Eptinezumab for Migraine Prevention in Patients 50 Years or Older: A Subgroup Analysis of PROMISE-1 and PROMISE-2

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Introduction

- Patients older than 50 with migraine pose unique challenges to preventive treatment due to the greater prevalence of comorbidities and use of concomitant medication.
- In addition, older individuals with migraine have an increased risk of dementia,[1] cognitive complaints,[2] medication overuse,[3] and sleep apnea.[4]
- Eptinezumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody which binds calcitonin gene-related peptide (CGRP) and is indicated for the preventive treatment of migraine in adults.[5]
  - 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.[6-9]
  - More than one-fifth (22.1% [385/1741]) of patients who received eptinezumab 100 mg, 300 mg, or placebo in PROMISE-1 and PROMISE-2 were ≥50 years old at baseline.

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 ≥50 years of age.

Methods

- PROMISE-1 (NCT02559895)[6,7]: 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 18–75 years of age with episodic migraine.
- PROMISE-2 (NCT02974153)[8,9]: a phase 3 randomized, double-blind, placebo-controlled multiple-dose study (100 or 300 mg IV every 12 weeks × 2 doses) in adults 18–65 years of age 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, and treatment-emergent adverse events (TEAEs).
- Data from patients treated with eptinezumab 100 mg, 300 mg, or placebo and who were ≥50 years of age at baseline were included in this post hoc analysis.
- For the 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.
- 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.
- All results are descriptive statistics, such as means, standard deviations, and rates.

Results

- Patients who were ≥50 years old at baseline were evenly distributed across treatment groups: 100 mg, n=132; 300 mg, n=127; placebo, n=126.
  - The mean age of all patients included in this analysis was 55.7 years; patients were predominantly female (336/385 [87%]) and white (360/385 [94%]) (**Table 1**).
  - More patients had chronic migraine (242/385 [63%]) than episodic migraine (n=143/385 [37%]).
  - Most patients (268/385 [70%]) had ≥1 cardiovascular risk factor at baseline and nearly one-fourth (90/385 [23%]) had ≥2 risk factors (**Table 2**).
- In patients with episodic and chronic migraine, reductions in MMDs over weeks 1–12 were greater in patients treated with eptinezumab (–4.1 and –8.1, respectively) than in patients who received placebo (–2.6 and –6.0, respectively) (**Table 3**).
- Reductions in MMDs in patients ≥50 years old were comparable to those in the total PROMISE-1 and PROMISE-2 populations[6,8] (**Figure 1**).
- In the pooled group of patients ≥50 years old, a greater percentage of eptinezumab-treated patients than patients receiving placebo were ≥50% migraine responders over Weeks 1–12 (**Figure 2**).
- In the pooled group of patients ≥50 years old, over twice as many eptinezumab-treated patients than placebo-treated patients were ≥75% migraine responders (**Figure 2**).
- Greater decreases in total acute headache medication days/month over Weeks 1–12 were noted for patients treated with eptinezumab than placebo (**Figure 3**).
- TEAE rates were similar across treatment groups (eptinezumab 100 mg, 46.6%; eptinezumab 300 mg, 53.5%; placebo, 52.4%; **Table 4**).
  - The most common TEAEs were nasopharyngitis (24/386 [6.2%]) and upper respiratory tract infection (24/386 [6.2%]).
  - Most TEAEs were mild or moderate in severity (≥96% of patients across arms).
  - TEAEs leading to treatment discontinuation occurred in 7 patients (eptinezumab 100 mg, n=2; eptinezumab 300 mg, n=1; placebo, n=4).
  - Serious TEAEs occurred in 6 patients (eptinezumab 100 mg, n=2; eptinezumab 300 mg, n=1; placebo, n=3).

Table 1. Baseline Demographics, Clinical Characteristics, and Medication Use of Patients ≥50 Years Old at Baseline

	Eptinezumab 100 mg (n=132)	Eptinezumab 300 mg (n=127)	Placebo (n=126)
Mean age, years (SD)	55.9 (4.4)	55.7 (4.9)	55.5 (4.9)
Sex: Female, n (%)	111 (84.1)	115 (90.6)	110 (87.3)
Race, n (%)			
White	124 (93.9)	121 (95.3)	115 (91.3)
Black or African American	5 (3.8)	4 (3.1)	8 (6.3)
Other	3 (2.3)	2 (1.6)	3 (2.4)
Mean (SD) BMI, kg/m²	27.5 (4.8)	26.5 (5.2)	28.0 (6.5)
Mean (SD) age at diagnosis, years	28.4 (12.9)	26.3 (11.0)	28.0 (12.0)
Mean (SD) duration of migraine diagnosis, years	27.5 (13.7)	29.4 (11.8)	27.6 (12.9)
Mean (SD) baseline headache days	16.9 (5.6)	16.2 (5.7)	16.1 (6.0)
Mean (SD) baseline migraine days	13.5 (5.1)	12.9 (5.4)	12.7 (5.3)
Medication-overuse headache diagnosis, n (%)	34 (25.8)	35 (27.6)	31 (24.6)
Chronic migraine diagnosis, n (%)	90 (68.2)	75 (59.1)	77 (61.1)
Baseline medication use in ≥10% of patients, n (%)			
Sumatriptan	41 (31.1)	49 (38.6)	63 (50.0)
Ibuprofen	38 (28.8)	41 (32.3)	35 (27.8)
Thomapyrin N	38 (28.8)	36 (28.3)	32 (25.4)
Paracetamol	20 (15.2)	19 (15.0)	14 (11.1)
Rizatriptan	21 (15.9)	15 (11.8)	14 (11.1)
Topiramate	8 (6.1)	13 (10.2)	14 (11.1)
Vitamins not otherwise specified	10 (7.6)	13 (10.2)	10 (7.9)

BMI, body mass index; SD, standard deviation.

Table 2. Medical History and Cardiovascular (CV) Risk Factors in Patients ≥50 Years of Age (Full Analysis Set)

	Eptinezumab 100 mg (n=132)	Eptinezumab 300 mg (n=127)	Placebo (n=126)
Medical history in ≥10% of total patients, n (%)			
Hysterectomy	19 (14.4)	28 (22.0)	27 (21.4)
Gastroesophageal reflux disease	25 (18.9)	20 (15.7)	15 (11.9)
Depression	19 (14.4)	20 (15.7)	20 (15.9)
Drug hypersensitivity	16 (12.1)	26 (20.5)	17 (13.5)
Insomnia	20 (15.2)	19 (15.0)	17 (13.5)
Menopause	26 (19.7)	14 (11.0)	14 (11.1)
Postmenopausal	18 (13.6)	19 (15.0)	17 (13.5)
Seasonal allergy	19 (14.4)	19 (15.0)	12 (9.5)
Tonsillectomy	16 (12.1)	15 (11.8)	15 (11.9)
Osteoarthritis	9 (6.8)	18 (14.2)	12 (9.5)
CV risk factors, n (%)			
Hypertension-related	15 (11.4)	13 (10.2)	7 (5.6)
Diabetes-related	1 (0.8)	0	3 (2.4)
Prior history of ischemic CV events or procedures	1 (0.8)	1 (0.8)	0
Obesity (body mass index ≥30 kg/m²)	37 (28.0)	25 (19.7)	43 (34.1)
Male and ≥45 years of age	21 (15.9)	12 (9.4)	16 (12.7)
Female and ≥55 years of age	61 (46.2)	54 (42.5)	49 (38.9)
Black or African American race	5 (3.8)	4 (3.1)	8 (6.3)
≥1 CV risk factor	100 (75.8)	81 (63.8)	87 (69.0)
≥2 CV risk factors	33 (25.0)	25 (19.7)	32 (25.4)

Table 3. Monthly Migraine Days (MMDs) Before and After Treatment in Patients ≥50 Years of Age

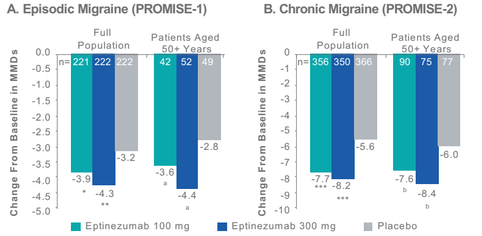
	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
PROMISE-1, n	42	52	49
Baseline, mean (SD)	8.9 (2.2)	8.5 (2.5)	8.3 (2.7)
Weeks 1–12, mean (SD)	5.1 (3.5)	4.1 (3.1)	5.7 (3.3)
Change from baseline, mean (SD)	–3.8 (3.1)	–4.4 (3.2)	–2.6 (3.5)
PROMISE-2, n	90	75	77
Baseline, mean (SD)	15.6 (4.6)	15.9 (4.8)	15.5 (4.6)
Weeks 1–12, mean (SD)	7.9 (6.2)	7.3 (6.1)	9.5 (5.9)
Change from baseline, mean (SD)	–7.7 (6.4)	–8.6 (6.7)	–6.0 (6.0)

SD, standard deviation.

Table 4. Summary of Treatment-Emergent Adverse Events (TEAEs) in Patients ≥50 Years of Age

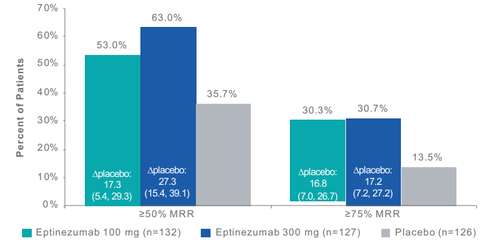
	Eptinezumab 100 mg (n=133)	Eptinezumab 300 mg (n=127)	Placebo (n=126)
Patients with any TEAE, n (%)	62 (46.6)	68 (53.5)	66 (52.4)
Mild	26 (19.5)	24 (18.9)	25 (19.8)
Moderate	32 (24.1)	42 (33.1)	36 (28.6)
Severe	4 (3.0)	2 (1.6)	4 (3.2)
Life-threatening	0	0	1 (0.8)
Most common TEAEs (≥2% of total patients), n (%)			
Nasopharyngitis	7 (5.3)	11 (8.7)	6 (4.8)
Upper respiratory tract infection	6 (4.5)	10 (7.9)	8 (6.3)
Urinary tract infection	4 (3.0)	7 (5.5)	3 (2.4)
Dizziness	4 (3.0)	5 (3.9)	3 (2.4)
Fatigue	5 (3.8)	4 (3.1)	2 (1.6)
Sinusitis	2 (1.5)	3 (2.4)	5 (4.0)
Back pain	3 (2.3)	3 (2.4)	3 (2.4)
Patients with any TEAE leading to treatment discontinuation, n (%)	2 (1.5)	1 (0.8)	4 (3.2)
Patients with any TEAE related to study drug, n (%)	14 (10.5)	18 (14.2)	13 (10.3)
Patients with any serious adverse event, n (%)	2 (1.5)	1 (0.8)	3 (2.4)
Syncope	1 (0.8)	0	1 (0.8)
Apnea	0	0	1 (0.8)
Breast cancer	0	1 (0.8)	0
Cellulitis	0	0	1 (0.8)
Chronic obstructive pulmonary disease	0	0	1 (0.8)
Depression suicidal	1 (0.8)	0	0
Gastric ulcer	1 (0.8)	0	0
Hematemesis	1 (0.8)	0	0
Migraine	0	0	1 (0.8)
Tibia fracture	1 (0.8)	0	0

Figure 1. Mean Change From Baseline in MMDs Over Weeks 1–12 in the Full Study Population and Patients ≥50 Years of Age in (A) PROMISE-1 and (B) PROMISE-2



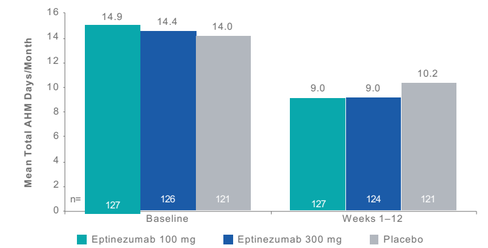
Differences between treatment groups was analyzed using an analysis of covariance model with change from baseline as the response variable and treatment and baseline migraine days as independent variables. *P<0.01; **P<0.001; ***P<0.0001 vs placebo (prespecified statistical testing).
[a]Treatment difference vs placebo (95% confidence interval) in change from baseline: 100 mg, -0.9 (-2.1, 0.3); 300 mg, -1.7 (-2.8, -0.6).
[b]Treatment difference vs placebo (95% confidence interval) in change from baseline: 100 mg, -1.6 (-3.4, 0.2); 300 mg, -2.4 (-4.2, -0.5).

Figure 2. Migraine Responder Rates Over Weeks 1–12 in Patients ≥50 Years of Age



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

Figure 3. Total Acute Headache Medication Days of Use Before and After Treatment in Patients ≥50 Years of Age



Total acute headache medication days is the sum of triptan, ergotamine, opioid, simple analgesic, and combination analgesic days of use. If a patient used two classes of medication on the same day, they were counted twice. Missing data were not imputed.
AHM, acute headache medication.

KEY POINTS

- Older patients with migraine pose a unique challenge to treatment due to increased likelihood of comorbities and concomitant medication use.
- In this post hoc analysis, patients ≥50 years old responded to eptinezumab treatment similarly to the entire population included in the clinical trials.
- In patients ≥50 years old, more eptinezumab treated patients were ≥50% or ≥75% MRR over Weeks 1-12 than patients who received placebo.

CONCLUSION

- In this post hoc subgroup analysis, the efficacy of eptinezumab in patients ≥50 years old with migraine was comparable to that in the overall population of the clinical trials, and eptinezumab was well tolerated in this subgroup.

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Disclosures

Dr Martin has been a consultant for Alder, Amgen, Biohaven, Lilly, Teva, and Theranica and has been a speaker for Amgen, Biohaven, Lilly, and Teva. **Dr Tassorelli** has been a principal investigator or collaborator for clinical trials sponsored by Alder, Allergan, electroCore, Eli Lilly, IBSA, Novartis, and Teva; has been a consultant or speaker for AbbVie, Allergan, Biohaven, electroCore, Eli Lilly, Novartis, and Teva; and has been an advisory board member for AbbVie, electroCore, Eli Lilly, Novartis, and Teva; is an associate editor with *The Journal of Headache and Pain*. **Drs Ettrup and Cady** 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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