Efficacy and Safety of Eptinezumab in Patients With Migraine and Self-Reported Aura: Post Hoc Analysis PROMISE-1 and PROMISE-2

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Messoud Ashina,[1] Peter McAllister,[2] Roger Cady,[3] Joe Hirman,[4] Anders Ettrup[5]

[1]Danish Headache Center, Rigshospitalet Glostrup, University of Copenhagen, Copenhagen, Denmark; [2]New England Institute for Neurology and Headache, Stamford, CT, USA; [3]Lundbeck La Jolla Research Center, San Diego, CA, USA; [4]Pacific Northwest Statistical Consulting, Inc., Woodinville, WA, USA; [5]H. Lundbeck A/S, Copenhagen, Denmark

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Introduction

- It is estimated that ~30% of patients with migraine experience aura—most commonly manifested as visual disturbances—occurring within 60 minutes before the headache pain begins.[1,2]
- Migraine with aura is associated with an increased risk of cardiovascular disease.[3-5]
- Eptinezumab is a humanized immunoglobulin G1 monoclonal antibody specific for calcitonin gene-related peptide and is indicated for the preventive treatment of migraine in adults.[6]
- 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.[7-10]
  - At screening, approximately 45% of patients in these studies reported that they had experienced aura with their migraines.

Objective

- This post hoc analysis of data from PROMISE-1 and PROMISE-2 was performed to evaluate the efficacy and safety of eptinezumab for the preventive treatment of migraine in patients with self-reported history of migraine with aura.

Methods

- PROMISE-1 (NCT02559895)[7,8]: 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 episodic migraine
- PROMISE-2 (NCT02974153)[8-10]: a phase 3 randomized, double-blind, placebo-controlled, multiple-dose study (100 or 300 mg IV every 12 weeks × 2 doses) in adults with chronic migraine
- In both studies, the primary efficacy outcome was the reduction in monthly migraine days (MMDs) over Weeks 1–12.
- Secondary and exploratory outcomes included ≥50% and ≥75% migraine responder rates, acute headache medication use, and treatment-emergent adverse events (TEAEs).
- Patients from PROMISE-1 and PROMISE-2 were pooled for all analyses, with the exception of the change from baseline in MMDs, due to the differences in patient populations at baseline.
- Data from patients treated with eptinezumab 100 mg, 300 mg, or placebo and who self-reported migraine with aura at screening were included in this post hoc analysis.
  - For these studies, migraine was defined using the International Classification of Headache Disorders, 3rd ed. (ICHD-3), and patients separately reported any experience of aura with their migraine.
  - Symptoms constituting aura were discussed with and explained by investigators to patients to improve accuracy of future symptom capture.
- For efficacy analyses, patient results were summarized within the treatment group to which they were randomly assigned. In the safety subpopulation, patients were analyzed according to the randomized treatment they received.
- All results are descriptive statistics, such as means, standard deviations, and rates.

Results

Analysis Population

- A total of 877/1741 (50.4%) patients who received eptinezumab 100 mg, 300 mg, or placebo in PROMISE-1 and PROMISE-2 reported a history of experiencing aura at screening.
  - The mean age of all patients in this analysis was 40.0 years, patients were predominantly female (761/877 [87%]), and predominantly white (751/877 [86%] (**Table 1**).
  - More patients had episodic migraine (507/877 [58%]) than chronic migraine (370/877 [42%]).
- In patients with episodic and chronic migraine, reductions in MMDs over Weeks 1–12 were greater in patients treated with eptinezumab (–4.1 and –7.4, respectively) than in patients who received placebo (–3.1 and –6.0, respectively) (**Table 2**).
- Reductions in MMDs in patients with self-reported migraine with aura were comparable to those in the total PROMISE-1 and PROMISE-2 populations[8,11] (**Figure 1**).
- In the pooled group of patients with aura, more than one-half of patients who received eptinezumab were ≥50% migraine responders over Weeks 1–12 (vs 39% of patients who received placebo) (**Figure 2**).
- In the pooled group of patients with aura, approximately one-fourth were ≥75% migraine responders over Weeks 1–12 (vs 18% of patients who received placebo).
- Reductions in acute headache medication use were larger with eptinezumab than placebo (**Figure 3**).
- TEAE rates were similar across treatment groups (eptinezumab 100 mg, 56.0%; eptinezumab 300 mg, 57.4%; placebo, 55.4%; **Table 3**).
  - The most common TEAEs were nasopharyngitis 65/877 (7.4%) and upper respiratory tract infection 65/877 (7.4%).
  - Most TEAEs were mild or moderate in severity.
  - TEAEs leading to treatment discontinuation occurred in 15 patients (100 mg, n=7; 300 mg, n=3; placebo, n=5).
  - Serious TEAEs occurred in 18 patients (100 mg, n=6; 300 mg, n=5; placebo, n=7).

Table 1. Baseline Demographics, Clinical Characteristics, and Cardiovascular Risk Factors in Patients With Self-Reported Migraine With Aura

	Eptinezumab 100 mg (N=282)	Eptinezumab 300 mg (N=301)	Placebo (N=294)
Mean age, yr (SD)	40.1 (10.9)	40.4 (11.1)	39.5 (11.0)
Sex: Female, n (%)	237 (84.0)	269 (89.4)	255 (86.7)
Race, n (%)			
White	250 (88.7)	261 (86.7)	240 (81.6)
Black or African American	22 (7.8)	30 (10.0)	43 (14.6)
Other	10 (3.5)	10 (3.3)	11 (3.7)
Mean BMI, kg/m² (SD)	28.7 (6.9)	27.9 (6.1)	28.8 (6.6)
Episodic or chronic migraine, n (%)			
Episodic migraine	167 (59.2)	173 (57.5)	167 (56.8)
Chronic migraine	115 (40.8)	128 (42.5)	127 (43.2)
Mean age at diagnosis, years (SD)	22.4 (11.0)	21.7 (9.7)	22.4 (10.3)
Mean duration of migraine diagnosis, years (SD)	17.6 (11.2)	18.8 (11.8)	17.1 (11.2)
Mean duration of chronic migraines, years (SD)	14.0 (11.1)	15.5 (12.4)	14.4 (12.0)
Mean baseline migraine, days (SD)	11.8 (5.0)	11.9 (5.3)	12.0 (5.4)
Mean baseline headache, days (SD)	14.4 (5.9)	14.6 (6.0)	14.7 (6.1)
Medication-overuse headache diagnosis, n (%)	45 (16.0)	50 (16.6)	44 (15.0)
Cardiovascular risk factors, n (%)			
Hypertension-related	16 (5.7)	10 (3.3)	10 (3.4)
Hyperlipidemia-related	0	0	1 (0.3)
Diabetes-related	1 (0.4)	0	1 (0.3)
Prior history of ischemic CV events or procedures	3 (1.1)	1 (0.3)	1 (0.3)
Obesity (BMI ≥30 kg/m²)	110 (39.0)	94 (31.2)	111 (37.8)
Male and ≥45 years	18 (6.4)	7 (2.3)	11 (3.7)
Female and ≥55 years	27 (9.6)	32 (10.6)	21 (7.1)
Race: Black or African American	22 (7.8)	30 (10.0)	43 (14.6)
≥1 CV risk factors	157 (55.7)	138 (45.8)	152 (51.7)
≥2 CV risk factors	33 (11.7)	34 (11.3)	40 (13.6)

BMI, body mass index; CM, chronic migraine; CV, cardiovascular; EM, episodic migraine; MHD, monthly headache day; MMD, monthly migraine day; SD, standard deviation.

Table 2. Monthly Migraine Days Before and After Treatment in Patients With Self-Reported Migraine With Aura

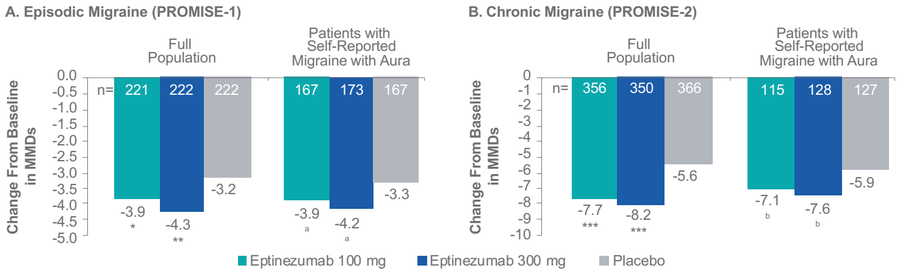
	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
PROMISE-1, n	167	173	167
Baseline, mean (SD)	9.0 (2.95)	8.7 (2.93)	8.4 (2.68)
Weeks 1–12, mean (SD)	5.0 (3.38)	4.5 (3.33)	5.3 (3.43)
Change from baseline, mean (SD)	–4.0 (3.37)	–4.2 (3.46)	–3.1 (3.91)
PROMISE-2, n	115	128	127
Baseline, mean (SD)	16.0 (4.42)	16.2 (4.81)	16.6 (4.42)
Weeks 1–12, mean (SD)	8.8 (6.57)	8.5 (6.90)	10.6 (6.53)
Change from baseline, mean (SD)	–7.1 (5.60)	–7.6 (6.19)	–6.0 (6.14)

Table 3. Summary of TEAEs in Patients With Self-Reported Migraine With Aura

	Eptinezumab 100 mg (N=284)	Eptinezumab 300 mg (N=303)	Placebo (N=294)
Patients with any TEAE, n (%) / Total number of TEAEs	159 (56.0) / 429	174 (57.4) / 435	163 (55.4) / 413
Most common TEAEs (≥2% of patients total), n (%)			
Nasopharyngitis	25 (8.8)	23 (7.6)	17 (5.8)
Upper respiratory tract infection	19 (6.7)	29 (9.6)	17 (5.8)
Sinusitis	9 (3.2)	13 (4.3)	15 (5.1)
Nausea	6 (2.1)	7 (2.3)	10 (3.4)
Bronchitis	5 (1.8)	8 (2.6)	9 (3.1)
Dizziness	8 (2.8)	5 (1.7)	9 (3.1)
Back pain	10 (3.5)	5 (1.7)	7 (2.4)
Fatigue	8 (2.8)	10 (3.3)	3 (1.0)
Influenza	3 (1.1)	10 (3.3)	7 (2.4)
Migraine	3 (1.1)	7 (2.3)	9 (3.1)
Arthralgia	4 (1.4)	7 (2.3)	8 (2.7)
Patients with any TEAE leading to treatment discontinuation, n (%)	7 (2.5)	3 (1.0)	5 (1.7)
Patients with any TEAE related to study drug, n (%)	37 (13.0)	49 (16.2)	27 (9.2)
Patients with any TEAE by maximum severity, n (%)			
Mild	64 (22.5)	71 (23.4)	60 (20.4)
Moderate	87 (30.6)	93 (30.7)	91 (31.0)
Severe	8 (2.8)	10 (3.3)	11 (3.7)
Life-threatening	0	0	1 (0.3)
Patients with serious TEAEs (≥2 patients), n (%)	6 (2.1)	5 (1.7)	7 (2.4)
Syncope	1 (0.4)	0	2 (0.7)
Migraine	1 (0.4)	0	1 (0.3)
Suicide attempt	1 (0.4)	1 (0.3)	0

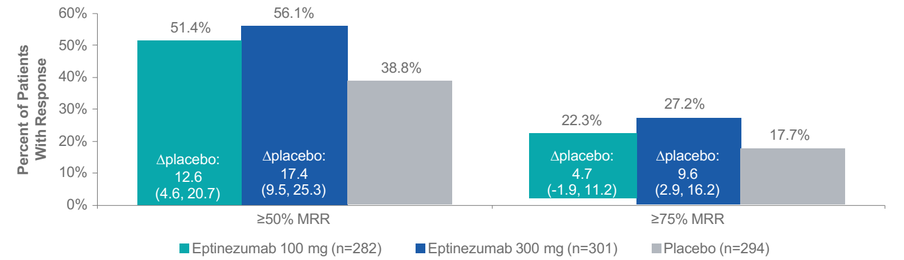
TEAE, treatment-emergent adverse event.

Figure 1. Mean Change From Baseline in MMDs Over Weeks 1–12 in the Full Study Population and Patients With Self-Reported Migraine With Aura in (A) PROMISE-1 and (B) PROMISE-2



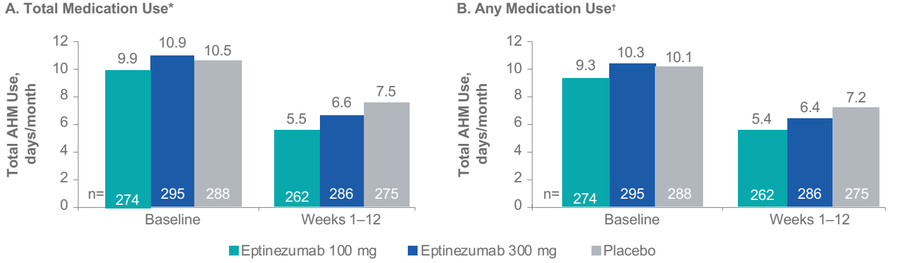
Differences between treatment groups was analyzed using an analysis of covariance model with change from baseline as the response variable and treatment and baseline migraine days as independent variables. *P<0.01; **P<0.001; ***P<0.0001 vs placebo (prespecified statistical testing). [a]Treatment difference vs placebo (95% confidence interval) in change from baseline: 100 mg, -0.5 (-1.2, 0.2); 300 mg, -0.9 (-1.5, -0.2). [b]Treatment difference vs placebo (95% confidence interval) in change from baseline: 100 mg, -1.3 (-2.7, 0.2); 300 mg, -1.7 (-3.1, -0.3).

Figure 2. Migraine Responder Rates Over Weeks 1–12 in Patients With Self-Reported Migraine With Aura



Δplacebo, difference from placebo (95% confidence interval). MRR, migraine responder rate.

Figure 3. Mean Acute Headache Medication Days/Month in Patients With Self-Reported Migraine With Aura: (A) Total Use and (B) Any Use



Acute headache medications (AHM) included combination analgesics, ergotamine, opioids, simple analgesics, and triptans. *If multiple drug classes were taken on a single day, the patient was counted for each drug class (and could be counted multiple times). †If multiple drug classes were taken on a single day, the patient was counted once.

KEY POINTS

- Given the associated risks of migraine with aura and the scarcity of specific data in patients with aura, this post hoc subgroup analysis assessed the efficacy and safety of eptinezumab for the preventive treatment of migraine in patients with a self-reported history of migraine with aura.
- The efficacy of eptinezumab in patients with self-reported migraine with aura was comparable to that in the overall populations of PROMISE-1 (episodic migraine) and PROMISE-2 (chronic migraine).
- More than half of patients with self-reported aura who received eptinezumab were ≥50% migraine responders over Weeks 1–12 (vs 39% of patients who received placebo).

CONCLUSION

- This subgroup analysis demonstrated efficacy with eptinezumab vs placebo and was well tolerated in patients with self-reported migraine with aura, consistent with full population results, suggesting clinical utility of eptinezumab treatment in this subpopulation of patients with coexisting migraine with aura.

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Disclosures

Dr Ashina has been a consultant, speaker, or scientific advisor for AbbVie/Allergan, Amgen, Eli Lilly, Lundbeck, Novartis, and Teva; has been a primary investigator for AbbVie/Allergan (ongoing)Alder/Lundbeck (ongoing), Amgen (ongoing), Eli Lilly, Novartis, and Teva trials; has received research grants from Lundbeck Foundation, Novartis, and Novo Nordisk Foundation. **Dr McAllister** reported receiving personal fees and research support from Abbvie, Amgen/Novartis, Biohaven, Eli Lilly, Lundbeck, and Teva. **Drs Cady and Ettrup** are employees of Lundbeck or one of its subsidiary companies and/or are stockholders in Lundbeck outside of the submitted work. **Dr Hirman** is an employee of Pacific Northwest Statistical Consulting, Inc., a contracted service provider of biostatistical resources for H. Lundbeck A/S.

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