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Eptinezumab Results for the Prevention of Episodic Migraine Over 1 Year in the PROMISE-1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy–1) Trial

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Introduction

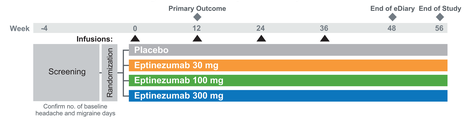
- Migraine is a highly prevalent, disabling, and costly neurologic disorder[1]
- Calcitonin gene-related peptide (CGRP) is a neuropeptide that plays an important role in migraine pathophysiology[2]
- Eptinezumab (ALD403) is an anti-CGRP IgG1 monoclonal antibody that rapidly and selectively binds to CGRP, inhibiting its biological activity[3]
  - Eptinezumab:
    - Binds the CGRP ligand with high affinity, resulting in potent and sustained inactivation of CGRP
    - Is designed for rapid onset and durability (reliable $t_{1/2}$ ~30 days)
    - Is the only anti-CGRP monoclonal antibody glycoengineered for reduced immune activation
    - Is the only anti-CGRP monoclonal antibody currently in development administered by quarterly iv infusion, allowing for 100% bioavailability within hours after infusion[3]
  - In phase 2 studies in episodic and chronic migraine,[4,5] and a phase 3 study in chronic migraine,[6] eptinezumab significantly reduced migraine days vs placebo, demonstrated migraine preventive efficacy, and was generally well tolerated
- Here we present the findings of the phase 3 PROMISE-1 trial (ALD403-CLIN-006; NCT02559895) in subjects with episodic migraine

Objectives

- To evaluate the preventive efficacy of eptinezumab in the phase 3 PROMISE-1 trial on the day after infusion and the cumulative benefit of repeat quarterly infusions through 1 year

Methods

PROMISE-1 Study Design (N=888)



- This was a phase 3, parallel-group, double-blind, randomized, placebo-controlled trial of repeat quarterly iv infusions of eptinezumab or placebo in subjects with episodic migraine
- Inclusion criteria included:
  - Male or female aged 18–75 years
  - Diagnosis of migraine at age ≤50 years by the criteria of the 2nd edition of the International Classification of Headache Disorders (ICHD-II)
  - History of migraine ≥12 months
    - 4–14 headache days/month, of which ≥4 met ICHD-II criteria for migraine
  - During the 28-day screening period, subjects used an eDiary and must have experienced ≤14 headache days, of which ≥4 were migraine days
- Exclusion criteria included:
  - Use of botulinum toxin and prophylactic headache medications prior to (4 and 2 months, respectively) and during the 28-day screening period
- Subjects completed an eDiary daily from screening visit through Week 48, with 90% compliance
- Eligible subjects were randomized and returned to the study site on Day 0 for the 1st infusion, which occurred ≥29 to ≤35 days after the screening visit
- Subjects randomized and dosed were to continue in the study for 56 weeks
- Treatment included 4 iv infusions of eptinezumab or placebo administered on Day 0, and at Weeks 12, 24, and 36
- Efficacy, safety, pharmacokinetic, and immunogenicity assessments were conducted

Efficacy Endpoints

Primary Endpoint	Mean change from baseline in monthly migraine days (MMD)	Weeks 1–12
Key Secondary Endpoints	≥75% migraine responder rate*	Weeks 1–4
	≥50% migraine responder rate* ≥75% migraine responder rate*	Weeks 1–12
	% of subjects with a migraine	Day 1 postdose
Secondary Endpoints	100% migraine responder rate†	Weeks 1–12

*% of subjects with migraine response (prespecified reduction from baseline in MMD). †% of subjects who were migraine-free for each 4-week interval on average over Weeks 1–12.

Statistical Hierarchy

- PROMISE-1 was a 4-arm study in which subjects were randomized to eptinezumab 30, 100, or 300 mg, or placebo in a 1:1:1:1 ratio
- A formal inferential testing algorithm was used to control statistical multiplicity, which tested the primary and all key secondary endpoints in a fixed sequence
- Due to a nonsignificant p-value for the 100-mg group vs placebo for the ≥75% migraine responder rate (Weeks 1-12) secondary endpoint, following the multiplicity algorithm, the remaining 100-mg key secondary endpoints and all 30 mg endpoints were not tested

Results

Baseline Characteristics and Demographics

	Placebo	Eptinezumab 30 mg	Eptinezumab 100 mg	Eptinezumab 300 mg
Safety population, n	**222**	**219**	**223**	**224**
Mean age, year	39.9	39.1	40.0	40.2
Mean weight, kg	82.4	82.0	82.4	80.2
Female, %	84	85	80	89
Mean years from migraine diagnosis	16.9	17.0	17.4	18.2
≥1 prophylactic medication, n (%)*	10 (5)	14 (6)	9 (4)	8 (4)
Efficacy population, n	**222**	**223**	**221**	**222**
Mean migraine days/month	8.4	8.7	8.7	8.6
Mean headache days/month	9.9	10.2	10.0	10.1
Mean triptan/ergotamine days†	1.5	1.4	1.5	1.6

*According to American Academy of Neurology/American Headache Society guidelines for migraine preventive treatment (medications identified by clinical review of coded medical data for medication use prior to study baseline); †Days with triptan or ergotamine use as recorded in eDiary averaged over 28-day screening period.

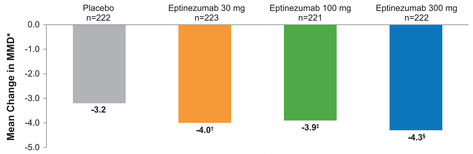
- Mean baseline migraine days were ~8.6 days/month across groups
- Baseline characteristics were balanced across treatment groups

Subject Disposition

Subjects n (%)	Placebo	Eptinezumab 30 mg	Eptinezumab 100 mg	Eptinezumab 300 mg	Overall
Full analysis population*	**222**	**223**	**221**	**222**	**888**
Week 12†	205 (91)	205 (92)	212 (94)	213 (95)	835 (93)
Week 24†	186 (83)	194 (87)	193 (86)	198 (88)	771 (86)
Week 36†	175 (78)	180 (80)	182 (81)	185 (83)	722 (80)
Week 48†	168 (75)	174 (78)	175 (78)	177 (79)	694 (77)
Discontinued treatment early‡	54 (24)	51 (23)	45 (20)	43 (19)	193 (22)
TEAE	6 (3)	11 (5)	5 (2)	5 (2)	27 (3)
Subject withdrew consent or lost to follow-up	45 (20)	30 (13)	32 (14)	34 (15)	141 (16)
Other	3 (1)	8 (4)	7 (3)	3 (1)	21 (2)

*Includes all subjects who received eptinezumab or placebo; †Subjects who attended each visit; ‡% based on all randomized subjects; §% based on full analysis population. TEAE, treatment-emergent adverse event.

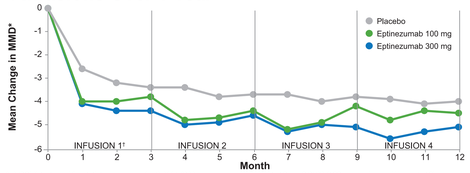
Mean Change in Monthly Migraine Days Weeks 1–12: Primary Endpoint



*Analysis of covariance (ANCOVA) model used to test for difference between treatment groups; †p=0.0046, unadjusted; ‡p=0.0182 vs placebo; §p=0.0001 vs placebo.

- Eptinezumab 100 and 300 mg significantly decreased MMD for Weeks 1–12 vs placebo

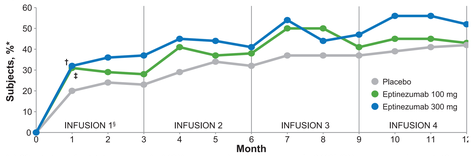
Mean Change in Monthly Migraine Days Through 4 Infusions Over 1 Year



*ANCOVA test used for statistical analysis; †p=0.0001 (300 mg vs placebo/Weeks 1–12); p=0.0182 (100 mg vs placebo/Weeks 1–12).

- Eptinezumab 300 mg sustained and delivered additional reduction in MMD through 1 year

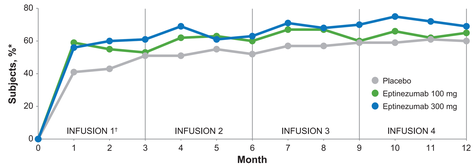
≥75% Migraine Responder Rate Through 4 Infusions Over 1 Year



*ANCOVA test used for statistical analysis; †p=0.0066 vs placebo; ‡p=0.0112 vs placebo; §p=0.0007 (300 mg vs placebo/Weeks 1–12); not significant (100 mg vs placebo/Weeks 1–12).

- For Weeks 1–4 (Month 1), significantly more eptinezumab subjects achieved ≥75% reduction in migraine days vs placebo
- >47% of eptinezumab 300-mg subjects achieved a ≥75% response after the 3rd and 4th infusions

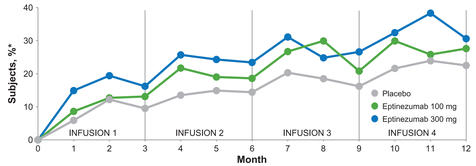
≥50% Migraine Responder Rate Through 4 Infusions Over 1 Year



*Stratified Cochran-Mantel-Haenszel test used for statistical analysis; †p=0.0001 (300 mg vs placebo/Weeks 1–12); p=0.0085 (100 mg vs placebo/unadjusted/Weeks 1–12).

- ≥50% migraine responder rate was achieved by more than half of all eptinezumab subjects over Weeks 1–12
- Over 69% of eptinezumab 300-mg subjects achieved ≥50% reduction in migraine days after the 3rd and 4th infusions

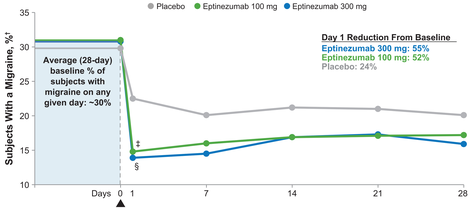
Monthly Migraine Freedom—100% Responder Rate—Through 4 Infusions Over 1 Year



*% of subjects with mean monthly freedom from migraine averaged over 3 months.

- Migraine freedom was achieved by 17% of eptinezumab 300-mg subjects each month, on average, over Weeks 1–12
- After the 3rd and 4th infusions, >30% of eptinezumab 300-mg subjects achieved monthly migraine freedom

Percentages of Subjects With a Migraine*



*Day 1 reduction from baseline in % of subjects with a migraine in eptinezumab vs placebo groups and daily % of subjects with a migraine averaged weekly for Days 1–28; †Stratified Cochran-Mantel-Haenszel test used for statistical analysis; ‡p=0.0312 vs placebo; §p=0.0159 vs placebo.

- Day 1 reductions from baseline in % of subjects with a migraine were sustained on average through Day 28

Safety Profile*

Subjects, n (%)	Placebo n=222	Eptinezumab 30 mg n=219	Eptinezumab 100 mg n=223	Eptinezumab 300 mg n=224
Any TEAE	132 (60)	128 (58)	141 (63)	129 (58)
Any serious TEAE†	6 (3)	4 (2)	4 (2)	3 (1)
Any TEAE leading to drug withdrawal	6 (3)	12 (6)	6 (3)	5 (2)
Most-frequent TEAEs‡				
Upper respiratory tract infection	16 (7)	25 (11)	22 (10)	23 (10)
Nasopharyngitis	12 (5)	14 (6)	17 (8)	14 (6)
Sinusitis	14 (6)	7 (3)	6 (3)	11 (5)

*Safety profile represents safety population; †All serious serious TEAEs judged unrelated to study drug; ‡≥5% in any treatment group.

- Occurrences of TEAEs were similar among treatment and placebo groups

Conclusions

- **Eptinezumab significantly reduced MMD over Weeks 1–12 vs placebo, and the reduction was sustained or improved with eptinezumab 300 mg after the 3rd and 4th infusions in subjects with episodic migraine**
- **The % of subjects with a migraine dropped by >50% on Day 1 after eptinezumab infusion compared with baseline and reductions were sustained through Day 28**
- **Subjects receiving eptinezumab 300 mg experienced a sustained benefit of fewer days with migraine over Weeks 1–12, and further improved with the subsequent 3 infusions**
  - **Additional benefit was achieved in 13%–18% of subjects in the ≥50% and ≥75% migraine responder rate groups, and in those subjects with migraine freedom**
- **Overall TEAE rates for eptinezumab were similar to placebo and the safety profile was consistent with previous eptinezumab studies**

References

1. Lipton RB, Silberstein SD. *Headache.* 2015;55:103-22; **2.** Ho TE, et al. *Nat Rev Neurol.* 2010; 6:573-82; **3.** Baker B, et al. *Cephalalgia.* 2017;37(suppl):109; **4.** Dodick DW, et al. *Lancet Neurol.* 2014;13:1100-7; **5.** Dodick D, et al. *Neurology.* 2017;88(suppl 16):S52.003; **6.** Lipton RB, et al. *Neurology.* 2018;90(suppl 15):S32.

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Disclosures

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