Eptinezumab Increases Days Free from Canonical Migraine-Associated Symptoms Within 1 Month of Treatment in Patients with Chronic Migraine

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10-024

Presented at the 2019 American Academy of Neurology Annual Meeting May 4-10, 2019 Philadelphia, PA

BACKGROUND

- Migraine is a disabling and costly neurological disorder and is estimated to affect more than 1.3 billion individuals worldwide, resulting in more than 47 million person-years lived with disability[1,2]
- In addition to the frequency of headache and migraine, a diagnosis of migraine (ICHD-3 criteria) is based on the individual having ≥2 of the following headache characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, or avoidance of physical activity. Also, during migraine, individuals must experience ≥1 of: nausea and/or vomiting, or photophobia and phonophobia[3]
- Migraine-associated symptoms can significantly worsen an individual's health-related quality of life[4]
- Calcitonin gene-related peptide (CGRP) plays an important role in migraine pathophysiology[5-7]
- Eptinezumab (ALD403) is a humanized IgG1 anti-CGRP monoclonal antibody that: binds the CGRP ligand with high affinity resulting in potent and sustained inactivation of CGRP, is designed for rapid onset and durability ($t_{1/2}$ of 27 days), and is administered quarterly by intravenous (IV) infusion, allowing for 100% bioavailability with immediate C_{max} at the end of infusion[8-10]
- In phase 2 studies in episodic and chronic migraine[11,12] and in phase 3 studies in episodic migraine (Podium Presentation 003)[13] and chronic migraine (Poster 10-006, eptinezumab significantly reduced migraine days versus placebo, demonstrated migraine preventive efficacy, and was generally well tolerated

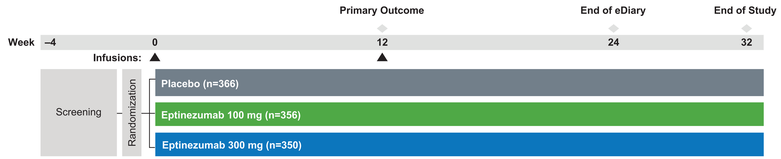
OBJECTIVE

- To evaluate changes in canonical migraine-associated symptom-free days in patients with CM after 2 quarterly infusions of eptinezumab vs placebo

METHODS

- This was a phase 3, parallel-group, double-blind, randomized, placebo-controlled trial of repeat quarterly IV infusions of eptinezumab or placebo in patients with chronic migraine (Figure 1)
- Patients were randomized to eptinezumab 100 mg, 300 mg, or placebo in a 1:1:1 ratio

Figure 1. PROMISE-1 Study Design



- Inclusion criteria included:
  - Male or female aged 18–65 years
  - Diagnosis of migraine at age ≤50 years by the criteria of the 3rd edition (beta) of the ICHD
  - History of chronic migraine ≥1 year prior to screening
  - During the 28-day screening period, subjects experienced ≥15 to ≤26 headache days, of which ≥8 were migraine days
  - Prescription or over-the-counter medication for acute or prophylactic treatment of migraine had been prescribed or recommended by a healthcare professional
  - Any prophylactic use of medications for headaches was stable for ≥3 months prior to screening
- Exclusion criteria included: use of botulinum toxin within 4 months prior to screening and during the 28-day screening period
- Patients with medication-overuse headache not associated with opiates or butalbital could be enrolled
- Patients completed an eDiary daily from screening visit through Week 24, with the screening period requiring ≥90% compliance (≥25 of 28 days)
- The primary efficacy endpoint was the mean change from baseline in monthly migraine days (MMDs) over Months 1–3 (Weeks 1–12)

CONCLUSIONS

- During the first month, treatment with eptinezumab resulted in 8–9 more days free from moderate or severe pain (vs 5 days with placebo); 7–8 more days free from avoidance of physical activity (vs 5 days with placebo); 7–8 more days free from pulsating (vs 5 days with placebo); 7 more days free from photophobia or phonophobia (vs 5 days with placebo); 7 more days free from nausea (vs 5 days with placebo); and 6–7 more days free from unilateral location (vs 4 days with placebo)
  - Results from post hoc analyses excluding patients experiencing 0 days of one of these symptoms during the 28-day screening period yielded similar results, as 94%–100% of patients experienced ≥1 day of the symptom
- During the first month, there was an increase of ~2 more days free from vomiting across treatment arms in all patients
  - In the post hoc analysis excluding patients with 28 days free from vomiting during the screening period, treatment with eptinezumab resulted in an increase of 4 more days free from vomiting (vs 3 days with placebo)
  - Smaller increases in days free from vomiting in the prespecified and post hoc analyses indicate that vomiting was not as frequently experienced as the other symptoms prior to treatment
- After Month 1, mean days free from individual symptoms were generally maintained over both infusion periods, with incremental increases after the 2nd infusion

- Days free from migraine-associated symptoms was captured as a tertiary endpoint via the eDiary
  - Baseline was result of the 28-day screening period
  - Patients with no migraine-associated symptom-free days were included as 0 days in the analysis; conversely, patients with all symptom-free days were included as 28 days
  - For patients who completed the eDiary for ≥21 and <28 days in a 28-day interval, then the results were normalized to 28 days by multiplying the observed results by the inverse of the completion rate (eg, if a patients did not complete the eDiary for 5 days, they were considered to have completed the eDiary on 82% of the days and the normalized results were the observed results × 1.22)
- Post hoc analyses of days free from each migraine-associated symptom were conducted that excluded patients who were free from the respective symptom during the entire 28-day screening period

RESULTS

Table 1. Baseline Demographics and Disease Characteristics (Safety Population)

	Eptinezumab 100 mg n=356	Eptinezumab 300 mg n=350	Placebo n=366
Age (years), mean (SD)	41.0 (11.72)	41.0 (10.36)	39.6 (11.28)
Sex, n (%)			
Male	49 (13.8%)	36 (10.3%)	41 (11.2%)
Female	307 (86.2%)	314 (89.7%)	325 (88.8%)
Race, n (%)			
White	332 (93.3%)	322 (92.0%)	321 (87.7%)
Black or African American	21 (5.9%)	23 (6.6%)	38 (10.4%)
Other*	3 (0.8%)	5 (1.4%)	7 (1.9%)
BMI (kg/m^2), mean (SD)	26.4 (4.98)	26.3 (7.14)	27.0 (5.56)
Age at migraine diagnosis (years), mean (SD)	22.8 (10.64)	22.0 (9.30)	22.6 (9.98)
Duration of migraine diagnosis (years), mean (SD)	18.3 (12.22)	19.0 (11.50)	17.0 (11.63)
Duration of chronic migraines (years), mean (SD)	11.6 (11.72)	12.3 (11.15)	11.6 (10.90)
Number of migraine days, mean (SD)†	16.1 (4.61)	16.1 (4.77)	16.2 (4.55)
Medication-overuse headache diagnosis, n (%)§			
Yes	139 (39.0%)	147 (42.0%)	145 (39.6%)

BMI, body mass index; SD, standard deviation. *Other includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and other. †As reported by the eDiary in the in the 28-day screening period. §Based on 3rd edition of the International Classification of Headache Disorders (beta).

- Demographics and baseline characteristics were balanced across treatment groups (Table 1)
- Patient retention for the Week 12 visit was 98.0% (100 mg), 98.3% (300 mg), and 97.3% (placebo), with 93.5% (100 mg), 94.6% (300 mg), and 91.8% (placebo) attending the Week 24 visit

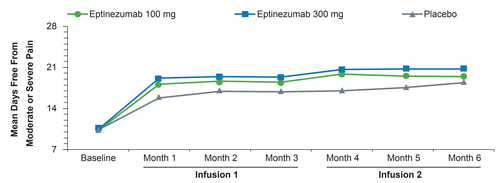
Table 2. Freedom from Migraine-Associated Symptoms During the 28-Day Screening Period

	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Moderate or severe pain			
All patients, n	356	349	366
Mean (SD) days without	10.3 (3.90)	10.4 (4.46)	10.4 (4.24)
Patients experiencing ≥1 day, n (%)	356 (100%)	349 (100%)	366 (100%)
Mean (SD) days without	10.3 (3.90)	10.4 (4.46)	10.4 (4.24)
Avoidance of physical activity			
All patients, n	356	349	366
Mean (SD) days without	12.4 (5.88)	12.2 (5.69)	12.1 (5.88)
Patients experiencing ≥1 day, n (%)	347 (97.5%)	343 (98.3%)	363 (99.2%)
Mean (SD) days without	12.0 (5.39)	11.9 (5.33)	12.0 (5.72)
Pulsating			
All patients, n	356	349	366
Mean (SD) days without	11.1 (5.36)	11.4 (5.82)	11.0 (5.40)
Patients experiencing ≥1 day, n (%)	349 (98.0%)	340 (97.4%)	358 (97.8%)
Mean (SD) days without	10.7 (4.84)	10.9 (5.22)	10.57 (4.81)
Photophobia or phonophobia			
All patients, n	356	349	366
Mean (SD) days without	13.4 (6.20)	14.0 (6.05)	13.18 (6.0)
Patients experiencing ≥1 day, n (%)	347 (97.5%)	338 (96.8%)	358 (97.8%)
Mean (SD) days without	13.1 (5.81)	13.6 (5.59)	12.9 (5.63)
Nausea			
All patients, n	356	349	366
Mean (SD) days without	14.6 (6.10)	14.6 (6.59)	14.9 (6.49)
Patients experiencing ≥1 day, n (%)	339 (95.2%)	335 (96.0%)	354 (96.7%)
Mean (SD) days without	13.9 (5.44)	14.0 (6.11)	14.5 (6.12)
Unilateral location			
All patients, n	356	349	366
Mean (SD) days without	13.5 (7.15)	13.2 (6.65)	13.4 (6.85)
Patients experiencing ≥1 day, n (%)	336 (94.4%)	333 (95.4%)	347 (94.8%)
Mean (SD) days without	12.6 (6.39)	12.5 (5.95)	12.55 (6.09)
Vomiting			
All patients, n	356	349	366
Mean (SD) days without	25.1 (4.33)	24.7 (4.81)	24.6 (4.91)
Patients experiencing ≥1 day, n (%)	192 (53.9%)	188 (53.9%)	200 (54.6%)
Mean (SD) days without	22.6 (4.60)	22.0 (5.10)	21.8 (5.15)

SD, standard deviation

- Eptinezumab 100 mg and 300 mg met the primary endpoint, significantly reducing MMDs across Months 1–3 vs placebo (100 mg, -7.7; 300 mg, -8.2; placebo, -5.6; p<0.0001 vs placebo both doses)
  - Further reductions were observed after an additional infusion (Months 4–6: 100 mg, -8.2; 300 mg, -8.8; placebo, -6.2)
- During the 28-day screening period, the population prevalence for ≥1 day of each symptom was between 94% and 100% (symptoms not mutually exclusive), with the exception of vomiting, for which ~54% of patients experienced ≥1 day (Table 2)

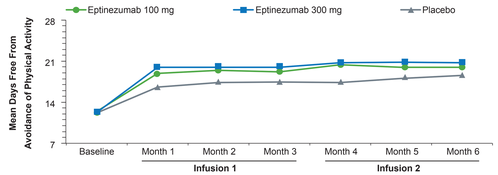
Figure 2. Mean Days Free From Moderate or Severe Pain (All Patients)



Includes patients experiencing 28 days free from moderate or severe pain during the 28-day screening period

- From baseline to Month 1, there was an increase of 7.9 (100 mg) and 8.7 (300 mg) in the mean number of days free from moderate or severe pain for eptinezumab-treated patients, compared with a 5.4-day increase with placebo (Figure 2)
- Days free from moderate or severe pain was generally maintained over both 3-month infusion periods, with a trend for increase observed after the 2nd quarterly infusion

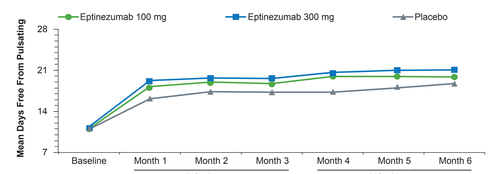
Figure 3. Mean Days Free From Avoidance of Physical Activity (All Patients)



Includes patient experiencing 28 days free from avoidance of physical activity during the 28-day screening period

- From baseline to Month 1, there was an increase of 6.5 (100 mg) and 7.7 (300 mg) in the mean number of days free from avoidance of physical activity for eptinezumab-treated patients, compared with a 4.5-day increase with placebo (Figure 3)
- Days free from avoidance of physical activity was generally maintained over both 3-month infusion periods

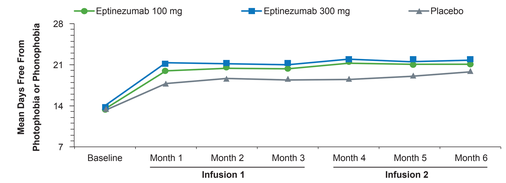
Figure 4. Mean Days Free From Pulsating (All Patients)



Includes patient experiencing 28 days free from avoidance of physical activity during the 28-day screening period

- From baseline to Month 1, there was an increase of 7.1 (100 mg) and 7.9 (300 mg) in the mean number of days free from pulsating for eptinezumab-treated patients, compared with a 5.2-day increase with placebo (Figure 4)
- Days free from pulsating was maintained over the first 3-month infusion period and incrementally increased after the 2nd quarterly infusion

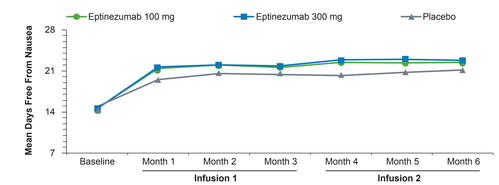
Figure 5. Mean Days Free From Photophobia or Phonophobia (All Patients)



Includes patients experiencing 28 days free from photophobia or phonophobia during the 28-day screening period

- From baseline to Month 1, there was an increase of 6.5 (100 mg) and 7.3 (300 mg) in the mean number of days free from photophobia or phonophobia for eptinezumab-treated patients, compared with a 4.6-day increase with placebo (Figure 5)
- Days free from photophobia or phonophobia was generally maintained over the first 3-month infusion period and incrementally increased after the 2nd quarterly infusion

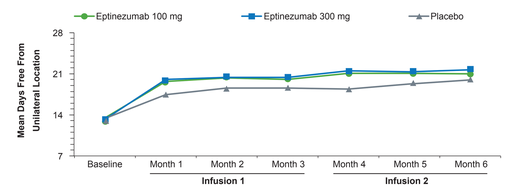
Figure 6. Mean Days Free From Nausea (All Patients)



Includes patients experiencing 28 days free from photophobia or phonophobia during the 28-day screening period

- From baseline to Month 1, there was an increase of 6.8 (100 mg) and 7.1 (300 mg) in the mean number of days free from nausea for eptinezumab-treated patients, compared with a 4.6-day increase with placebo (Figure 6)
- Days free from nausea was generally maintained over both 3-month infusion periods, with a trend for increase observed after the 2nd quarterly infusion

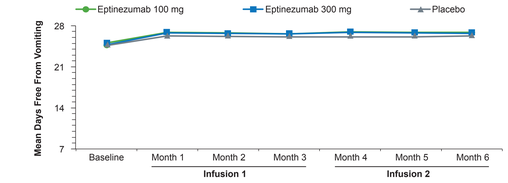
Figure 7. Mean Days Free From Unilateral Location (All Patients)



Includes patient experiencing 28 days free from unilateral location during the 28-day screening period

- From baseline to Month 1, there was an increase of 6.2 (100 mg) and 6.8 (300 mg) in the mean number of days free from unilateral location for eptinezumab-treated patients, compared with a 4.1-day increase with placebo (Figure 7)
- Days free from unilateral location was generally maintained over both 3-month infusion periods, with a trend for increase observed after the 2nd quarterly infusion

Figure 8. Mean Days Free From Vomiting (All Patients)



Includes patient experiencing 28 days free from vomiting during the 28-day screening period

- From baseline to Month 1, there was a similar increase in the mean number of days free from vomiting across treatment groups (100 mg, 1.8; 300 mg, 2.1; placebo, 1.6), which was stable across both quarterly infusion periods (Figure 8)
- 54% of patients experienced ≥1 day of vomiting during the 28-day screening period
  - In the post hoc analysis that excluded patients with 28 days free from vomiting during the screening period, baseline mean for days free from vomiting decreased from ~25 days across treatment groups to ~22 days
  - In addition, there was a 3.7 (100 mg) and 3.9 (300 mg) increase in the mean number of days free from vomiting for eptinezumab-treated patients, compared with a 3.3-day increase with placebo, which was maintained across both infusion periods
- Aside from vomiting, results of post hoc analyses for the other canonical migraine-associated symptoms were similar to the prespecified analyses, due to >94% of patients experiencing ≥1 day of these symptoms during the 28-day screening period

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Acknowledgments: The authors thank Nicole Coolbaugh of The Medicine Group (New Hope, PA, USA) for providing medical writing support, which was funded by Alder BioPharmaceuticals, Inc. (Bothell, WA, USA) in accordance with Good Publication Practice guidelines.

Disclosures: J. Schim: *Consultant, scientific advisor, or speaker:* Allergan, Amgen, Acorda, Avanir, Depomed, ElectroCore, Eli-Lilly, Novartis, Pernix, Promius, Supernus, Teva Pharmaceuticals, Upshire-Smith; Stock options: Alder BioPharmaceuticals; *Research support:* Allergan, Amgen, Eli Lilly. **P.J. Goadsby:** *Grants and personal fees:* Amgen, Eli Lilly; *Personal fees:* Alder BioPharmaceuticals, Allergan, Autonomic Technologies, Biohaven Pharmaceuticals, Dr Reddy's Laboratories, Electrocore, eNeura, Impel Neuropharma, MundiPharma, Novartis, Teva Pharmaceuticals, Trigemina, WL Gore; Personal fees: MedicoLegal work, Massachusetts Medical Society, Up-to-Date, Oxford University Press, Wolters Kluwer; Patents: magnetic stimulation for headache assigned to eNeura without fee. **E. Kassel, R. Cady:** *Full-time employee:* Alder BioPharmaceuticals; *Stockholder:* Alder BioPharmaceuticals. **D. Biondi:** *Full-time employee at the time of the study:* Alder BioPharmaceuticals; *Stockholder:* Alder BioPharmaceuticals. **J. Hirman:** *Contracted service provider:* Alder BioPharmaceuticals.

This study was funded by Alder BioPharmaceuticals, Inc.