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ORIGINAL COMMUNICATION

A 24-week prospective, multicenter, real-world study on eptinezumab's effectiveness and safety in migraine prevention (EMBRACE II)

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Abstract

Introduction We evaluated the effectiveness, tolerability, and safety of eptinezumab in preventing high-frequency episodic migraine (HFEM) and chronic migraine (CM) over 24 weeks in real-world. We also assessed its impact during the first treatment week, in patients failing monoclonal antibodies targeting the calcitonin gene-related peptide (anti-CGRP mAbs), and the effects of dose escalation to 300 mg in patients requiring enhanced control.

Methods EMBRACE II is a multicenter ($n = 22$), prospective, 24-week, real-world study involving consecutive patients with HFEM or CM who had failed > 3 preventive treatments. Eptinezumab (100 mg, with the option for escalation to 300 mg at week 12) was administered quarterly. Primary endpoint: change in monthly migraine days (MMD), for HFEM or monthly headache days (MHD), for CM, between weeks 21–24 and baseline. Secondary endpoints: changes in monthly analgesic intake (MAI), Numerical Rating Scale (NRS), Headache Impact Test (HIT-6), Migraine Disability Assessment Scale (MIDAS), Migraine Interictal Burden Scale (MIBS-4), and responder rates.

Results Of the 215 participants who had received ≥ 1 eptinezumab dose, 74 were treated for ≥ 24 weeks and considered for effectiveness analysis. Eptinezumab significantly ($p < 0.001$) reduced MMD/MHD (− 10.5), MAI (− 15.6), NRS (− 2.2), HIT-6 (− 9.9), MIDAS (− 48.7), and MIBS-4 (− 4.3). ≥ 50% responders were 69%, ≥ 75% responders 39.2%, and 100% responders 4.1%.

Comparing the first week with the last baseline week, a significant reduction in migraine days was observed (− 3.7; $p < 0.001$). Significant improvements were seen in patients failing anti-CGRP mAbs (32.4%) and in those escalating to 300 mg (33.8%). Half of the subjects reported being "very much improved" or "much improved". The adverse events were infrequent (2.8%).

Conclusions This real-world study documents that 24-week eptinezumab treatment is rapidly effective and well tolerated in migraine patients with multiple therapeutic failures (including anti-CGRP mAbs). One-third of patients escalated to 300 mg at week 12, achieving further significant migraine-related disability reduction.

Keywords Eptinezumab · CGRP · Migraine · Treatment · Real-world · Disability

Introduction

Migraine is a highly prevalent and debilitating neurological disorder that may progressively worsen due to factors such as inadequate or ineffective treatments [1, 2].

The introduction of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway has marked a paradigm shift in migraine management, providing the first specific and selective preventive treatment for the condition [3]. Anti-CGRP mAbs combine robust efficacy with excellent tolerability, promoting high therapeutic adherence and offering sustained prophylactic benefits, thus representing a major advancement in migraine care.

The first three approved anti-CGRP mAbs—erenumab, fremanezumab, and galcanezumab—are administered subcutaneously. They reach peak plasma concentration approximately five days after dosing, contributing to their rapid

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onset of therapeutic action [4]. Eptinezumab, a mAb targeting the CGRP, is unique as the first intravenous therapy for migraine prevention [5]. Its 100% bioavailability and ability to reach peak plasma concentration within 30 min of infusion allow for an exceptionally rapid onset of action, with therapeutic effects often noticeable within 1–2 h after administration [6]. These pharmacokinetic properties underlie the findings of the RELIEF study, which demonstrated that intravenous eptinezumab, administered to patients eligible for migraine prevention and experiencing moderate to severe migraine attacks, significantly shortened the time to both headache relief and symptom resolution compared to control treatment [7].

Real-world studies are essential for broadening our understanding of specific drugs by evaluating their performance in unselected, often more complex patient populations [8]. These studies provide valuable insights, such as long-term effects and potential predictors of treatment outcomes. Notably, a recent review of real-world studies on anti-CGRP mAbs has shown that their effectiveness may in some cases exceed the efficacy observed in randomized controlled trials, highlighting their potential in broader clinical settings [9]. Understanding the impact of eptinezumab in real-world contexts is essential for optimizing treatment strategies, addressing unmet needs, and guiding evidence-based clinical practice.

The 12-week EMBRACE study, conducted in 26 patients with high-frequency episodic migraine (HFEM, ≥ 8 migraine days/month) or chronic migraine (CM, headache on ≥ 15 days/month for > 3 months, with migraine features on ≥ 8 days/month), demonstrated that eptinezumab is highly effective, safe, and well-tolerated—even in hard-to-treat populations with multiple prior preventive treatment failures, including those involving anti-CGRP mAbs [10]. Building on these findings, the EMBRACE II study aims to evaluate the effectiveness, tolerability, and safety of eptinezumab for HFEM and CM prevention over 24 weeks in a real-world setting. This study expands on previous research by including a larger patient cohort and assessing eptinezumab's impact during the first treatment week, its use in patients with prior anti-CGRP mAb failures, and the effects of dose escalation to 300 mg in those requiring enhanced migraine control.

Methods

The EMBRACE (EptinezuMaB in ReAl-world evidenCE) study is a multicenter, prospective, real-world investigation including all consecutive outpatients with HFEM or CM treated at 22 headache centers across eight regions representing northern, central and southern Italy (Lombardy, Liguria, Emilia-Romagna, Marche, Latium, Abruzzo, Campania and Sicily). Migraine was diagnosed according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria [11]. Preregistered with ClinicalTrials.gov (ID: NCT05570149), the study commenced on February 24, 2023, and is ongoing [12]. EMBRACE serves as a supplementary trial within the Italian Migraine Registry (I-GRAINE) [13]. The study protocol was approved by the Lazio Area 5 Review Board (N. 177/SR/24) and was mutually recognized by the ethics committees of all participating centers.

We included patients who provided informed consent and had experienced at least three prior failures of preventive migraine treatments—beta-blockers, tricyclic antidepressants, antiepileptics, or onabotulinumtoxinA (for CM patients)—in accordance with Italian Medicine Agency (AIFA) guidelines [14]. Treatment failure was defined as the absence of a clinically meaningful improvement after 3 months, poor tolerability, or the presence of contraindications. These patients received intravenous eptinezumab, administered quarterly at either 100 mg or 300 mg. They were informed about the drug's characteristics, including the efficacy and tolerability profiles of both doses, as reported in the DELIVER study, which involved a population more comparable to ours [15]. The initial recommendation was 100 mg for the first administration unless the patient opted otherwise. From the second administration onward, they had the option to escalate to 300 mg based on their perceived improvement and personal preference. Eptinezumab was diluted in 100 mL of 0.9% saline solution and infused intravenously over 30 min. After each infusion, patients were observed for a minimum of 30 min. Subjects with cardio-cerebrovascular disorders (e.g., myocardial infarction, angina, uncontrolled hypertension, peripheral arterial disease, stroke, or transient ischemic attack), other conditions deemed clinically significant by the investigator, or prior treatment with onabotulinumtoxinA within 3 months before enrollment were excluded from the study.

The participants were instructed to keep a paper-and-pencil headache diary throughout the 28-day baseline period and the entire study duration. This diary recorded monthly migraine days (MMD) for individuals with HFEM, monthly headache days (MHD) for those with CM, monthly analgesic intake (MAI), and pain severity using the Numerical Rating Scale (NRS). Migraine-related disability was assessed through the Headache Impact Test (HIT-6) and the Migraine Disability Assessment Scale (MIDAS), while the burden of migraine during headache-free periods was measured with the Migraine Interictal Burden Scale (MIBS-4). Patient-reported satisfaction with eptinezumab treatment was evaluated using the Patient Global Impression of Change (PGIC) questionnaire. The participants were also encouraged to promptly report any adverse events. Data on MMD/MHD,

MAI, NRS, HIT-6, MIDAS; MIBS-4, and AEs were collected during patient visits every 12 weeks.

The primary endpoint was the change in the average number of headache days (of any type) from baseline to weeks 21–24 in the overall migraine population. The secondary endpoints included the proportion of patients achieving reductions of ≥ 50%, ≥ 75%, and 100% in MMD or MHD, as well as changes in MAI, NRS, HIT-6, MIDAS and MIBS-4 score at the same time points in the overall migraine population, in patients with HEFM and in those with CM. Additionally, the number of headache days during the first week post-infusion was assessed. The Patient Global Impression of Change (PGIC) was evaluated at both weeks 12 and 24.

Statistical methods

The demographic and clinical characteristics of patients at baseline were expressed as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. The differences in selected demographic and clinical variables between HFEM and CM patients were assessed using the unpaired Student's t-test for continuous variables and the χ^2 test for categorical variables. Normality was evaluated using the one-sample Kolmogorov–Smirnov test. When the assumptions for the χ^2 test were not met, Fisher's exact test was applied. In cases where the normality assumption was violated, the non-parametric Mann–Whitney U test was used for continuous variables.

The changes in quantitative outcomes during follow-up (baseline, weeks 9–12 and week 21–24) were described as mean change ± SD. A repeated-measures ANOVA with pairwise post-hoc comparisons was applied to compare the mean of quantitative outcomes across three time points (baseline, weeks 9–12, and weeks 21–24), assuming normality and homogeneity of variances. In cases where the data were not normally distributed and the sphericity was not assumed, the Friedman test followed by the related post-hoc test was applied. The changes in categorical variables over time were assessed with the McNemar test or the Stuart–Maxwell test. The small sample size and the imbalance in certain clinical features necessitated focusing the statistical analysis on univariate testing. Stratified analyses were conducted to identify potential confounders, with some results included in the supplementary material, while others were performed as sensitivity analyses.

The ≥ 50%, ≥ 75% and 100% response rate (RR) at weeks 9–12 and 21–24 in the overall sample and in subgroups of patients stratified based on whether they had failed previous therapies with anti-CGRP mAbs and of patients with migraine who escalated eptinezumab dose from 100 to 300 mg at the second administration (week 12), was evaluated using the McNemar test or the Stuart–Maxwell test. Statistical significance was set at $p < 0.05$. All data analyses were conducted using SPSS v13 for Windows (IBM Corp., Armonk, NY, USA).

Results

As of 26 November 2024, a total of 215 patients had received at least one dose of eptinezumab and were included in the safety analysis (F/M = 166/49; HFEM/CM = 52/163; previously treated with at least one anti-CGRP mAb = 50). Among these, 74 individuals completed at least 24 weeks of follow-up (≥ 3 doses of eptinezumab) and were included in the effectiveness analysis (Fig. 1). The variation in the number of doses received simply reflects the different initiation times of treatment among patients and do not introduce selection bias as confirmed by a sensitivity analysis comparing patients who completed 12 weeks of treatment with those who had not reached this time point. No significant differences were found in any of the key predictive features of outcomes. The initial eptinezumab dose was 100 mg for 73 participants and 300 mg for one—a plastic surgeon with a long-standing history of highly disabling chronic migraine who opted for the higher dose. Their demographic and clinical characteristics are reported in Table 1.

The patients with CM showed a significantly higher MAI than those with HFEM (29.7 ± 27.3 vs. 10.2 ± 43.6; $p < 0.001$). Twenty-four subjects (32.4%) had previously undergone at least 12 months of unsuccessful treatment with a

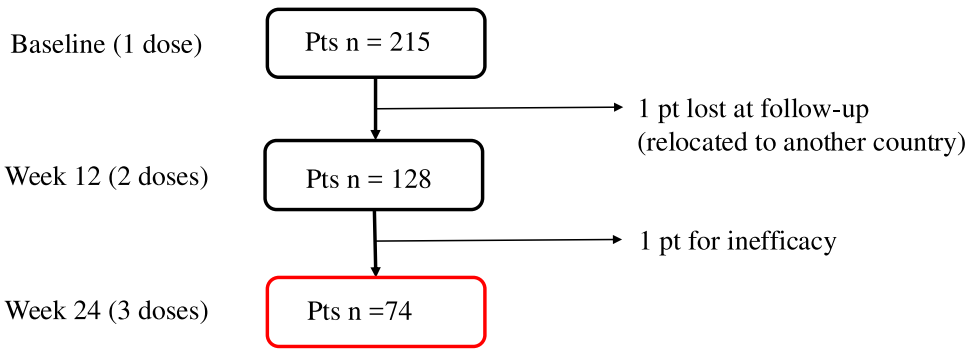

Fig. 1 Patients' disposition

Table 1 Baseline demographic and clinical characteristics of migraine patients stratified by diagnosis

Variables	Number (%) or mean ± SD			
	All patients	HFEM	CM	*p*-value
Patients	74	12	62	
Age, *years*	47.9 ± 11.9	51.8 ± 10.9	47.2 ± 12.0	0.235
Females	54 (73)	10 (83.3)	44 (71.0)	0.494
BMI	23.7 ± 4.2	25.5 ± 4.2	23.4 ± 4.1	0.115
Age at onset, *years*	23.7 ± 4	25.5 ± 4.2	18.1 ± 7.8	0.724
MMD	11.8 ± 2.3	11.8 ± 2.3	–	–
MHD	23.8 ± 5.5	–	23.8 ± 5.5	–
NRS	8.0 ± 1.1	7.9 ± 1.2	8.0 ± 1.1	0.912
Medication overuse	41 (66.1)	–	41 (66.1)	–
Medication overuse duration, *years*	4.8 ± 6.6	–	4.8 ± 6.6	–
Unilateral pain	52 (70.3)	10 (83.3)	42 (67.7)	0.491
UAS	43 (58)	7 (58.4)	36(58.1)	0.986
CAPS	0.65 ± 1.3	1.4 ± 1.5	0.61 ± 1.3	0.592
Allodynia	13 (17.6)	2 (16.7)	11(17.7)	0.929
ASC-12	1.4 ± 2.6	1.3 ± 2.3	1.4 ± 2.7	0.999
Dopaminergic symptoms	30(40.5)	2 (16.7)	28 (45.2)	0.107
MAI	26.5 ± 26.0	10.2 ± 43.6	29.7 ± 27.3	< 0.001
Pts using concomitant prophylaxis	28 (44.4)	4 (50.0)	24 (43.6)	0.999
Prior treatment failures	4.2 ± 1.9	4.3 ± 1.8	4.2 ± 1.9	0.887
Pts with prior treatment failures with anti-CGRP mAbs	24 (32.4)	3 (25)	21 (33.9)	0.999
Pts with prior treatment failure to OnabotulinumtoxinA*	55 (96.5)	6 (85.7)	49(98.0)	0.232
Pts with ≥ 1 comorbidity	29 (39.2)	4 (33.4)	25 (40.3)	0.754
Pts with psychiatric comorbidities	23 (31.1)	1 (8.4)	22 (35.5)	0.090
HIT-6	65.0 ± 6.8	62.8 ± 8.9	65.5 ± 6.3	0.569
MIDAS	78.7 ± 41.9	61.4 ± 35.3	82.2 ± 42.5	0.097
MIBS-4	7.8 ± 3.7	3.4 ± 3	8.6 ± 3.2	< 0.001
None (0)	2 (2.7)	1(8.3)	1(1.6)	
Mild (1–2)	6 (8.1)	5(41.7)	1 (1.63)	
Moderate (3–4)	15 (20.3)	5(41.7)	10 (16.1)	
Severe (> 4)	51(68.9)	1 (8.3)	50 (80.6)	†

*Proportion calculated based on the total number of subjects treated with OnabotulinumtoxinA ($N = 57$)

– not applicable

† the conditions for applying the χ^2 test were not met

HFEM high frequency episodic migraine; *CM* chronic migraine; *BMI* Body Mass Index; *MHD* monthly headache days; *MMD* monthly migraine days; *MAI* monthly analgesic intake; *NRS* Numeric Rating Scale; *UAS* unilateral cranial autonomic symptoms; *CAPS* Cranial Autonomic Parasympathetic Symptom Scale; *ASC-12* Allodynia Symptom Checklist; *Dopaminergic symptoms*: presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis; *HIT-6* Headache Impact Test-6, *MIDAS* Migraine Disability Assessment Scale; *MIBS-4* Migraine Interictal Burden Scale-4

subcutaneous mAb (erenumab, $n = 23$; galcanezumab, $n = 1$) (Supplementary Table 1). The interval between discontinuation of the prior anti-CGRP mAb and initiation of eptinezumab was ≥ 5 months in 19 patients (79.2%) and < 5 months (average: 2.4 ± 1.2 months) in 5 patients (20.8%).

At week 12, 25 individuals (33.8%) escalated the eptinezumab dose from 100 to 300 mg, to enhance clinical outcomes (Supplementary Table 2). Of these, 19 patients requested a dose increase to improve their response rate, while 6 patients opted for the escalation to reduce both ictal and interictal disability.

From baseline to weeks 21–24, eptinezumab resulted in a statistically significant reduction ($p < 0.001$) in MMD/MHD (− 10.5 ± 10.4)—the primary endpoint—across the overall migraine patient population. Significant improvements were also observed in all secondary endpoints, including MAI (− 15.6 ± 25.4), NRS (− 2.2 ± 2.3), HIT-6 (− 9.9 ± 11.6), MIDAS (− 48.7 ± 42.9), and MIBS-4 (− 4.3 ± 3.7) (Table 2;

Table 2 Change in clinical outcomes at weeks 9–12 and weeks 21–24 in the 74 patients who received three doses of eptinezumab

Comparison	Parameter	All (N = 74)		HFEM (N = 12)		CM (N = 62)	
		Change (mean ± SD)	*p*-value*	Change (mean ± SD)	*p*-value*	Change (mean ± SD)	*p*-value*
Weeks 9–12 vs. baseline	MMD/MHD	– 8.7 ± 8.6	< 0.001	–	–	–	–
	MMD	–	–	–0.3 ± 6.3	0.899	–	–
	MHD	–	–	–	–	–10.6 ± 8.2	< 0.001
	MAI	– 12.8 ± 25.9	< 0.001	– 1.8 ± 5.7	0.104	– 15.0 ± 27.7	< 0.001
	NRS	– 1.9 ± 2.3	< 0.001	– 2.6 ± 2.7	0.007	– 1.8 ± 2.2	< 0.001
	HIT-6	– 6.7 ± 9.6	< 0.001	– 2.0 ± 4.8	0.177	– 7.7 ± 10.1	< 0.001
	MIDAS	– 34.5 ± 41.1	< 0.001	– 25.2 ± 28.7	0.032	– 36.3 ± 43.1	< 0.001
	MIBS-4	– 3.8 ± 3.9	< 0.001	– 1.2 ± 2.9	0.785	– 4.3 ± 3.9	< 0.001
Weeks 21–24 vs. baseline	MMD/MHD	**–10.5 ± 10.4**	**< 0.001**	–	–	–	–
	MMD	–	–	0.9 ± 9.4	0.741	–	–
	MHD	–	–	–	–	–13.7 ± 8.9	< 0.001
	MAI	– 15.6 ± 25.4	< 0.001	– 0.5 ± 10.6	0.241	– 18.5 ± 26.5	< 0.001
	NRS	– 2.2 ± 2.3	< 0.001	– 1.8 ± 1.9	0.007	– 2.3 ± 2.4	< 0.001
	HIT-6	– 9.9 ± 11.6	< 0.001	– 2.8 ± 4.5	0.054	– 11.4 ± 12.1	< 0.001
	MIDAS	– 48.7 ± 42.9	< 0.001	– 21.1 ± 29.5	0.030	– 54.1 ± 43.2	< 0.001
	MIBS-4	– 4.3 ± 3.7	< 0.001	– 0.6 ± 3.1	0.998	– 5.0 ± 3.3	< 0.001
Weeks 21–24 vs. weeks 9–12	MMD/MHD	– 1.8 ± 6.9	0.009	–	–	–	–
	MMD	–	–	1.2 ± 4.7	0.413	–	–
	MHD	–	–	–	–	–2.8 ± 6.01	0.046
	MAI	– 2.8 ± 7.7	0.193	1.3 ± 6.3	0.504	– 3.6 ± 7.7	0.104
	NRS	– 0.3 ± 1.9	0.266	0.75 ± 2.3	0.275	– 0.44 ± 1.8	0.057
	HIT-6	– 3.1 ± 7.5	0.097	– 0.83 ± 3.4	0.411	– 3.5 ± 8.0	0.056
	MIDAS	– 13.1 ± 32.2	0.001	– 2.2 ± 15.7	0.999	– 15.9 ± 33.9	0.010
	MIBS-4	– 0.5 ± 2.3	0.998	0.6 ± 1.2	0.554	– 0.7 ± 2.4	0.452

*p-value of post hoc pairwise comparisons in repeated measures analysis

– not applicable

MMD, monthly migraine days; *MHD*, monthly headache days; MMD/MHD; *MAI*, monthly analgesic intake; *NRS*, Numerical Rating Scale; *HIT-6*, Headache Impact Test-6; *MIDAS*, Migraine Disability Assessment Scale; *MIBS-4*, Migraine Interictal Burden Scale

Primary endpoint is highlighted in **bold**

supplementary Table 3). In patients with HFEM, significant reductions were recorded for NRS (− 1.8 ± 1.9; $p = 0.007$) and MIDAS (− 21.1 ± 29.5; $p = 0.030$), with a trend toward improvement in HIT-6 (− 2.8 ± 4.5; $p = 0.054$). Reductions in MMD, MAI, and MIBS-4 did not reach statistical significance. Conversely, in individuals with CM, eptinezumab induced a statistically significant reductions ($p < 0.001$) in all clinical outcomes, i.e. MHD (− 13.7 ± 8.9), MAI (− 18.5 ± 26.5), NRS (− 2.3 ± 2.4), HIT-6 (− 11.4 ± 12.1), MIDAS (− 54.1 ± 43.2), and MIBS-4 (− 5.0 ± 3.3).

At weeks 21–24, the proportions of patients achieving ≥ 50%, ≥ 75%, and 100% response rates compared to baseline were 69%, 39.2%, and 4.1%, respectively (HFEM: 50%, 17%, and 8.3%; CM: 73%, 43.5%, and 3.2%). Notably, in the overall population, these response rates were significantly higher at weeks 21–24 compared to weeks 9–12 (≥ 50%: 69% vs 56.8%, $p < 0.05$; ≥ 75%: 39.2% vs 18.9%, $p = 0.001$). Among patients with CM, the proportion of ≥ 50% responders and ≥ 75% responders were also significantly higher at weeks 21–24 vs. weeks 9–12 (73% vs 59.7% and 43.5% vs 22.6%, $p = 0.001$) (Fig. 2).

From weeks 9–12 to weeks 21–24, eptinezumab further achieved statistically significant reductions in MMD/MHD (− 1.8 ± 6.9; $p = 0.009$), and MIDAS (− 13.1 ± 32.2; $p = 0.001$) (Table 2). No significant changes were observed in MMD, MAI, NRS, HIT-6, MIDAS, or MIBS-4 among HFEM patients during this period. Patients with CM exhibited statistically significant reductions in MHD (− 2.8 ± 6.0; $p = 0.046$), and MIDAS (− 15.9 ± 33.9; $p = 0.010$), though no significant reduction was observed in MAI (− 3.6 ± 7.7; $p = 0.104$), NRS (− 0.44 ± 1.8; $p = 0.057$), HIT-6 (− 3.5 ± 8.0; $p = 0.056$) and MIBS-4 (− 0.7 ± 2.4; $p = 0.452$).

A statistically significant reduction in migraine days during the first week of treatment compared the last week before treatment was observed in the overall migraine population (− 3.7 ± 2.2; $p < 0.001$), in patients with HFEM

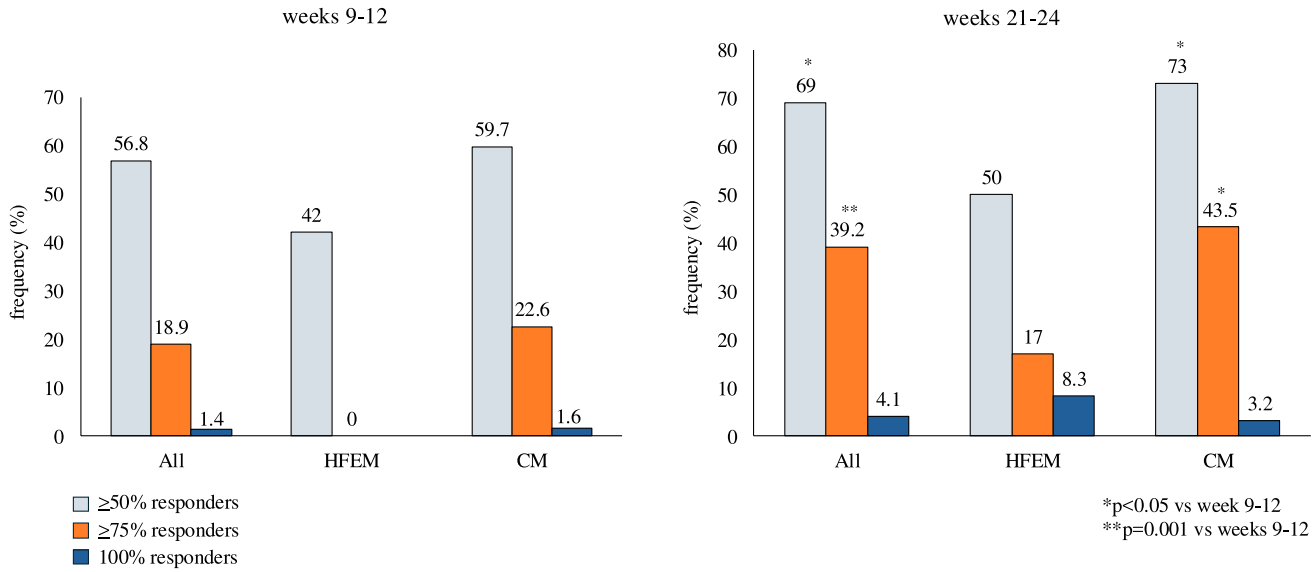

Fig. 2 Responders at weeks 9–12 (left) and weeks 21–24 (right) in the overall patient population. *All*: total patient population; *HFEM*: patients with high-frequency episodic migraine; *CM*: patients with chronic migraine. ≥50% responders: proportion of patients with a ≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥75% responders: proportion of patients with a ≥ 75% reduction in monthly migraine/headache days compared to baseline; 100% responders: proportion of patients with a 100% reduction in monthly migraine/headache days compared to baseline

Table 3 Change in migraine frequency during the first week of treatment versus the last week before treatment in the 74 patients who received three doses of eptinezumab

	All ($n = 74$)	HFEM ($N = 12$)	CM ($N = 62$)
Migraine days during last week before treatment	5.7 ± 1.8	3.1 ± 0.7	6.2 ± 1.5
Migraine days during the first week of treatment	1.9 ± 1.7	1.7 ± 1.8	2.0 ± 1.7
Change	− 3.7 ± 2.2	− 1.5 ± 2.1	− 4.2 ± 1.0
p-value*	< 0.001	0.039	< 0.001

*p-value of nonparametric test for two paired samples

(− 1.5 ± 2.1; $p = 0.039$), and in those with CM (− 4.2 ± 1.0; $p < 0.001$) (Table 3).

Treatment with eptinezumab resulted in statistically significant improvements across MMD/MHD, NRS, MIDAS and MIBS-4 at weeks 21–24 compared to baseline in patients with prior failure to anti-CGRP mAbs (Table 4). In patients who had escalated their eptinezumab dose to 300 mg (Table 5), significant improvements were observed across all clinical outcomes at weeks 21–24 compared to baseline. In patients with prior anti-CGRP mAb failure, 58% achieved a ≥ 50% reduction in migraine frequency and 33.3% achieved a ≥ 75% reduction (Fig. 3). Similarly, among patients who escalated to 300 mg, 56% and 32% reached ≥ 50% and ≥ 75% response rates, respectively (Fig. 4).

Half of the patients in the overall migraine population reported being "very much improved" (32.4%) or "much improved" (17.6%), while 35.1% described themselves as "minimally improved," and only 14.9% reported no change (Fig. 5). Among patients with prior failure to anti-CGRP mAbs, the corresponding proportions were 8.3%, 45.8%, 16.7%, and 29.2%, respectively. In those who escalated the eptinezumab dose, the proportions were 8%, 44%, 20%, and 28%, respectively (Fig. 5).

Six patients (2.8%) reported at least one adverse event, including constipation ($n = 1$), hair effluvium ($n = 1$), drowsiness ($n = 1$), fatigue ($n = 1$), and mild hyposmia ($n = 1$). No patients discontinued treatment due to adverse events. One patient discontinued due to lack of efficacy, while another was lost to follow-up after relocating to another country.

Discussion

In this multicenter, prospective, 24-week real-world study, eptinezumab significantly reduced migraine frequency, monthly analgesic use, pain severity, as well as both ictal and interictal disability compared to baseline in migraine patients who had previously failed at least three treatments. On average, eptinezumab reduced migraine frequency by 10.5 days, with 69% of subjects classified as responders, 39.2% as super-responders, and 4.1% as absolute responders

Table 4 Change in clinical outcomes at weeks 9–12 and weeks 21–24 in the 24 subjects with prior failure of anti-CGRP mAb treatment

Comparison	Parameter	Change (mean ± SD)	*p*-value*
Weeks 9–12 vs. baseline	MMD/MHD	– 9.7 ± 8.2	**< 0.001**
	MAI	– 22.0 ± 41.6	0.337
	NRS	– 1.4 ± 1.8	**0.003**
	HIT-6	– 8.9 ± 11.7	0.250
	MIDAS	– 29.4 ± 24.6	**0.001**
	MIBS-4	– 3.7 ± 3.6	**0.007**
Weeks 21–24 vs. baseline	MMD/MHD	– 11.8 ± 10.5	**< 0.001**
	MAI	– 23.5 ± 39.9	0.063
	NRS	– 1.3 ± 1.7	**< 0.001**
	HIT-6	– 11.6 ± 13.9	0.091
	MIDAS	– 29.0 ± 34.7	**< 0.001**
	MIBS-4	– 3.7 ± 4.0	**< 0.001**
weeks 21–24 vs. weeks 9–12	MMD/MHD	– 2.1 ± 6.6	0.061
	MAI	– 1.5 ± 4.4	0.999
	NRS	0.1 ± 1.1	0.520
	HIT-6	– 2.6 ± 3.9	0.999
	MIDAS	– 0.65 ± 26.5	0.190
	MIBS-4	0 ± 1.8	0.087

*p-value of post hoc pairwise comparisons in repeated measures analysis

MMD monthly migraine days; *MHD* monthly headache days; *MAI* monthly analgesic intake; *NRS* numerical rating scale; *HIT-6* Headache Impact Test-6; *MIDAS* migraine disability assessment scale; *MIBS-4* Migraine Interictal Burden Scale

Bold: $p < 0.05$

Table 5 Change in clinical outcomes at weeks 9–12 and 21–24 in the 25 patients with migraine who escalated eptinezumab dose from 100 to 300 mg at week 12

Comparison	Parameter	Change (mean ± SD)	*p*-value*
Weeks 9–12 vs. baseline	MMD/MHD	– 8.0 ± 7.8	**0.017**
	MAI	– 21.3 ± 40.8	0.102
	NRS	– 1.4 ± 1.8	**0.017**
	HIT-6	– 9.0 ± 11.4	**0.016**
	MIDAS	– 29.4 ± 24.6	**< 0.001**
	MIBS-4	– 3.8 ± 3.6	**0.001**
Weeks 21–24 vs. baseline	MMD/MHD	– 9.3 ± 11.2	**< 0.001**
	MAI	– 23.4 ± 39.0	**0.002**
	NRS	– 1.4 ± 1.7	**0.004**
	HIT-6	– 13.0 ± 15.0	**< 0.001**
	MIDAS	– 34.9 ± 44.4	**0.001**
	MIBS-4	– 3.8 ± 4.0	**< 0.001**
Weeks 21–24 vs. weeks 9–12	MMD/MHD	– 1.2 ± 8.0	0.867
	MAI	– 2.0 ± 5.1	0.609
	NRS	– 0.1 ± 1.2	0.857
	HIT-6	– 3.7 ± 6.7	0.981
	MIDAS	– 0.7 ± 26.5	0.709
	MIBS-4	0 ± 1.7	0.999

*p-value of post hoc pairwise comparisons in repeated measures analysis

MMD monthly migraine days; *MHD* monthly headache days; *MAI* monthly analgesic intake; *NRS* numerical rating scale; *HIT-6* Headache Impact Test-6; *MIDAS* migraine disability assessment scale. Bold: $p < 0.05$

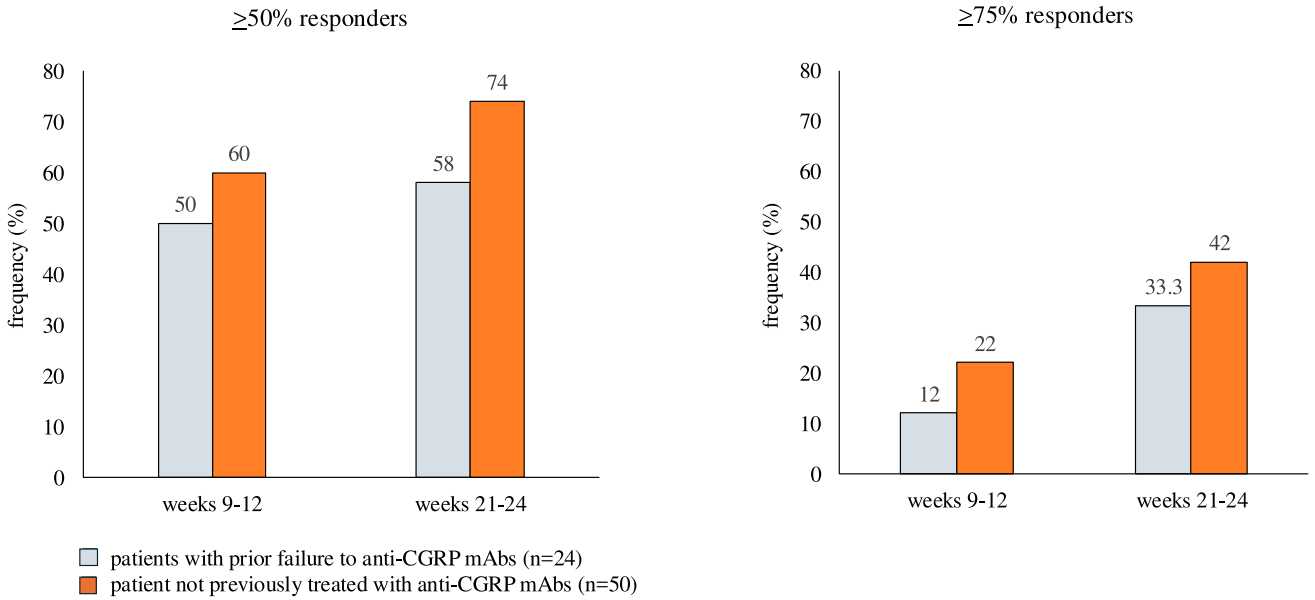

Fig. 3 Responders at weeks 9–12 and weeks 21–24 in patients with prior failure to monoclonal antibodies targeting CGRP pathway (anti-CGRP mAbs; $n = 24$) and in those not previously treated with anti-CGRP mAbs ($n = 50$). ≥50% responders: proportion of patients with a≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥75% responders: proportion of patients with a≥ 75% reduction in monthly migraine/headache days compared to baseline

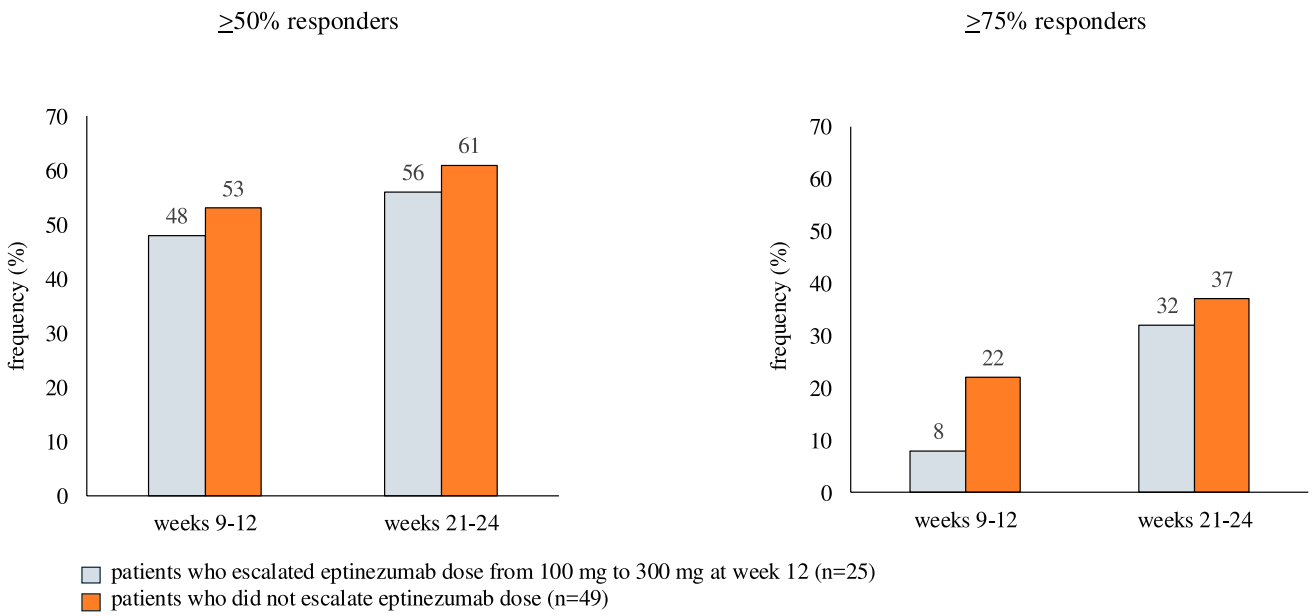

Fig. 4 Responders at weeks 9–12 and weeks 21–24 in patients who escalated the eptinezumab dose to 300 mg at week 12 ($n = 25$) versus those who did not ($n = 49$). ≥50% responders: proportion of patients with a≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥75% responders: proportion of patients with a≥ 75% reduction in monthly migraine/headache days compared to baseline

after six months of therapy. Response rates showed a significant improvement between weeks 21–24 compared to weeks 9–12. Additionally, half of the patients reported feeling "very much improved" or "much improved." The treatment was safe and well-tolerated, with adverse events being infrequent and mild; only one patient discontinued treatment.

Eptinezumab's effectiveness, measured by reductions in migraine frequency, MAI, and MIBS-4, as well as response and super-response rates, was greater in patients with CM

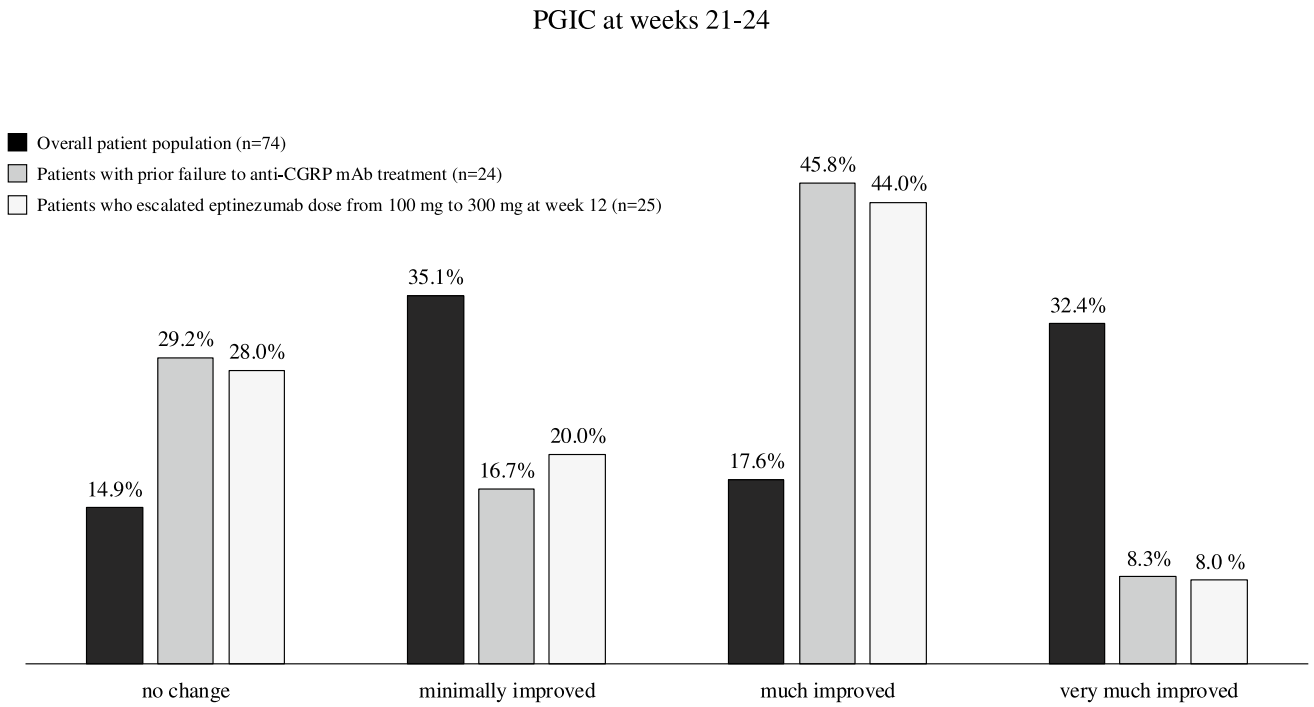

Fig. 5 Patient Global Impression of Change (PGIC) at weeks 21–24 in the overall patient population ($n = 74$, black bars), in patients with prior failure to monoclonal antibodies targeting CGRP pathway (anti-CGRP mAbs; $n = 24$, gray bars), and in patients who escalated the eptinezumab dose to 300 mg at week 12 ($n = 25$, light gray bars)

than in those with HFEM. However, this difference may be attributed to the small sample size of HFEM patients (12/74; 16.2%), which limits the ability to draw definitive conclusions from this subgroup.

The proportion of ≥ 50% and ≥ 75% responders to eptinezumab in this real-world study appears higher than that reported in the corresponding DELIVER randomized controlled trial, where ≥ 50% response rates ranged from 52 to 59% and ≥ 75% response rates ranged from 21 to 28% with the 100 mg and 300 mg doses, respectively [15]. This finding is particularly noteworthy given that our study population was more complex and harder to treat, with a significantly higher proportion of patients with CM (83.8% vs. 46%), MO (66.1% vs 13%), and a greater percentage of individuals with at least three prior therapeutic failures (100% vs. 37%). This trend aligns with findings from other studies, where anti-CGRP mAbs have demonstrated greater efficacy in real-world compared to randomized controlled trials [9, 16–18]. Potential explanations for this discrepancy include a more pronounced placebo effect in real-world settings, where patients are often more engaged with their healthcare providers, or an increased CGRP activity in more complex migraine patients, which could enhance the therapeutic effects of anti-CGRP treatments.

Clinically meaningful data from this real-world study include the very rapid onset of action of eptinezumab, its effectiveness in patients with prior mAb treatment failures, and the effective escalation from 100 to 300 mg in one-third of the patients by week 12.

Eptinezumab's effectiveness was evident as early as the first week of treatment, with a significant reduction in migraine days. This rapid onset of action is particularly important for patients with high migraine frequency or disability, long disease duration, medication overuse, or comorbidities. The quick action may be attributed to the favorable pharmacokinetic properties of the intravenous eptinezumab (Tmax: 30 min) [6]. Such an early response offers a distinct clinical advantage.

Remarkably, eptinezumab also demonstrated strong effectiveness at weeks 21–24 also in the 24 patients (32.4%) who had previously failed a 12-month treatment regimen with anti-CGRP mAbs. Switching to a different anti-CGRP mAb when the first proves ineffective is known to offer potential clinical benefits [19]. This approach is largely supported by retrospective and observational studies, which have mainly examined the outcomes of switching from anti-CGRP mAbs to mAbs targeting the CGRP receptor. Our study further reinforces this strategy, demonstrating ≥ 50% and ≥ 75% response rates of 58% and 33%, respectively, at 24 weeks in patients previously unresponsive to 12 months of anti-CGRP mAb therapy. However, the favorable outcomes of therapeutic switching could also be influenced by a potential carry-over effect from the previous treatment with anti-CGRP mAbs or by

the overall impact of long-term anti-CGRP treatment on the course of the disease [20–22].

One-third of patients (33.8%) opted to increase their eptinezumab dose from 100 to 300 mg at week 12, despite having already achieved improvements in both primary and secondary efficacy endpoints. This decision was motivated by a desire to further maximize the therapeutic benefits of eptinezumab. Following dose escalation, these patients experienced a significant additional reduction in disability, as reflected by improvement in HIT-6 score, alongside a trend toward decreased analgesic use compared to the 100 mg dose. Furthermore, the proportion of ≥ 75% responders increased from 8 to 32%. These findings underscore the importance of discussing the potential for dose escalation to 300 mg, not only in patients with an inadequate response to the 100 mg dose but also in responders with more complex or disabling conditions, to optimize treatment outcomes. However, we cannot exclude that the observed improvement in outcomes may also be partially influenced by patients' expectations.

In terms of safety, adverse events were rare (2.8%), mild, and transient, with none leading to treatment discontinuation. The discrepancy in adverse event frequency compared to the DELIVER study (41–42%) may be explained by differences in how adverse events were assessed in clinical practice versus randomized controlled trials. Additionally, the patients in our study had, on average, failed at least three prior preventive treatments, which may have led them to underreport or downplay mild adverse events, given their prior experience with less tolerable therapies.

This study has several limitations. The sample size is relatively small, with a much higher proportion of patients affected by CM (83.8%) and a smaller number with HFEM. Additionally, due to AIFA regulations, we excluded patients with less severe migraine (fewer than 8 MMD) and those who had failed fewer than three classes of preventive treatments. Another limitation is the use of paper-and-pencil diaries instead of electronic ones, which may have impacted the accuracy and consistency of data collection. Lastly, an inherent limitation of real-world studies is the potential confounding influence of migraine's natural history, placebo effect, and patient-driven lifestyle changes.

However, the study also has notable strengths. Its prospective, multicenter design, which involved 22 headache centers across approximately half of Italy's regions, ensures broad geographic representation from northern, central, and southern Italy. This enhances the generalizability of the findings to a diverse population. Moreover, patients were meticulously clinically characterized through face-to-face interviews, utilizing the shared semi-structured questionnaire of the Italian Migraine Registry [13]. This questionnaire was administered by headache specialists specifically trained for this purpose, contributing to the reliability and depth of the data.

Conclusion

Our study demonstrates that, in a real-world setting, eptinezumab significantly improves migraine outcomes after 24 weeks of treatment by reducing frequency, analgesic use, pain severity, and both ictal and interictal disability in individuals with migraine who have experienced multiple therapeutic failures—most of whom (66.1%) presented with medication overuse, while maintaining a favorable tolerability profile. The clinical benefits observed after 24 weeks of treatment were significantly greater than those achieved after 12 weeks. Moreover, eptinezumab's therapeutic effect manifests rapidly, with improvements evident as early as the first week of treatment. These beneficial effects were observed not only in the general migraine population but also in patients who have failed prior subcutaneous anti-CGRP mAbs. One-third of the patients chose to escalate their dose to 300 mg at week 12, achieving a further significant reduction in migraine-related disability.

Further studies are warranted to validate and extend these findings in larger, more diverse populations, including individuals with lower migraine frequency. Additionally, future research should focus on better characterizing the subset of patients who may benefit from dose escalation, as well as defining the optimal timing for dose adjustments. A more precise quantification of the clinical benefits associated with dose escalation is also needed to guide individualized treatment strategies.

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Author contributions PB, CA, SC and AM designed the study, PB and CA drafted the manuscript, AM and SB carried out data analysis, PB, CA, GE, AD, FdO, PS, SR, LV, MS, RV, VD, GV, MB, AR, MBdP, FB, DM, FB, LC, SM, MA, AV, BO, MD, LB, FP, CC, GS, GQ, PT, AS, FG, BP, AC, RM, MF, ST, GF, SB, SC, AM and the Italian Migraine Registry study group performed data collection, PB, CA and SB revised the manuscript. The author(s) read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest Piero Barbanti received travel grants, honoraria for advisory boards, speaker panels or clinical investigation studies from Abbvie, Alder, Allergan, Amgen, Angelini, Assosalute, Bayer, Biohaven, ElectroCore, Eli-Lilly, Fondazione Ricerca e Salute, GSK, Lundbeck, Lusofarmaco, 1MED, MSD, New Penta, Noema Pharma, Novartis, Organon, Orion Pharma, Pfizer, Stx-Med, Teva, Viatris, Visufarma, Zambon and serves as President with Italian Association of Headache Sufferers. Cinzia Aurilia received travel grants from Eli-Lilly, FB-Health, Lusofarmaco and Teva, honoraria from Novartis, Eli-Lilly and Teva. Gabriella Egeo received travel grants and honoraria from Eli-Lilly, Novartis, New Penta and Ecupharma. Alberto Doretti received travel grants and honoraria from Eli Lilly, Zambon, Teva, Abbvie, Neopharmed Gentili, and Lundbeck. Florindo d'Onofrio received travel grant, honoraria as a speaker or for partecipating in advisory boards from Novartis, Teva, Neopharmed Gentili, Qbgroup srl, K link srl and Eli-Lilly. Mattia Sansone received honorarium for speaker activities from Lundbeck. Giovanna Viticchi received honoraria for speaker activities and participating in advisory boards from Eli-Lilly, AbbVie, Teva and Boehringer Ingelheim. Marco Bartolini received honoraria for speaker activities from Lusofarmaco and Neopharmed. Angelo Ranieri received honoraria for speaker activities, advisory boards, consulting, editorial contribution and travel grants from Novartis, Teva, Eli-Lilly, VyvaMed Srl, CPM Srl, CTP SrlK link srl, Lundbeck, AIM Education Srl, Momento Medico Srl. Davide Mascarella received educational grant from Eli Lilly and travel grant from Abbvie, Eli Lilly, and Teva. Paola Torelli received travel grant, honoraria as a speaker, or for participating in advisory boards from Novartis, Teva, Eli Lilly, and Allergan. Roberta Messina received honoraria for speaker activities and participating in advisory boards from Abbvie, Biomedia, Eli Lilly, Lundbeck, Organon, Pfizer and Teva. Massimo Filippi is the Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almi- rall, Biogen, Horizon, Merck, Novartis, Roche, and Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Horizon, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participa- tion in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Horizon, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Gen- zyme, and Takeda; scientific direction of educational events for Bio- gen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, and Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Italian Ministry of Health, Fondazi- one Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). Sabina Cevoli received honoraria for speaker panels from Teva and Novartis. Paola Scatena, Steno Rinalduzzi, Luisa Vinciguerra, Rosario Vecchio, Valeria Drago, Monica Laura Bandettini di Poggio, Francesco Baldisseri, Fabio Brusaferri, Luigi Caputi, Stefano Messina, Massimo Autunno, Alessandro Valenza, Bianca Orlando, Marisa Distefano, Laura Borrello, Francesca Pistoia, Cecilia Camarda, Gennaro Saporito, Giacomo Querzola, Antonio Salerno, Francesca Gragnani, Barbara Petolicchio, Antonio Carnevale, Sofia Tavani, Giulia Fiorentini, Stefano Bonassi and Alice Mannocci have no disclosures to declare.

Ethical approval The study was conducted in accordance with principles outlined in the Declaration of Helsinki. The study protocol received approval by Lazio Area 5 Review Board (N. 177/SR/24) and mutually recognized by other local Institutional Review Boards.

Informed consent and consent to participate Eligible participants provided informed consent to participate in the study and were subsequently enrolled.

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