Long-Term Safety and Tolerability of Erenumab in Episodic Migraine: A Pooled Analysis From Two Clinical Trials and Their Extension Phases

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Background

Erenumab (erenumab-aooe in the United States) is a fully human monoclonal antibody targeting the canonical calcitonin gene-related peptide receptor[1]

The short-term efficacy and safety of erenumab has been established in several placebo-controlled studies in episodic migraine (EM)[2-4] and chronic migraine (CM)[5]

The longer-term safety of erenumab in EM was recently assessed in the 3-year open-label extension phase (OLEP) of the phase 3 LIBERTY study (NCT03096834)6 and in the 5-year OLEP of a phase 2 study (NCT01952574)[7]

To assess the long-term safety of erenumab using pooled data from the double-blind treatment phases (DBTP) and OLEPs of two clinical trials in EM?

Methods

Studies contributing to the pooled analysis

- Patients (18–65 years) with EM (4–14 migraine days per month) were enrolled in two multicenter studies conducted across Europe, North America and Australia
- Detailed inclusion and exclusion criteria have been reported previously[2,8]
- Pooled safety analysis included two double-blind, randomized trials and their OLEPs
  - Both studies consisted of a screening phase, a 4-week baseline phase, a 12-week DBTP, an OLEP ranging from 3 to 5 years, and a safety follow-up visit (12 or 16 weeks after the last dose of investigational product) **(Table 1)**
- In both trials, patients received subcutaneous erenumab (70 mg or 140 mg) or placebo once monthly during the DBTP and erenumab (70 mg or 140 mg) in the OLEP (see **Table 1** for trial design details)
  - Lower doses (7 mg or 21 mg in the DBTP of NCT01952574) were excluded from the DBTP analysis
- The studies were completed at the time of analysis

Table 1. Summary of studies included in the pooled analysis

Study	Patient population	Study design	Safety analysis set			
			DBTP	N	OLEP	N
NCT03096834	18–65 years; EM (4–14 migraine days per month) for ≥12 months prior to screening; 2–4 preventive treatment failures	12-week multicenter, randomized DBTP; 3-year OLEP	Placebo	124	Erenumab 140 mg	240
			Erenumab 140 mg	119		
NCT01952574	18–60 years; EM (4–14 migraine days per month) for ≥12 months prior to screening	12-week multicenter, randomized, DBTP; 5-year OLEP	Placebo	153	Erenumab 70 mg	383*
			Erenumab 70 mg	106	Erenumab 140 mg	250†

*Patients receiving lower doses of erenumab (7 mg or 21 mg) were excluded from the DBTP but were included in the OLEP after switching to 70 mg

†N=250 patients switched from 70 mg to 140 mg during the OLEP and were included in both 70 mg and 140 mg rows

Methods

Safety evaluations

- Safety endpoints included the incidence of adverse events (AE), serious AEs (SAE), and development of anti-erenumab antibodies
- Data were collected for all AEs and SAEs and coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) (V17.1, V20.1) at the time of analysis
- Grading categories for AEs were determined according to the Common Terminology Criteria for Adverse Events Version 4.03
- Immunogenicity of erenumab was evaluated using an electrochemiluminescence-based bridging immunoassay for the detection of anti-erenumab binding antibodies
    - For patients whose sera tested positive in the immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies

Statistical analysis

- The safety analysis set included patients who received at least one dose of erenumab (70 mg or 140 mg) or placebo
- The incidence of AEs and SAEs were summarized as the exposure-adjusted patient incidence rates (EAIR) per 100 patient-years (r) during the DBTP and OLEP, by the treatment received when the AE occurred

$$r = \frac{\text{total number of patients reporting at least one AE}}{\text{total time at risk in years (summed across all patients)}} \text{ X } 100$$

- The incidence of patients who developed anti-erenumab antibodies (binding or neutralizing) was expressed as percent of the total number of patients in the corresponding treatment group

Results

- Of 729 patients randomized across both studies, 502 received erenumab (70 mg or 140 mg) or placebo in the 12-week DBTP and 623 received erenumab (70 mg or 140 mg) in the 3- or 5-year OLEP
- The cumulative duration of exposure to erenumab during the DBTP and OLEP was 54.3 and 1899.5 patient-years, respectively

Results

Adverse events and serious adverse events

- The incidence of AEs and SAEs rates were similar across all treatment groups during the DBTP and OLEP, the majority of which were mild to moderate (**Table 2**)
- Overall EAIR AE rates during the OLEP were similar to those observed during the DBTP; no new AEs emerged over time
- No deaths were reported during the DBTP; two deaths occurred during the OLEP
- Discontinuation rates were low in both the DBTP and OLEP
  - In total, 3 of 225 patients (1.3%; r = 5.6) in the DBTP and 30 of 623 (4.8%; r = 2.4) in the OLEP discontinued the study drug due to AEs

Table 2. Exposure-adjusted incidence rates of AEs in the DBTP and OLEP

	DBTP (12 weeks)				OLEP (Up to 5 years)		
	Placebo	Erenumab			Erenumab		
	(N = 277) n [r]	70 mg (N = 106) n [r]	140 mg (N = 119) n [r]	All (N = 225) n [r]	70 mg (N = 383)* n [r]	140 mg (N = 490)* n [r]	All (N = 623) n [r]
Any AE	149 [357.5]	57 [326.2]	65 [363.7]	122 [345.1]	323 [141.7]	431 [136.6]	555 [171.6]
Grade ≥ 2	59 [102.7]	23 [98.0]	14 [54.0]	37 [74.9]	249 [68.5]	334 [53.0]	440 [69.3]
Grade ≥ 3	3 [4.5]	3 [11.5]	3 [10.9]	6 [11.2]	55 [8.7]	66 [5.6]	109 [9.3]
Grade ≥ 4	0 [0]	0 [0]	0 [0]	0 [0]	1 [0.1]	6 [0.5]	7 [0.5]
Serious AEs	1 [1.5]	1 [3.8]	2 [7.3]	3 [5.6]	30 [4.5]	59 [4.9]	83 [7.0]
AEs leading to discontinuation	3 [4.5]	3 [11.5]	0 [0]	3 [5.6]	16 [2.3]	14 [1.1]	30 [2.4]
Fatal AEs	0 [0]	0 [0]	0 [0]	0 [0]	1 [0.1]	1 [0.1]	2 [0.2]

N, number of patients who received at least one dose of erenumab or placebo; n, number of patients reporting at least one occurrence of an adverse events; r, exposure-adjusted patient incidence rate per 100 patient-years (n/total time at risk * 100); *N=250 patients switched from 70 mg to 140 mg during the OLEP and were included in both 70 mg and 140 mg columns

Results

Adverse events and serious adverse events

- The most commonly observed AEs in the short-term and long-term analyses included nasopharyngitis, injection site pain, fatigue, and back pain **(Table 3)**

Table 3. Exposure-adjusted incidence rates of AEs in the DBTP and OLEP

	DBTP (12 weeks)				OLEP (Up to 5 years)		
	Placebo	Erenumab			Erenumab		
	(N = 277) n [r]	70 mg (N = 106) n [r]	140 mg (N = 119) n [r]	All (N = 225) n [r]	70 mg (N = 383)* n [r]	140 mg (N = 490)* n [r]	All (N = 623) n [r]
Most frequent AEs (r > 15 in any treatment phase)							
Nasopharyngitis	24 [38.2]	6 [23.3]	5 [18.6]	11 [20.9]	82 [14.1]	172 [18.0]	224 [24.0]
Injection site pain	9 [13.8]	2 [7.7]	7 [26.3]	9 [17.1]	10 [1.5]	26 [2.1]	34 [2.8]
Fatigue	5 [7.6]	4 [15.6]	3 [11.1]	7 [13.3]	19 [2.8]	26 [2.1]	44 [3.6]
Back Pain	6 [9.1]	1 [3.8]	5 [18.6]	6 [11.2]	30 [4.6]	54 [4.5]	81 [6.9]
AEs of interest							
Constipation	2 [3.0]	3 [11.6]	1 [3.6]	4 [7.5]	9 [1.3]	31 [2.5]	40 [3.2]
Hypertension	2 [3.0]	2 [7.6]	1 [3.6]	3 [5.6]	14 [2.1]	32 [2.6]	46 [3.7]

N, number of patients who received at least one dose of erenumab or placebo; n, number of patients reporting at least one occurrence of an adverse events; r, exposure-adjusted patient incidence rate per 100 patient-years (n/total time at risk * 100); *N=250 patients switched from 70 mg to 140 mg during the OLEP and were included in both 70 mg and 140 mg columns

Results

Immunogenicity

- The post-baseline incidence of anti-erenumab antibodies was low (3.6% in the DBTP and 6.6% in the OLEP; **Table 4**)
  - Neutralizing antibodies were reported post-baseline in 0.5% of patients in the DBTP and 0.3% in the OLEP

Table 4. Anti-erenumab antibodies during long-term analysis

	DBTP (12 weeks)			OLEP (Up to 5 years)		
	Erenumab			Erenumab		
	70 mg (N = 106) n (%)	140 mg (N = 119) n (%)	All (N = 225) n (%)	70 mg (N = 383)* n (%)	140 mg (N = 490)* n (%)	All (N = 623) n (%)
Subjects with post-baseline result during DBTP or OLEP	106	115	221	380	457§	617
Antibody positive result post-baseline with a negative or no result at DBTP baseline/ prior to first OLEP dose						
Anti-erenumab antibody positive†	8 (7.5)	0 (0)	8 (3.6)	29 (7.6)	12 (2.5)	41 (6.6)
Transient‡	0 (0)	0 (0)	0 (0)	23 (79.3)	8 (66.7)	31 (75.6)
Neutralizing antibody positive†	1 (0.9)	0 (0)	1 (0.5)	2 (0.5)	0 (0)	2 (0.3)
Transient‡	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)	1 (50.0)

*N = 250 patients switched from 70 mg to 140 mg during the OLEP and were included in both 70 mg and 140 mg columns; †% based on number of subjects with a post-baseline result during the DBTP or OLEP; ‡% based on number of subjects with positive antibody result; §excluding subjects who previously had erenumab antibody positive result on erenumab 70 mg during the OLEP

Conclusions

- Erenumab demonstrated a favorable safety and tolerability profile, both in the short-term as well as in the long-term analysis, supporting its use as a treatment for migraine prevention in adults
- These integrated data suggest that there are no new safety signals with erenumab therapy in this patient population beyond the safety profile described in the existing product label

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