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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]

OBJECTIVE

- 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 (NCT03096834, NCT01952574)

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

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

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

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 per 100 patient-years (r) during the DBTP and OLEP, by the treatment received when the AE occurred

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

- 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

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 exposure-adjusted AE rates during the OLEP were similar to those observed during the DBTP; no new AEs emerged over time
- The most commonly observed AEs in the short-term and long-term analyses included nasopharyngitis, injection site pain, fatigue, and back pain
- 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 (0.0)	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)
Most frequent AEs (r>15 in any treatment arm 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

Immunogenicity

- The post-baseline incidence of anti-erenumab antibodies was low (3.6% in the DBTP and 6.6% in the OLEP; **Table 3**)
  - Neutralizing antibodies were reported post-baseline in 0.5% of patients in the DBTP and 0.3% in 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

RESULTS (CONTINUED)

Table 3. 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-AMG334 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

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