Patients With Migraine Who Achieved a ≥75% Reduction in Monthly Migraine Days With Eptinezumab Treatment: Subgroup Analysis of PROMISE-1 and PROMISE-2

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Presented at the International Headache Congress; September 8–12, 2021; Virtual meeting

Introduction

- Eptinezumab is a humanized monoclonal antibody that specifically and strongly binds calcitonin gene-related peptide, preventing it from binding to its receptor, and is indicated for the preventive treatment of migraine in adults.[1]
- In the pivotal phase 3 trials, PROMISE-1 and PROMISE-2, eptinezumab 100 mg and 300 mg demonstrated rapid and sustained reductions in migraine frequency in patients with episodic migraine (EM) and chronic migraine (CM).[2-5]
- The ≥75% migraine responder rates (MRRs; ie, percentage of patients with ≥75% reduction in monthly migraine days) over Weeks 1–12 with eptinezumab were similar in both studies— ~26% in PROMISE-1 (patients with EM) and ~30% in PROMISE-2 (patients with CM)—and were greater than with placebo (~16% across studies).[2,3]
- It has been suggested that this threshold represents a "tipping point" in migraine prevention, with patients achieving ≥75% MRR in a phase 2 eptinezumab study experiencing much greater improvements in patient-reported outcomes (PROs) than patients with lower thresholds of response.[6]

Objective

- To confirm the impact of experiencing a ≥75% reduction from baseline in monthly migraine days on other aspects of migraine in a larger study population.

Methods

- PROMISE-1 (NCT02559895)[2,4]: a phase 3 randomized, double-blind, placebo-controlled, multiple-dose study of eptinezumab (30, 100, or 300 mg IV every 12 weeks × 4 doses) in adults with EM.
- PROMISE-2 (NCT02974153)[3,5]: a phase 3 randomized, double-blind, placebo-controlled, multiple-dose study (100 or 300 mg IV every 12 weeks × 2 doses) in adults with CM.
- Data from patients treated with eptinezumab 100 mg, 300 mg, or placebo who achieved a ≥75% MRR over Weeks 1–12 were included in this post hoc analysis.
  - For the purposes of this analysis, only patients receiving 100 mg or 300 mg doses of eptinezumab were included; therefore, any "eptinezumab pooled" groups included those two dose levels.
- A daily eDiary was used throughout each study to obtain a daily report (irrespective of headache occurrence) and to capture headache events and migraine days.
  - Reductions in monthly migraine days were based on the reduction in the number of migraine days recorded in the eDiary during the baseline period compared with the average monthly number of migraine days recorded over the treatment interval.
- Both studies captured the 36-item Short-Form Health Survey (SF-36; v2.0) at site visits throughout the study, and PROMISE-2 also captured the 6-item Headache Impact Test (HIT-6), patient-identified most bothersome symptom (PI-MBS), and Patient Global Impression of Change (PGIC) at site visits throughout the study.
- Descriptive statistics were used to evaluate the consistency of ≥75% MRR within and across dosing intervals, as well as the changes in patient-reported outcomes.

Results

- A total of 326/1149 (28.4%) eptinezumab-treated patients achieved ≥75% MRR over Weeks 1–12 across studies compared with 91/588 (15.5%) placebo patients (**Table 1**).
- Within studies, baseline demographics and clinical characteristics of patients with ≥75% migraine responders over Weeks 1–12 were similar across treatment arms, with slight differences in the PROMISE-1 and PROMISE-2 populations (**Table 2**).
  - Patients in PROMISE-1 were younger and with a smaller proportion of white patients and a higher mean body mass index; the clinical relevance of these differences is undetermined.
- Across studies, >90% of these patients achieved a monthly ≥75% MRR for ≥2 of 3 individual study months during Weeks 1–12, suggesting consistency of response within the first dosing interval (**Figure 1**).
- The consistency of ≥75% migraine response over Weeks 13–24 was similar between treatment arms, with >70% of EM and >80% of CM patients maintaining ≥75% MRR over Weeks 13–24 (**Figure 2**).
- In ≥75% migraine responders, patients with EM generally reported normative levels (score of ~50) of quality of life across the SF-36 domains of bodily pain, social functioning, and role-physical at baseline (**Table 3**).
  - At week 12, mean scores improved by 3.0–6.7 points for bodily pain, 2.2–3.2 points for social functioning, and 2.5–4.7 points for role-physical domains.
- Patients with CM generally reported severely impacted quality of life (scores below 1–2 standard deviations from the mean) at baseline (**Table 3**).
  - At week 12, SF-36 scores across the domains increased 8.1–10.1 points for bodily pain, 6.0–8.4 points for social functioning, and 7.1–8.6 points for role-physical domains.
- For CM patients with ≥75% MRR during Weeks 1–12, the mean (standard deviation) change from baseline to Week 12 in HIT-6 total score in the pooled eptinezumab group was –11.7 (8.2) points.
  - At Week 12, 136/211 (64.5%) eptinezumab-treated patients with ≥75% MRR had *little to no* or *some* headache-related life impact (HIT-6 total score).
- On item 1 of the HIT-6 (ie, frequency of severe pain during headache), the percentage of eptinezumab-treated patients reporting *very often* or *always* decreased from 60.7% (baseline) to 18.0% (Week 12) (**Figure 3**).
- More than 80% of eptinezumab-treated patients with ≥75% MRR reported *much or very much* improvement on the PI-MBS (177/211 [83.9%]) and PGIC (178/211 [84.4%]) measures. Similar results were achieved in placebo patients with ≥75% MRR during Weeks 1–12 (PI-MBS: 42/55 [76.4%]; PGIC: 44/55 [80.0%]).

Table 1. ≥75% Migraine Responder Rates in PROMISE-1 and PROMISE-2

	Eptinezumab 100 mg	Eptinezumab 300 mg	Eptinezumab Pooled	Placebo
PROMISE-1 (EM), n/N (%)	49/221 (22.2)	66/222 (29.7)	115/443 (26.0)	36/222 (16.2)
P value vs placebo	0.1126	0.0007		
PROMISE-2 (CM), n/N (%)	95/356 (26.7)	116/350 (33.1)	211/706 (29.9)	55/366 (15.0)
P value vs placebo	0.0001	<0.0001		
Combined (EM+CM), n/N (%)	144/577 (25.0)	182/572 (31.8)	326/1149 (28.4)	91/588 (15.5)

CM, chronic migraine; EM, episodic migraine; MRR, migraine responder rate.

Table 2. Baseline Demographics and Clinical Characteristics of ≥75% Migraine Responders

	Eptinezumab 100 mg	Eptinezumab 300 mg	Eptinezumab Pooled	Placebo
PROMISE-1 (EM), n	49	66	115	36
Mean age, years (SD)	39.1 (12.2)	40.1 (11.2)	39.7 (11.6)	37.3 (11.1)
Sex: Female, n (%)	39 (79.6)	57 (86.4)	96 (83.5)	32 (88.9)
Race, n (%)				
White	43 (87.8)	58 (87.9)	101 (87.8)	26 (72.2)
Black or African American	2 (4.1)	7 (10.6)	9 (7.8)	9 (25.0)
Other	4 (8.2)	1 (1.5)	5 (4.3)	1 (2.8)
Mean (SD) BMI, kg/m^2	28.0 (7.5)	29.8 (7.3)	29.0 (7.4)	29.3 (6.7)
Mean (SD) age at diagnosis, years	19.9 (9.2)	21.0 (9.4)	20.5 (9.3)	24.9 (9.9)
Mean (SD) duration of migraine diagnosis, years	19.3 (11.0)	19.0 (11.2)	19.1 (11.1)	12.4 (8.1)
Mean (SD) baseline migraine days	8.8 (2.9)	8.5 (2.9)	8.6 (2.8)	8.3 (3.1)
Mean (SD) baseline headache days	10.0 (2.7)	10.4 (3.3)	10.3 (3.1)	9.9 (3.4)
PROMISE-2 (CM), n	95	116	211	55
Mean age, years (SD)	43.9 (11.2)	41.1 (10.1)	42.3 (10.6)	39.9 (11.9)
Sex: Female, n (%)	80 (84.2)	102 (87.9)	182 (86.3)	50 (90.9)
Race, n (%)				
White	90 (94.7)	108 (93.1)	198 (93.8)	47 (85.5)
Black or African American	5 (5.3)	6 (5.2)	11 (5.2)	6 (10.9)
Other	0	2 (1.7%)	2 (0.9)	2 (3.6)
Mean (SD) BMI, kg/m^2	26.3 (4.1)	26.5 (4.9)	26.4 (4.5)	28.1 (5.3)
Mean (SD) age at diagnosis, years	24.1 (10.1)	23.0 (9.4)	23.5 (9.7)	23.2 (10.0)
Mean (SD) duration of migraine diagnosis, years	19.7 (12.4)	18.1 (11.3)	18.8 (11.8)	16.7 (13.0)
Mean (SD) duration of chronic migraine, years	10.3 (12.3)	10.8 (11.0)	10.6 (11.6)	13.2 (12.5)
Mean (SD) baseline migraine days	15.7 (4.2)	15.0 (4.4)	15.3 (4.3)	17.0 (4.5)
Mean (SD) baseline headache days	19.6 (2.5)	20.0 (3.1)	19.8 (2.9)	21.2 (2.9)
Medication-overuse headache diagnosis, n (%)	38 (40.0)	44 (37.9)	82 (38.9)	21 (38.2)

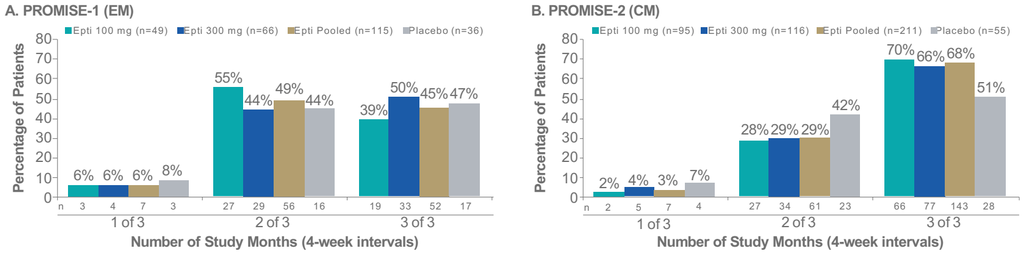
A ≥75% migraine responder was defined as a patient who achieved a ≥75% reduction in mean monthly migraine days over Weeks 1–12. BMI, body mass index; CM, chronic migraine; EM, episodic migraine; N/A, not applicable; SD, standard deviation.

Table 3. Change From Baseline to Week 12 in SF-36 Bodily Pain, Social Functioning, and Role-Physical Domains in ≥75% Migraine Responders

	Eptinezumab 100 mg	Eptinezumab 300 mg	Eptinezumab Pooled	Placebo
PROMISE-1 (EM), n	49	66	115	36
Bodily pain				
Baseline, mean (SD)	46.2 (10.0)	48.5 (9.3)	47.5 (9.6)	50.6 (8.5)
Week 12, mean (SD)	52.7 (8.3)	54.7 (7.2)	53.9 (7.7)	53.4 (8.5)
Change from baseline, mean (SD)	6.7 (7.8)	5.9 (7.7)	6.2 (7.7)	3.0 (9.6)
Social functioning				
Baseline, mean (SD)	50.6 (8.2)	51.4 (8.1)	51.1 (8.1)	51.6 (8.4)
Week 12, mean (SD)	53.9 (5.1)	53.9 (6.3)	53.9 (5.8)	53.3 (6.3)
Change from baseline, mean (SD)	3.2 (7.5)	2.2 (7.1)	2.6 (7.3)	2.4 (8.0)
Role-physical				
Baseline, mean (SD)	49.1 (8.9)	50.1 (7.9)	49.7 (8.3)	50.9 (7.0)
Week 12, mean (SD)	53.8 (6.6)	54.2 (5.0)	54.0 (5.7)	52.9 (6.5)
Change from baseline, mean (SD)	4.7 (7.9)	3.9 (7.5)	4.3 (7.7)	2.5 (8.7)
PROMISE-2 (CM), n	95	116	211	55
Bodily pain				
Baseline, mean (SD)	40.1 (9.6)	40.1 (9.4)	40.1 (9.5)	42.9 (8.9)
Week 12, mean (SD)	49.2 (8.1)	50.2 (7.6)	49.7 (7.8)	50.9 (7.8)
Change from baseline, mean (SD)	9.4 (9.7)	10.1 (9.2)	9.8 (9.4)	8.1 (9.5)
Social functioning				
Baseline, mean (SD)	42.6 (10.8)	43.0 (9.7)	42.8 (10.2)	47.1 (10.3)
Week 12, mean (SD)	51.1 (6.8)	51.1 (7.4)	51.1 (7.2)	52.9 (6.4)
Change from baseline, mean (SD)	8.4 (9.5)	8.0 (9.1)	8.2 (9.3)	6.0 (10.1)
Role-physical				
Baseline, mean (SD)	42.3 (9.0)	42.2 (8.7)	42.2 (8.8)	44.7 (9.8)
Week 12, mean (SD)	49.4 (6.8)	50.7 (6.9)	50.1 (6.9)	53.4 (4.3)
Change from baseline, mean (SD)	7.1 (9.7)	8.6 (8.7)	7.9 (9.2)	8.4 (8.6)

A ≥75% migraine responder was defined as a patient who achieved a ≥75% reduction in mean monthly migraine days over Weeks 1–12. BMI, body mass index; CM, chronic migraine; EM, episodic migraine; SD, standard deviation.

Figure 1. Monthly ≥75% Migraine Response in Patients Achieving ≥75% Migraine Response over Weeks 1–12 in (A) PROMISE-1 and (B) PROMISE-2



A ≥75% migraine responder was defined as a patient who achieved a ≥75% reduction in mean monthly migraine days over Weeks 1–12. A study month was defined as a 4-week interval (ie, weeks 1-4, 5-8, and 9-12). CM, chronic migraine; EM, episodic migraine.

Figure 2. Subsequent Infusions With ≥75% Migraine Response in Patients Achieving ≥75% Migraine Response During the First Infusion (Weeks 1–12)

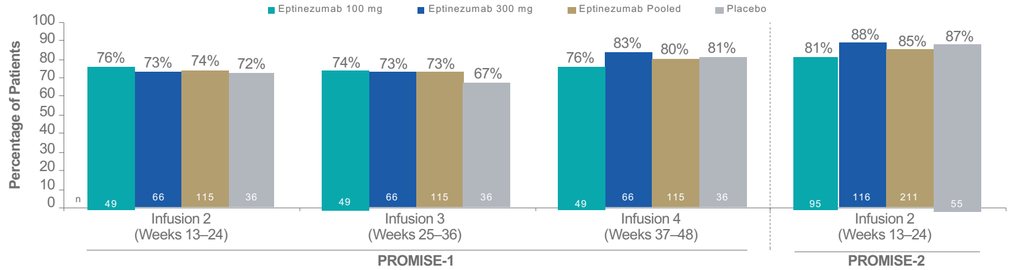
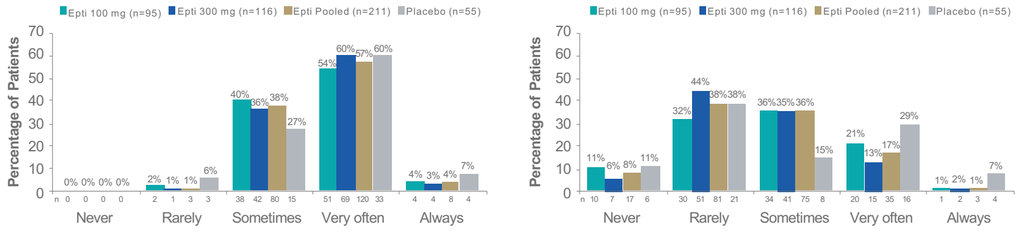


Figure 3. Responses to HIT-6 Item 1 (Severe Pain) in ≥75% Migraine Responders Over Weeks 1–12 in PROMISE-2 at (A) Baseline and (B) Week 12



Item 1 of the 6-item Headache Impact Test (HIT-6) asked "When you have headaches, how often is the pain severe?" A ≥75% migraine responder was defined as a patient who achieved a ≥75% reduction in mean monthly migraine days over Weeks 1–12.

KEY POINTS

- This post hoc subgroup analysis of data from PROMISE-1 and PROMISE-2 evaluated the consistency of ≥75% migraine response over Weeks 1–12 within and across dosing intervals, and assessed the impact of ≥75% migraine response on PROs captured in each study.
- 28.4% of eptinezumab-treated (100 mg or 300 mg) patients achieved ≥75% migraine response over Weeks 1–12 compared with 15.5% of placebo patients.
- Across studies, >90% of patients with ≥75% migraine response over Weeks 1–12 achieved a monthly ≥75% MRR for ≥2 of 3 individual study months during that period.
- In patients with EM and CM, >70% and >80%, respectively, maintained ≥75% migraine response over the second dosing interval (Weeks 13–24).
- In patients with ≥75% migraine response over Weeks 1–12, clinically meaningful improvements were observed for SF-36 domains across patients with EM and CM, as well as for HIT-6, PI-MBS, and PGIC in patients with CM.

CONCLUSIONS

- More patients receiving eptinezumab achieved a ≥75% MRR compared with placebo across patients with EM and CM, and that level of response remained largely consistent across 24 to 48 weeks of treatment.
- For patients with CM achieving ≥75 MRR, clinically meaningful improvements in PROs indicated substantial improvements in quality of life, headache-related life impact, and symptomatology.

References

1. Vyepti [package insert]. Bothell, WA: Lundbeck Seattle BioPharmaceuticals, Inc.; 2020.
2. Ashina M, et al. *Cephalalgia*. 2020;40(3):241-254.
3. Lipton RB, et al. *Neurology*. 2020;94(13):e1365-e1377.
4. Smith TR, et al. *Clin Ther*. 2020;42(12):2254-2265.e3.
5. Silberstein S, et al. *J Headache Pain*. 2020;21(1):120.
6. Cady R, Lipton RB. *Headache*. 2018;58:1092-1095.

Disclosures

Dr Lipton has been a consultant, advisory board member, and/or has received honoraria from Lundbeck Seattle BioPharmaceuticals, Allergan, American Academy of Neurology, American Headache Society, Amgen, Biohaven Pharmaceuticals, BioVision, Boston Scientific, Dr. Reddy's Laboratories, electroCore Medical, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Pernix, Pfizer, Supernus, Teva Pharmaceuticals, Trigemina, Vector, and Vedanta. In addition, he has received compensation from eNeura and Biohaven Pharmaceuticals, has stock or stock options in Biohaven Pharmaceuticals, and has received research support from Amgen, Migraine Research Foundation, and National Headache Foundation. **Dr. Charleston** has received personal compensation for serving as a consultant for Allergan/AbbVie, Alder, and Biohaven and for serving as an Expert Witness for Vaccine Injury Compensation Program. In addition, he is a non-compensated Associate Editor with Headache and has a non-compensated relationship as a Board Member at Large with Alliance for Headache Disorders Advocacy. **Dr Tassorelli** has received honoraria for the participation in advisory boards for Allergan, ElectroCore, Eli Lilly, Novartis, and Teva; has been a speaker for Allergan, Eli Lilly, Novartis and Teva; has been a PI or collaborator in clinical trials sponsored by Alder, Amgen, Eli Lilly, and Teva; and has received grants from the European Commission, the Italian Ministry of Health, and the Italian Ministry of University. **Drs Brevig and Cady** are employees of Lundbeck or one of its subsidiary companies and are stockholders in Lundbeck. **Dr Hirman** is an employee of Pacific Northwest Statistical Consulting, Inc., a contracted service provider of biostatistical resources for H. Lundbeck A/S.

Acknowledgments

This study was sponsored by H. Lundbeck A/S (Copenhagen, Denmark). The authors thank The Medicine Group, LLC (New Hope, PA, USA) for providing medical writing support, which was funded by H. Lundbeck A/S (Copenhagen, Denmark) in accordance with Good Publication Practice guidelines.