Reductions in Acute Headache Medication Use After Eptinezumab Treatment in Patients With Chronic Migraine and Medication-Overuse Headache: Exploratory Analysis of PROMISE-2

Robert P. Cowan[1], Michael J. Marmura[2], Hans-Christoph Diener[3], Amaal J. Starling[4], Jack Schim[5], Joe Hirman[6], Thomas Brevig[7], Roger Cady[8-10]

[1]Stanford Health Care, Palo Alto, CA, United States; [2]Jefferson Headache Center, Philadelphia, PA, United States; [3]Medical Faculty of the University of Duisburg-Essen, Institute for Medical Informatics, Biometry and Epidemiology, Essen, Germany; [4]Mayo Clinic Arizona, Scottsdale, AZ, United States; [5]The Neurology Center of Southern California, Carlsbad, CA, United States; [6]Pacific Northwest Statistical Consulting, Inc., Woodinville, WA, United States; [7]H. Lundbeck A/S, Valby, Denmark; [8]Lundbeck LLC, Deerfield, IL, United States; [9]RK Consults, Ozark, MO, United States; [10]Missouri State University, Springfield, MO, United States

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Introduction

- According to the Chronic Migraine Epidemiology and Outcomes (CaMEO) study, 22.9% of the 13,624 survey respondents reported that they were current users of acute prescription migraine medications, with 34.5% of current users taking acute headache medication (AHM) while receiving concomitant migraine preventive treatment.[1]
- An important aim of preventive treatment is to reduce reliance on AHM, or at least optimize combinatorial treatments using AHMs,[2] as inappropriate and/or excessive use can lead to side effects[3,4] and, in some patients, the development and persistence of medication-overuse headache (MOH).[5–9]
- Eptinezumab is a humanized monoclonal antibody targeting calcitonin gene-related peptide and is approved for migraine prevention.
- In the PROMISE-2 trial, individuals who received eptinezumab (100 or 300 mg via IV infusion once every 12 weeks) for preventive treatment of chronic migraine (CM) achieved greater reductions in migraine and headache frequency, impact, and AHM use than did patients who received placebo.[10,11]
- In this post hoc analysis, the relationships between headache frequency reduction and changes in AHM use in adults with CM, not only in the full PROMISE-2 study population, but also in the subpopulations of patients with MOH and patients with MOH who achieved ≥50% reduction in migraine frequency over the course of treatment, were examined.

Objective

- This post hoc analysis of data from PROMISE-2 examined the relationships between headache frequency reduction and changes in AHM use in the subpopulation of adults with CM and MOH, including those who achieved ≥50% reduction in migraine frequency over the course of treatment.

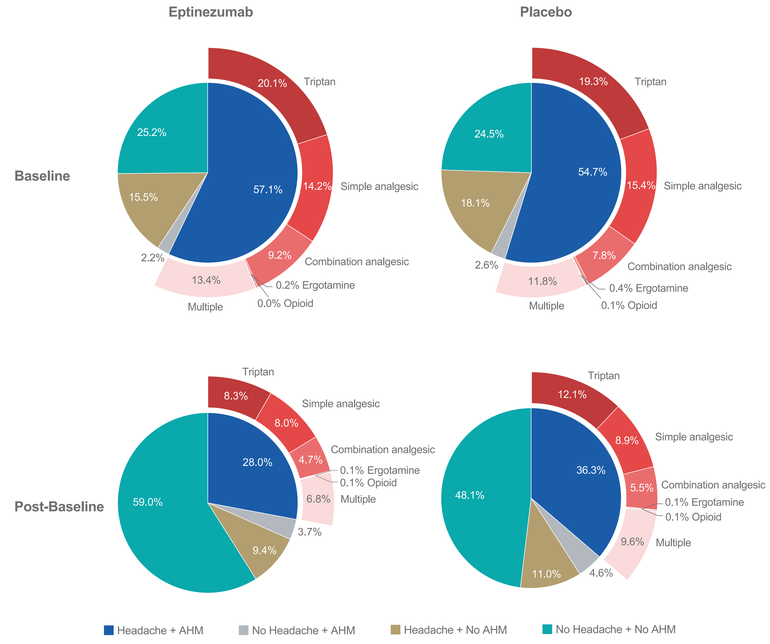
Methods

- PROMISE-2 was a double-blind, randomized, placebo-controlled phase 3 trial (NCT02974153)[10] evaluating the safety and efficacy of intravenously administered eptinezumab (100 mg or 300 mg, every 12 weeks for up to 2 doses) in adults (18–65 years) with CM (ICHD-3β[5] diagnostic criteria).
- Patients with a dual diagnosis of CM and MOH (diagnosed using ICHD-3β criteria[5]) were enrolled if any barbiturate or prescription opioid use was limited to ≤4 days/month during the run-in period.
- Patients were permitted to use acute medication throughout the study.
- Changes in AHM use were evaluated in the subgroup of patients with CM and MOH, as well as in patients with CM and MOH experiencing ≥50% reduction in monthly migraine days (MMDs) over Weeks 1–24.
- Data for the eptinezumab groups (100 mg and 300 mg) were pooled, given that the dose levels demonstrated similar efficacy and safety in the total population and subpopulation with MOH.[10,12,13]
- Patients used a daily electronic diary (eDiary) to record whether they experienced a headache (headache episodes or migraine attacks), if they used an AHM, and what type of AHM was used (ergotamine, triptan, analgesic, opioid, or combination analgesic). Data from all days with completed eDiary evening reports were included in analysis.
- During screening (baseline) and treatment (Weeks 1–24), days were categorized into four groups: headache with AHM use, headache with no AHM use, no headache with AHM use, and no headache with no AHM use. The distribution of AHM type on headache days with AHM use was also evaluated.
- Statistical methods were descriptive in nature and lacked pre-specification; thus, no claims of statistically significant/definitive conclusions were made.

Results

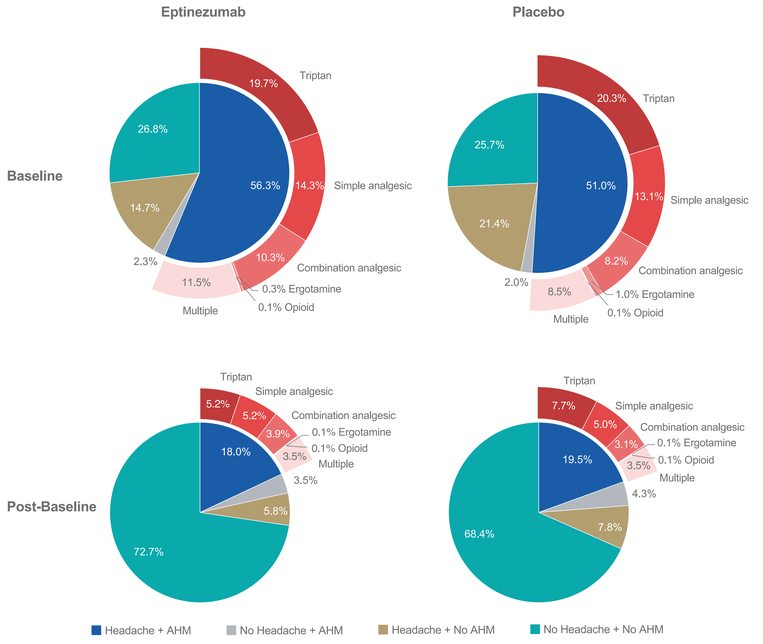
- Patients were predominantly female (88.2%) and white (91.0%).
- At screening, 40.2% (431/1072) of patients with CM had a diagnosis of MOH, and 52.2% of these were ≥50% migraine responders over Weeks 1–24.
- Across the CM+MOH subpopulation, 11,305 study days from the baseline/screening period and 61,536 study days from the post-baseline period (Weeks 1–24) were included in analysis based on eDiary completeness (**Table 1**).
- In patients with CM and MOH (**Figure 1**), including those with ≥50% migraine response over Weeks 1–24 (**Figure 2**), days with headache and AHM use comprised 51.0–57.1% of the baseline period (placebo and eptinezumab groups).
- Relative to baseline, the proportion of days with both headache and AHM use decreased 29.1% points (eptinezumab) versus 18.4% points (placebo) in the MOH subgroup (**Figure 1**), and 38.3% points versus 31.5% points, respectively, in the CM+MOH+≥50% response subgroup during Weeks 1–24 (**Figure 2**).
- The proportion of days with headache and triptan use decreased 11.8% (eptinezumab) and 7.2% (placebo) in the MOH subgroup over Weeks 1–24 (**Figure 1**) relative to baseline values (20.1% for eptinezumab, 19.3% for placebo).
- The proportion of days with headache and triptan use decreased 14.5% (eptinezumab) and 12.6% (placebo) in the MOH ≥50% responder subgroup (**Figure 2**) over Weeks 1–24, notably below the diagnostic threshold of MOH.
- The proportion of days with headache but no AHM use decreased 6.1% points (eptinezumab) versus 7.1% points (placebo), respectively, in the MOH subgroup (**Figure 1**) and 8.9% points versus 13.6% points, respectively, in the CM+MOH+≥50% response subgroup (**Figure 2**).
- In all three populations, patients reported no headache and no AHM use for approximately 25% of days during the baseline period.
- The proportion of days with no headache and no AHM use increased to 59.0% (eptinezumab) and 48.1% (placebo) during Weeks 1–24 in the MOH subgroup (**Figure 1**) and to 72.7% and 68.4%, respectively, in the CM+MOH+≥50% migraine response subgroup over Weeks 1–24 (**Figure 2**).
- Across populations, days with AHM use in the absence of headache were uncommon during baseline (2.0–2.6% of days), and only increased slightly during the post-baseline period.

Figure 1. Percent of Study Days With AHM Use Among Patients With CM and MOH by Headache Status*



*Headache status was categorized as with or without headache. AHM type included for days with headache and AHM use. AHM, acute headache medication; CM, chronic migraine; MOH, medication-overuse headache. Multiple refers to multiple AHM types used instead of a single type. Post-baseline refers to Weeks 1–24.

Figure 2. Percent of Study Days With AHM Use Among Patients With CM and MOH Who Experienced ≥50% Response Over Weeks 1–24 by Headache Status*



*Headache status was categorized as with or without headache. AHM type included for days with headache and AHM use. AHM, acute headache medication; CM, chronic migraine; MOH, medication-overuse headache. Multiple refers to multiple AHM types used instead of a single type. Post-baseline refers to Weeks 1–24.

Table 1. Number of Days with Completed Electronic Diary Reports by Population and Time Period

	Eptinezumab		Placebo	
	Baseline	Weeks 1–24	Baseline	Weeks 1–24
CM+MOH, N=431 (eptinezumab, n=286; placebo n=145)	7,500	41,113	3,805	20,423
CM+MOH+≥50% response, N=225 (eptinezumab, n=176; placebo, n=49)	4,652	25,855	1,263	6,850

KEY POINTS

- Patients with a dual diagnosis of CM and MOH are an understudied group presented with limited treatment options.
- This post hoc analysis of data from PROMISE-2 examined the relationships between headache frequency reduction and changes in AHM use in the subpopulation of adults with CM and MOH, including those who achieved ≥50% reduction in migraine frequency over the course of treatment.

CONCLUSIONS

- Eptinezumab was associated with greater reductions in headache frequency and days of AHM use versus placebo in patients with CM and MOH.
- The magnitude of effect was clinically relevant in the subgroup of CM patients with MOH who experienced ≥50% response, suggesting that eptinezumab treatment can lead to improving acute response and decreasing MOH risk.
- Across analysis groups, reductions in the proportions of patients with headache but no AHM use were observed, suggesting that these patients were experiencing milder symptoms which were not significant enough to impact function and warrant treatment.
- There were slight increases in the proportions of each analysis group with no headache but with AHM use, a finding that could suggest these patients may be treating during an aura or while having premonitory symptoms and may be anticipating a migraine within hours of occurrence.
- Future work is needed to generalize post hoc findings to a larger population of patients seeking relief from other headache disorders (such as episodic migraine) and headache features (such as most bothersome symptom, headache severity, and headache impact).

References

1. Hutchinson S, Lipton RB, Ailani J, et al. *Mayo Clin Proc.* 2020;95(4):709-718.
2. Ailani J, Burch RC, Robbins MS. *Headache.* 2021;61(7).
3. Tajti J, Majláth Z, Szok D, Csáti A, Vécsei L. *Expert Opin Drug Saf.* 2015;14(6).
4. Thorlund K, Toor K, Wu P, et al. *Cephalalgia.* 2017;37(10).
5. Vandenbussche N, Laterza D, Lisicki M, et al. *J Headache Pain.* 2018;19(1).
6. Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia.* 2018;38(1).
7. Diener HC, Dodick D, Evers S, et al. *Lancet Neurol.* 2019;18(9):891-902.
8. Thorlund K, Sun-Edelstein C, Druyts E, et al. *J Headache Pain.* 2016;17(1):107.
9. Schwedt TJ, Alam A, Reed ML, et al. *J Headache Pain.* 2018;19(1):38.
10. Lipton RB, Goadsby PJ, Smith J, et al. *Neurology.* 2020;94(13):e1365-e1377.
11. Silberstein S, Diamond M, Hindiyeh NA, et al. *J Headache Pain.* 2020;21(1):120.
12. Diener HC, Marmura MJ, Tepper SJ, et al. *Headache.* 2021;61(1):125-136.
13. Martin V, Nagy AJ, Janelidze M, et al. Impact of Baseline Characteristics on the Efficacy and Safety of Eptinezumab in Patients With Migraine: Subgroup Analyses of PROMISE-1 and PROMISE-2. *Clin Ther.* 2022; in press, corrected proof.

Disclosures

Dr. Cowan has been a consultant and/or advisory board member for Alder, Allergan, Amgen, ATI, electroCore, eNeura, Novartis, Teva, and Zosano; served on a speaker's bureau for Biohaven and as an expert consultant for GLG, Guidepoint Global, Impel, Satsuma, Spherix Global Insights, Teva, Theranica, XOC, and Zosano; and received royalties from Penguin/Avery and Springer. **Dr. Marmura** has received grants for research (no personal compensation) from Allergan/Abbvie, electroCore, and Teva; served as a consultant and/or advisory board member for Alder/Lundbeck, Amgen/Novartis, and Theranica; participated in a speaker's bureau for Amgen/Novartis and Eli Lilly; and received royalties from Cambridge, Demos Medical, and MedLink. **Dr. Diener** has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations over the last 3 years from Allergan, Eli Lilly, Lundbeck, MSD, Novartis, Pfizer, Teva, and Weber & Weber; received financial research support from Allergan and electroCore, headache research support from the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union; and served on editorial boards for *Cephalalgia* and *Lancet Neurology*. **Dr. Starling** has received consulting fees from Alder, Amgen, Eli Lilly, eNeura, Impel, Lundbeck, Novartis, and Theranica. **Dr. Schim** has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Acorda, Allergan, Amgen, Avanir, Depomed, electroCore, Eli Lilly, Novartis, Pernix, Promius, Supernus, Teva Pharmaceuticals, and Upsher-Smith; holds stock and/or stock options in Alder/Lundbeck, which sponsored research in which JS was involved as an investigator; and has received research support from Allergan, Amgen, and Eli Lilly. **Dr. Hirman** is an employee of Pacific Northwest Statistical Consulting, Inc., a contracted service provider of biostatistical resources for H. Lundbeck A/S. **Dr. Brevig** is an employee of H. Lundbeck A/S. **Dr. Cady** was an employee of Lundbeck or one of its subsidiary companies at the time of study.

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