Efficacy and safety of eptinezumab in chronic migraine: Randomized controlled trial in a predominantly Asian population

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Data presented here are from a large-scale, phase 3 clinical trial to determine the efficacy and safety of eptinezumab, a monoclonal antibody targeted against CGRP, for the preventive treatment of migraine in a predominantly Asian population with chronic migraine.

Background

- Migraine is the second most burdensome neurological disorder in Asia.[1]
- The International Headache Society (IHS) recommends acute and preventive pharmacological treatment to improve the management of migraine[2,3]; however, there is a substantial unmet need in use of effective preventive treatment within Asian countries.[4,5]
- Eptinezumab, a monoclonal antibody targeted against calcitonin gene-related peptide and approved for migraine prevention,[6] demonstrated acceptable tolerability as well as early and sustained reductions in migraine frequency in primarily Western participants with episodic and chronic migraine (CM) in placebo-controlled trials.[7,8]
- In a smaller phase 3 trial, eptinezumab 100 mg showed numerically favorable efficacy compared to placebo in a predominantly Asian population with CM and medication-overuse headache, with no new safety signals identified[9]; however, the efficacy and safety of eptinezumab in Asian populations with CM from a large-scale trial have not been previously reported.

Objective

- To evaluate the efficacy and safety of eptinezumab for the preventive treatment of migraine in a predominantly Asian population with CM.

Methods

- SUNRISE was a phase 3, multiregional, randomized, double-blind, placebo-controlled clinical trial that evaluated eptinezumab 100 mg and 300 mg for the preventive treatment of migraine (ClinicalTrials.gov: NCT04921384).
- The trial comprised a screening period (28–30 days); double-blind, placebo-controlled period (12 weeks; efficacy and safety); dose-blinded extension period (12 weeks; safety assessments only); and safety follow-up period (8 weeks) (**Figure 1**).
- Adults (18–75 years)—diagnosed with CM with a history of ≥15 monthly headache days and ≥8 monthly migraine days (MMDs) during the 3 months prior to screening and confirmed during the screening period—were randomized 1:1:1 to intravenous eptinezumab 100 mg, eptinezumab 300 mg, or placebo at baseline.
- Safety over the placebo-controlled period was assessed in the all-participants-treated set (all randomized participants who received an infusion of double-blind trial medication). Safety over the extension period was assessed in the all-participants-treated-extension set (all randomized participants who received an infusion of dose-blinded trial medication during the extension period). Efficacy was assessed in the full analysis set (all participants treated in the placebo-controlled period who had a valid assessment of baseline MMDs and ≥1 valid post-baseline 4-week assessment of MMDs across Weeks 1–12).
- Endpoints presented here:
  - **Primary endpoint:** Change from baseline in MMDs (Weeks 1–12)
  - **Key secondary endpoints:** Proportion of participants with ≥50% reduction from baseline in MMDs (Weeks 1–12); proportion of participants with ≥75% reduction from baseline in MMDs (Weeks 1–4; Weeks 1–12); and proportion of participants experiencing migraine on the day after dosing (Day 1)
  - **Patient-reported outcomes (as secondary endpoints):** Patient Global Impression of Change (PGIC) score at Week 12 and patient-identified most bothersome symptom (PI-MBS) score at Week 12
  - **Safety endpoints:** Treatment-emergent adverse events (TEAEs), vital signs, laboratory test values, and electrocardiogram parameter values
- The primary and key secondary efficacy outcomes were analyzed using a statistical hierarchy controlling for multiple comparisons. *P*-values presented are for each eptinezumab dose group *vs* placebo.
  - For the primary efficacy endpoint, the change from baseline was analyzed using a mixed model for repeated measures, with month, treatment, and location as fixed factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline MMDs-by-month interaction. An unstructured variance matrix was used to model within-participant errors.

Results

Participants (**Figure 2**)

- Of 983 participants randomized, 978 (99%) were treated and 939 (96%) completed the placebo-controlled period; 96% of participants who entered the extension period completed it.
- Most participants were from Asia (63%), with the remainder from Europe (37%); participants had a mean of 17.4 baseline MMDs and 42% had medication-overuse headache as a concurrent diagnosis.

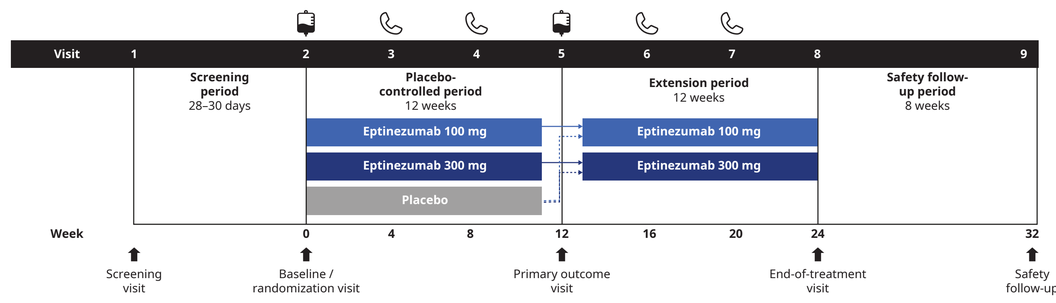
Efficacy outcomes

- The mean changes from baseline in MMDs across Weeks 1–12 were –7.2 (100 mg), –7.5 (300 mg), and –4.8 (placebo); $p<0.0001$ for both doses *vs* placebo (**Figure 3**), with similar changes in MMDs across each 4-week interval (**Figure 3**).
- Eptinezumab 100 mg and 300 mg demonstrated odds ratios >2 compared to placebo for achieving ≥50% reduction in MMDs over Weeks 1–12 (**Figure 4**), as well as ≥75% reduction in MMDs over Weeks 1–4 and Weeks 1–12 (**Figure 4**).
- The proportion of participants experiencing migraine on Day 1 was lower with both doses of eptinezumab than with placebo (**Figure 4**).
- PGIC and PI-MBS scores showed greater improvements with eptinezumab than with placebo at each time point across Weeks 1–12 (**Figure 5**).

Safety outcomes

- The rate of TEAEs was comparable across groups during the placebo-controlled period, with few serious TEAEs (<2%) or TEAEs leading to withdrawal (<2%) (**Table 1**).
  - A similar safety profile was observed during the 12-week extension period (**Table 1**).
- During each treatment period, the most common TEAE was COVID-19, followed by nasopharyngitis (**Table 1**).
- TEAEs, vital signs, laboratory values, and electrocardiograms did not show new safety signals compared to previous trials of eptinezumab.[7-9]

Figure 1. SUNRISE trial design



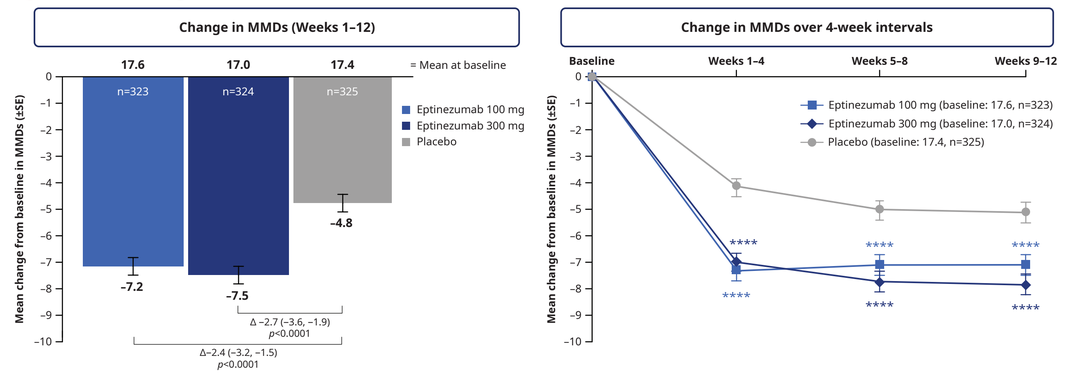
Visits 1, 2, 5, 8, and 9 were conducted in the clinic; Visits 3, 4, 6, and 7 were conducted by telephone.

Figure 2. Baseline participant demographics

- **978 randomized and treated** (**327** to eptinezumab 100 mg, **326** to eptinezumab 300 mg, and **325** to placebo)
- **939 (96%) completed the 12-week placebo-controlled period**
- **63% Asia** (Japan, Mainland China, South Korea, and Taiwan)[a]; **37% Europe** (Georgia, Poland, Slovakia, and Spain)[a]
- Mean of **17.4 baseline MMDs**[b]
- **86%** female[a]; Mean age of **42 years**[a]
- **42%** had a concurrent diagnosis of MOH[a]

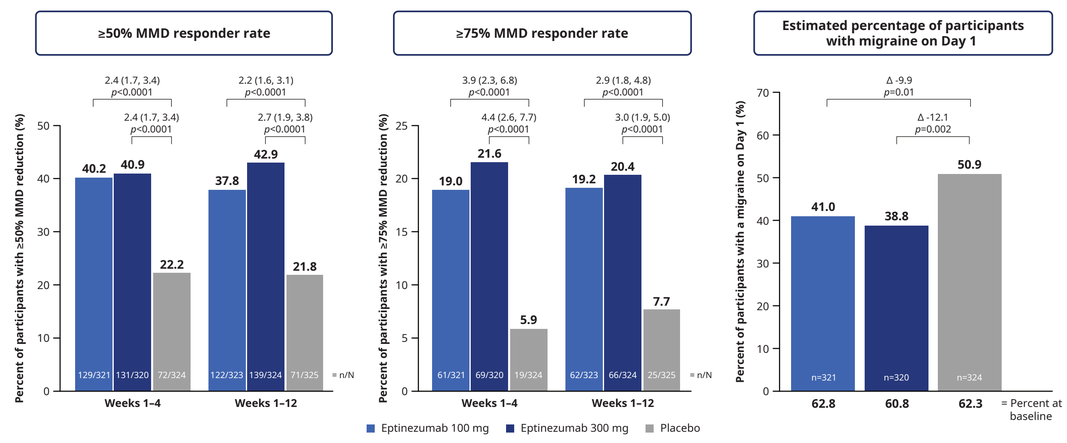
[a]Demographic/baseline data are from the all-participants-treated set (total N=978). [b]Data are from the full analysis set (total N=972). MMDs, monthly migraine days; MOH, medication-overuse headache.

Figure 3. Change from baseline in MMDs over Weeks 1–12 and 4-week intervals



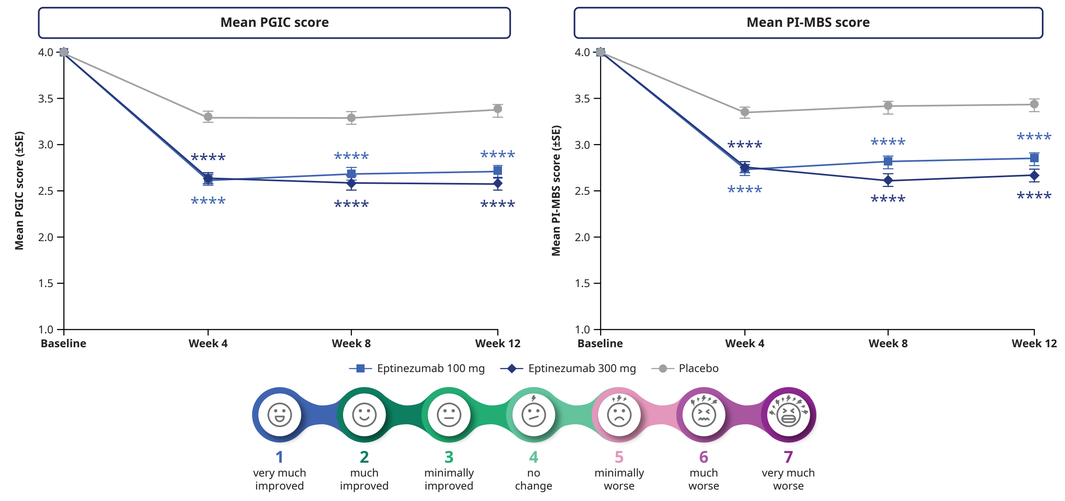
Analyzed in the full analysis set (total N=972). The estimated means, mean differences from placebo, and 95% confidence intervals were calculated by a mixed models for repeated measures analysis with month (Weeks 1–4, Weeks 5–8, Weeks 9–12), site location, and treatment as factors; baseline score as a continuous covariate; and interaction terms for treatment-by-month and baseline score-by-month. Estimates and tests over Weeks 1–12 used equal weights for each 4-week interval. Comparisons for change in MMDs over 4-week intervals (Weeks 1–4, 5–8, and 9–12) were not controlled for multiplicity. ****$p<0.0001$ *vs* placebo. Δ, least-squares mean difference from placebo (95% confidence interval); MMDs, monthly migraine days; SE, standard error.

Figure 4. Responder endpoints: ≥50% MMD responder rate, ≥75% MMD responder rate, and percentage of participants with migraine on Day 1



Analyzed in the full analysis set (total N=972). **MMD responder rates:** ≥50% and ≥75% MMD responders were participants with ≥50% and ≥75% reduction from baseline in MMDs, respectively. Odds ratios (95% confidence intervals) and *p*-values *vs* placebo are provided. Comparisons were based on a logistic regression models including baseline MMDs as a continuous covariate and treatment as a factor. The comparison for ≥50% MMD responder rate (Weeks 1–4) was not a key secondary endpoint and not controlled for multiplicity. **Migraine on Day 1:** The percentage of participants with migraine at baseline was derived based on the average percentage of participants with migraine across the 28-day screening period. The percentage of participants with migraine on the day after first dosing was derived based on available eDiary data on Day 1 (unless the eDiary data on Day 1 were missing, in which case the percentage of days with migraine across Weeks 1–4 for the participant was imputed if ≥14 of 28 days of eDiary data were available). Percentage-point differences and *p*-values *vs* placebo are provided, with comparisons computed using the extended Cochran–Mantel–Haenszel test adjusting for the stratification factor (MMDs at baseline [<17 or ≥17]). Δ, mean difference from placebo; eDiary, electronic diary; MMDs, monthly migraine days.

Figure 5. Patient-reported improvements: Mean PGIC score and mean PI-MBS score



Analyzed in the full analysis set (total N=972). PGIC and PI-MBS used identical rating scales to measure change relative to the start of the trial, with scores ranging from 1 (very much improved) to 7 (very much worse), and 4 = no change. The representative baseline value of 4.0 is deterministic and not based on individual data at baseline. ****$p<0.0001$ *vs* placebo. PGIC, Patient Global Impression of Change; PI-MBS, patient-identified most bothersome symptom; SE, standard error.

Table 1. Summary of TEAEs during the placebo-controlled period and during the extension period

	Placebo-controlled period (Weeks 1–12)			Extension period (Weeks 13–24)			
Participants, n (%)	Eptinezumab 100 mg (n=327)[a]	Eptinezumab 300 mg (n=326)[a]	Placebo (n=325)[a]	Eptinezumab 100 mg–100 mg (n=262)[b]	Eptinezumab 300 mg–300 mg (n=256)[b]	Placebo–Eptinezumab 100 mg (n=128)[b]	Placebo–Eptinezumab 300 mg (n=131)[b]
TEAEs	**123 (37.6)**	**105 (32.2)**	**109 (33.5)**	**111 (42.4)**	**100 (39.1)**	**46 (35.9)**	**56 (42.7)**
Serious adverse events	**5 (1.5)**	**3 (0.9)**	**4 (1.2)**	**8 (3.1)**	**3 (1.2)**	**5 (3.9)**	**3 (2.3)**
TEAEs leading to withdrawal	**4 (1.2)**	**4 (1.2)**	**2 (0.6)**	**0**	**0**	**2 (1.6)**	**0**
TEAEs leading to infusion interruption/termination	**3 (0.9)**	**1 (0.3)**	**0**	**1 (0.4)**	**0**	**0**	**2 (1.5)**
Most common TEAEs (≥2% of either arm)							
COVID-19	**18 (5.5)**	**15 (4.6)**	**14 (4.3)**	**17 (6.5)**	**20 (7.8)**	**8 (6.3)**	**13 (9.9)**
Nasopharyngitis	**11 (3.4)**	**11 (3.4)**	**16 (4.9)**	**11 (4.2)**	**9 (3.5)**	**5 (3.9)**	**4 (3.1)**
Upper respiratory tract infection	**6 (1.8)**	**6 (1.8)**	**9 (2.8)**	**9 (3.4)**	**6 (2.3)**	**3 (2.3)**	**4 (3.1)**
Urinary tract infection	**7 (2.1)**	**5 (1.5)**	**3 (0.9)**	**6 (2.3)**	**4 (1.6)**	**1 (0.8)**	**5 (3.8)**

[a]Data from the placebo-controlled period are from the all-participants-treated set (total N=978). [b]Data from the extension period are from the all-participants-treated-extension set (total N=777); groups refer to the randomly allocated treatment sequence assigned at baseline (i.e., eptinezumab throughout, or placebo followed by eptinezumab). COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Key Points

- **Eptinezumab met the primary endpoint and all key secondary efficacy endpoints in the SUNRISE trial.**
- When compared to placebo, eptinezumab 100 mg and 300 mg demonstrated statistically significant reductions in MMDs across Weeks 1–12, with greater rates of ≥50% (Weeks 1–12) and ≥75% (Weeks 1–4; Weeks 1–12) reductions from baseline in MMDs, and a lower estimated percentage of participants experiencing migraine on Day 1.
- Both eptinezumab doses were associated with better PGIC and PI-MBS scores across Weeks 1–12 compared to placebo.
- Both doses of eptinezumab were generally well tolerated, with no new safety signals identified relative to prior migraine trials.

Conclusion

- **In a predominantly Asian population with CM, eptinezumab 100 mg and 300 mg demonstrated statistically significant reductions in MMDs and were associated with better patient-reported outcomes when compared to placebo, with efficacy observed as early as Day 1 and sustained through 12 weeks, and with a well-tolerated safety profile consistent with previous trials.**

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Declarations of conflicting interests

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