≤4 days per month were eligible for participation if use was stable for ≥2 months prior to and through the screening period of the study.
- Use and quantities of other acute migraine medications (e.g., triptans, nonsteroidal anti-inflammatory drugs, simple analgesics) were not restricted.

### Outcomes and Assessments

- Patients completed a daily eDiary from the time of screening through week 24 regardless of whether a headache occurred and reported any headache events. The daily eDiary also captured acute medication use.
- Patient Global Impression of Change (PGIC) included a single question concerning the patient's impression of change in their disease status since the start of the study and incorporates multiple domains of health, including activity limitations, symptoms, emotions, and overall quality of life. Responses on the 7-point Likert scale ranged from very much improved to very much worse.
  - PGIC was administered 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 about the type of migraine-associated MBS symptom, the specific migraine attack (e.g., most recent), or the specific phase of migraine attack.[12]
  - 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 patient-identified (PI)-MBS severity since the beginning of the study. The rating scale was identical to the one used for PGIC.
- Acute migraine medication days (a day of triptan or ergot use) was measured by daily eDiary and aggregated to establish 4 week estimate for the screening phase and for the two post-treatment dosing intervals (Weeks 1–12; 13–24)[13]
- HIT-6 (6-item Headache Impact Test) measured the impact of migraine on the ability to function normally in daily life.
  - Scores of ≥60 denote severe life impact, 56–59 indicate substantial life impact, 50–55 represent some life impact, and ≤49 demonstrates little or no life impact.
  - HIT-6 was administered at screening, on day 0, and at weeks 4, 12, 16, 24, and 32.

### Statistical Analysis

- The purpose of the analysis is to evaluate a threshold of headache days to act as a clinically meaningful treatment goal rather than the treatment differences when that threshold is achieved; thus, data for the active and placebo arms were pooled.
- All available data points for HIT-6 total score, PGIC, PI-MBS, and days of acute medication use were combined for weeks 4, 12, 16, and 24 and analyzed by the following subgroups after their first study dose based on their MHDs in the previous 4 weeks: 0–4 (super response); 5–9 (moderate response); 10–15 (marginal response); >15 (poor response).
  - A "patient month" corresponded to the 4-week study intervals.

## Results

### Patient Global Impression of Change

- Of patient-months with ≤4 MHDs, on average, 40.9% and 44.8% were associated with "very much" or "much" improved PGIC, respectively. In contrast, on average, 22.9%, 10.4%, and 3.2% of patient-months with 5–9, 10–15, and >15 MHDs, respectively, reported "very much" improved PGIC, and 47.0%, 36.5%, and 16.2% reported "much" improved PGIC (**Figures 1A, 1B**).

### Patient-Identified Most Bothersome Symptom

- Of patient-months with ≤4 MHDs, on average, 41.5% and 43.6% were associated with "very much improved" and "much improved" PI-MBS, respectively. In contrast, on average, 23.4%, 10.8%, and 3.5% of patient-months with 5–9, 10–15, and >15 MHDs, respectively, reported "very much improved" PI-MBS, and 44.3%, 33.1%, and 14.0% reported "much improved" PI-MBS (**Figure 2**).

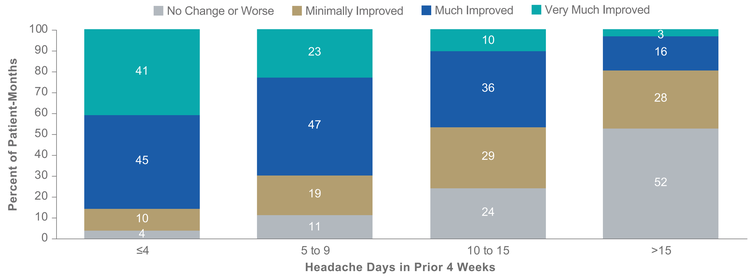
### Days of Acute Medication Use

- Acute medication use for >15 days accounted for, on average, 1.6%, 2.5%, 6.1%, and 46.9% of patient-months with ≤4, 5–9, 10–15, and >15 MHDs, respectively (**Figures 3A, 3B**). Importantly, on average, 96.1% of patient-months with ≤4 MHDs were associated with ≤4 acute medication use days, compared to, on average, 13.7% of patient-months with >15 MHDs.

### 6-item Headache Impact Test

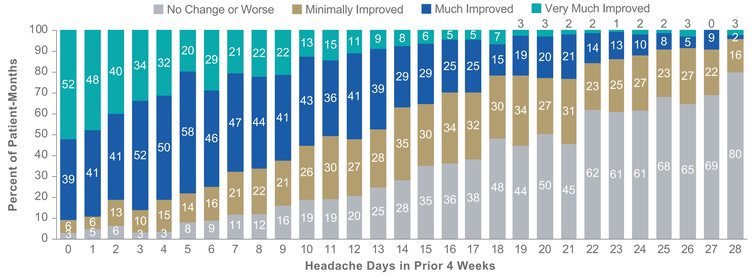
- Of patient-months with ≤4 MHDs, on average, 37.1% and 30.5%, were associated with "little to none" or "some" HIT-6 impairment, respectively. In contrast, on average, 19.9%, 10.1%, and 3.7% of patient-months with 5–9, 10–15, and >15 MHDs, respectively, reported "little to none" HIT-6 impairment, and 27.7%, 18.1%, and 9.1% reported "some" HIT-6 impairment (**Figure 4**).

### Figure 1A. Patient Global Impression of Change (PGIC) Response by MHD Subgroups[a]



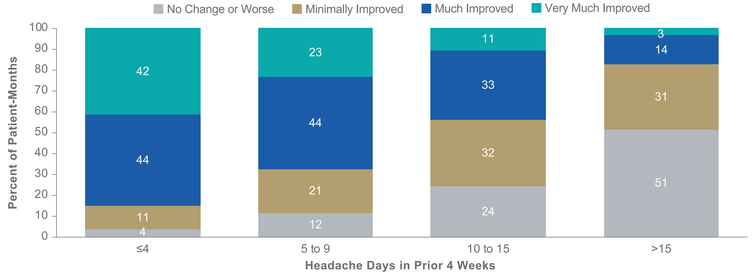

Weeks 4, 8, 12, 20, and 24 data combined.
[a]Monthly headache day (MHD) subgroups were defined by the number of MHDs in the previous 4 weeks.

### Figure 1B. PGIC Response Across 0–28 MHDs



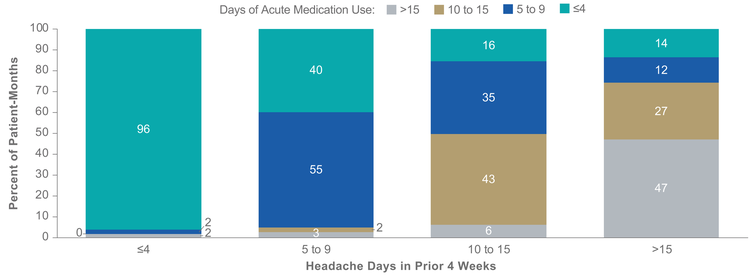

Weeks 4, 8, 12, 20, and 24 data combined.

### Figure 2. Patient-Identified Most Bothersome Symptom (PI-MBS) by MHD Subgroups[a]



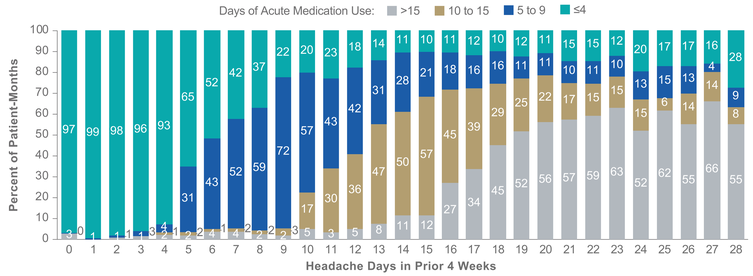

Weeks 4, 8, 12, 20, and 24 data combined.
[a]Monthly headache day (MHD) subgroups were defined by the number of MHDs in the previous 4 weeks.

### Figure 3A. Days of Acute Medication Use by MHD Subgroups[a]



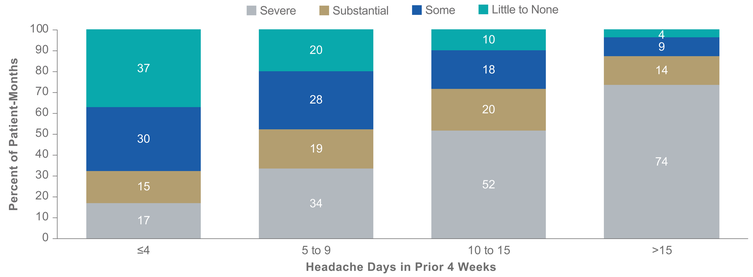

Weeks 4, 8, 12, 20, and 24 data combined.
[a]Monthly headache day (MHD) subgroups were defined by the number of MHDs in the previous 4 weeks.

### Figure 3B. Days of Acute Medication Use Across 0–28 MHDs




Weeks 4, 8, 12, 20, and 24 data combined.

### Figure 4. Headache Impact Test (HIT-6) Life Impact by MHD Subgroups[a]




Weeks 4, 8, 12, 20, and 24 data combined.
[a]Monthly headache day (MHD) subgroups were defined by the number of MHDs in the previous 4 weeks.

## KEY POINTS

- Migraine is associated with a substantial burden of illness that affects people most during their prime earning and family-building years,[1,14] yet current standards take a slow, stepwise, one-size-fits-all approach to attack treatment and disease prevention.
- Overall, data from this post hoc analysis of PROMISE-2 support the use of 4 or fewer MHDs as a targeted treatment goal for patients with CM. Specifically, patients in PROMISE-2 who had ≤4 MHDs in the prior 4 weeks had a higher percentage of patient-months reporting "very much improved" and "much improved" on the PGIC and PI-MBS, and "little to none" or "some" HIT-6 life impact.
- In addition, virtually none of the patients in the ≤4 MHD subgroup reported acute migraine medication use on >10 days. Further, the use of acute medication paralleled headache frequency, suggesting additional benefits to helping patients reach ≤4 MHDs.
- Treatment goals should be to get the patient to ≤4 MHDs rather than just focusing on a 50% reduction in monthly migraine frequency,[4] which for patients with high migraine frequency may still be substantial. In addition, having clearly articulated treatment goals will help improve communication between patients and health care providers and clarify meaningful treatment outcomes.

## CONCLUSION

- In this post hoc analysis, patients improving to ≤4 MHDs achieved improved patient-reported outcomes with substantially decreased acute medication use, suggesting that 4 MHDs may be a useful treatment goal to be used by health care providers for patients with CM.

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### Disclosures

**RK** has no disclosures to report. **DF** serves on advisory boards for Allergan, Amgen, Biohaven Biopharmaceuticals, electroCore, Eli Lilly, Impel, Invex, Lundbeck, Revance, Supernus, Teva, Theranica, and Zosano. She receives grant support from Allergan, Eli Lilly, Merck, and Zosano. She receives honoraria for serving as a contributing author to MedLink Neurology and Medscape and as a member of the Editorial Board of *Neurology Reviews*. **JH** is an employee of Pacific Northwest Statistical Consulting, Inc., a contracted service provider of biostatistical resources for H. Lundbeck A/S. **RC** was an employee of Lundbeck or one of its subsidiary companies at the time of the study.

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