Effect of Erenumab on Monthly Migraine Days and Monthly Migraine Attacks in Patients with Episodic Migraine

Peer Tfelt-Hansen[1]*, Messoud Ashina[1], Hans-Christoph Diener[2], Shannon Ritter[3], Gabriel Paiva Da Silva Lima[4], Soeren Rasmussen[4], Ronald Zielman[5]

[1]Danish Headache Center, Department of Neurology, Rigshospitalet- Glostrup Hospital, University of Copenhagen, Glostrup, Denmark; [2]Medical Faculty of the University Duisburg-Essen, Institute for Medical Informatics, Biometry and Epidemiology, Germany; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [4]Amgen Inc., Thousand Oaks, CA, USA; [5]Novartis Pharma AG, Basel, Switzerland

INTRODUCTION

- Erenumab (in the US, erenumab-aooe) is a fully human monoclonal antibody against the canonical calcitonin gene-related peptide (CGRP) receptor [1]
- In the four randomized controlled trials evaluating erenumab for prevention of EM, the primary efficacy outcome was reduction in **monthly migraine days** (MMD)[2-5]
- A reduction in **monthly migraine attacks** (MMA) as an efficacy outcome has not been previously reported for erenumab
- The decrease in MMDs after administration of erenumab observed in patients with EM could theoretically be a consequence of a decrease in MMA and/or to a shortening of the duration of migraine attacks
- A reduction in MMA would indicate a real preventative effect by preventing the occurrence of migraine attacks and not only shortening the duration of attacks

OBJECTIVE

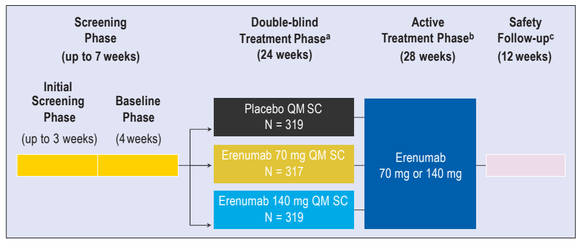
- The objective of this study was to evaluate the effect of erenumab on the MMA frequency in patients with EM

METHODS

Study design

- We conducted an analysis of the data from the STRIVE study (NCT02456740), which was a randomized, double-blind, placebo-controlled, Phase 3 study of erenumab in patients with EM (N=955) (**Figure 1**)

Figure 1. Study design



[a]Randomized; [b]Re-randomized; [c]16 weeks after last dose of placebo or erenumab
SC, subcutaneous; QM, once per month

Outcomes

- Outcome measures assessed included change from baseline to the last 3 months of assessment (mean over months 4, 5 and 6) in MMD and MMA and the proportion of patients who achieved ≥50% reduction in MMD and MMA from baseline

Outcomes (Continued)

- For analysis, a **migraine day** was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine headache as recorded in the electronic diary. Any calendar day on which acute migraine-specific medication was used was also counted as a migraine day
  - A qualified migraine headache was defined as a migraine with or without aura lasting at least 30 minutes and manifesting with at least two headache features, at least one associated non-headache feature, or both
- A **migraine attack** was defined as an episode of any qualified migraine headache or migraine specific medication intake
  - A migraine attack that was interrupted by sleep, or temporarily remitted, and then recurred within 48 hours was considered as one attack. Additionally, an attack treated successfully with medication but with relapse within 48 hours and a migraine attack lasting more than 48 hours was counted as one attack
- Pre-specified exploratory (change from baseline in MMA) or post-hoc analyses (≥50% reduction in MMA from baseline) were conducted using the efficacy analyses set
  - The efficacy analysis set included patients who received at least one dose of erenumab or placebo and had at least one post baseline measurement for migraine days per month during the double-blind treatment phase (DBTP), analyzed according to randomly assigned trial regimen

Statistical analysis

- To facilitate the comparison between MMD and MMA, change from baseline to the last 3 months (mean over months 4, 5, and 6) in MMD and proportion of patients who achieved ≥50% reduction in MMD (the primary and secondary endpoint reported in the primary publication)[4] were also reported here
  - The detailed statistical analyses for reporting the primary, secondary and exploratory endpoints have already been published[4]
  - For the 50% MMA responder rate Cochran-Mantel-Haenszel test was used, common odds ratio, associated 95% confidence intervals (CIs) and p values were also reported stratified by stratification factors (i.e., region and prior/current treatment with migraine prophylactic medication)

RESULTS

- The mean MMD at study baseline was 8.3 days, the change from baseline in least square mean (LSM, %), was −1.8 (−22%) days with placebo, −3.2 (−39%) days with erenumab 70 mg and −3.7 (−44%) days with erenumab 140 mg over the final 3 months of the DBTP (**Table 1**)
- The mean MMA at baseline was 5.1 for placebo and 5.2 for the erenumab 70 mg/140 mg groups. The change from baseline in MMA (LSM, %) was −1.3 (−26%) with placebo, −1.9 (−40%) with erenumab 70 mg and −2.2 (−43%) with erenumab140 mg over the final 3 months of the DBTP (**Table 1**)

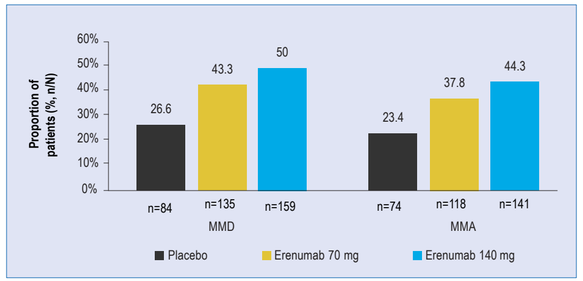
Table 1: Clinical responses for MMD and MMA over the final 3 months of the DBTP (mean over months 4, 5, and 6)[a]

	MMD			MMA		
	Placebo (N=316)	Erenumab 70 mg (N=312)	Erenumab 140 mg (N=318)	Placebo (N=316)	Erenumab 70 mg (N=312)	Erenumab 140 mg (N=318)
Baseline (SD)	8.25 (2.51)	8.31 (2.45)	8.33 (2.48)	5.12 (1.49)	5.24 (1.48)	5.16 (1.42)
LSM change from baseline (SE)[b]	−1.83 (0.18)	−3.23 (0.18)	−3.67 (0.18)	−1.32 (0.09)	−1.99 (0.09)	−2.22 (0.09)
LSM % change from baseline	−22%	−39%	−44%	−26%	−40%	−43%
LSM difference vs. placebo (95% CI)[b,c]	-	−1.40 (−1.88 to −0.92)	−1.85 (−2.33 to −1.37)	-	−0.67 (−0.93 to −0.42)	−0.91 (−1.16 to −0.65)
p value[d]		p<0.001	p<0.001		p<0.001	p<0.001

[a]The analysis included patients who underwent randomization, received at least one dose of the randomly assigned trial regimen, and had at least one post-baseline measurement for migraine days per month during the DBTP (efficacy analysis set). [b]LSM changes from baseline in MMD during the DBTP are shown. [c]The adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. [d]p<0.001 for all pairwise comparisons between erenumab and placebo. p-values are nominal without multiplicity adjustment
CI, confidence interval; DBTP, double-blind treatment phase; LSM, least-square mean; MMA, monthly migraine attacks; MMD, monthly migraine days; SE, standard error

- During the DBTP, a statistically significant greater reduction in both MMD and MMA was observed in erenumab groups as compared with placebo
- The proportion of patients achieving ≥50% reduction from baseline in MMD and MMA were similar for each treatment group (**Figure 2**)

Figure 2: Proportion of patients who achieved ≥50% reduction in MMA and MMD over last three months of the DBTP from baseline (efficacy analysis set)



DBTP, double-blind treatment phase; MMA, monthly migraine attacks; MMD, monthly migraine days; n, number of responders at corresponding visit; N, number of patients in the analysis set

CONCLUSIONS

- The current analysis of a large randomized clinical trial with erenumab suggests that the MMD and MMA decrease in parallel, which supports that erenumab prevents the occurrence of migraine attacks (and not only shortens the duration of migraine attacks)
- Over the last three months of DBTP, MMD and MMA were significantly reduced with erenumab 70 mg and 140 mg compared to placebo
- The proportion of patients achieving ≥50% reduction from baseline in MMD and MMA were also significantly higher in erenumab 70 mg and 140 mg groups compared to placebo

RESULTS (Continued)

- The odds of achieving ≥50% reduction in MMD and MMA from baseline over the last three months of the DBTP were significantly higher in patients treated with erenumab as compared to those treated with placebo (**Table 2**)

Table 2: Proportion of patients achieving a ≥50% reduction from baseline in MMD and MMA

	Placebo (N=316)	Erenumab 70 mg (N=312)	Erenumab 140 mg (N=318)
≥50% reduction from baseline in MMD %(n/N)	26.6% (84/316)	43.3% (135/312)	50% (159/318)
Odds ratio (95% CI)[a]		2.13 (1.52 to 2.98)[b]	2.81 (2.01 to 3.94)[b]
≥50% reduction from baseline in MMA %(n/N)	23.4% (74/316)	37.8% (118/312)	44.3% (141/318)
Odds ratio (95% CI)[a]		2.02 (1.42 to 2.87)[b]	2.70 (1.90 to 3.84)[b]

[a]p<0.001 for all pairwise comparisons between each erenumab dose and placebo; [b]The common odds ratios and p-values are obtained from a CMH test, stratified by stratification factors region and prior/current treatment with migraine prophylactic medication
CI, confidence interval; MMA, monthly migraine attacks; MMD, monthly migraine days

REFERENCES

1. Shi L, et al. *J Pharmacol Exp Ther*. 2016;356:223–231.
2. Sun H, et al. *Lancet Neurol* 2016;15:382–390.
3. Dodick DW, et al. *Cephalalgia* 2018;38:1026–1037.
4. Goadsby PJ, et al. *N Eng J Med* 2017;377:2123–2132.
5. Reuter U, et al. *Lancet* 2018;392:2280–2228.

DISCLOSURES

Peer Tfelt-Hansen — No disclosure; **Messoud Ashina** — Consultant or scientific advisor for Allergan, Amgen, Alder, Eli Lilly, Lundbeck, Novartis, and Teva; primary investigator for Allergan, Amgen, Eli Lilly, ElectroCore, Novartis and Teva; grants from Lundbeck Foundation, Novo Nordisk Foundation; research grant from Novartis. **Hans-Christoph Diener** —received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Alder, Allergan, Amgen, Electrocore, Lilly, Lundbeck, Novartis, Pfizer, Teva and Weber & Weber. Financial support for research projects was provided by Allergan and Electrocore. Headache research of HCD is supported by the German Research Council (DFG) and the German Ministry of Education and Research (BMBF); no ownership interest and does not own stocks of any pharmaceutical company; serves on the editorial boards of Cephalalgia and Lancet Neurology; chairs the Clinical Guidelines Committee of the German Society of Neurology. **Gabriel Paiva Da Silva Lima and Soeren Rasmussen** — employees and stocks: Amgen Inc. **Shannon Ritter** —employee and stocks: Novartis. **Ronald Zielman** —employee: Novartis

FUNDING SOURCE

This study was supported by Amgen Inc., Thousand Oaks, CA, USA. Erenumab is co-developed by Novartis and Amgen.

ACKNOWLEDGMENTS

Medical writing support was provided by **Nisha Narayanan** and design support by **Ravi Sankar Moganti** both of Novartis Healthcare Pvt. Ltd., Hyderabad, India. The final responsibility for the content lies with the authors.