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ORIGINAL RESEARCH

Real-World Response and Super-Response to Eptinezumab over 48 Weeks in Migraine: The Prospective Multicenter EMBRACE III Study

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ABSTRACT

Introduction: Long-term (> 24 weeks) real-world evidence of eptinezumab's effectiveness is limited. We evaluated ≥ 50% and ≥ 75% response rates over 48 weeks in patients with high-frequency episodic migraine (HFEM) or chronic migraine (CM).

Methods: EMBRACEIII (NCT05570149) is a prospective, multicenter, observational study. Adults with HFEM or CM who experienced ≥ 3 preventive treatment failures received eptinezumab 100 mg intravenously every 12 weeks, with optional 300 mg escalation after week 12 for inadequate response. Co-primary endpoints

Piero Barbanti and Cinzia Aurilia contributed equally to this study.

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were ≥ 50% and ≥ 75% reductions in monthly migraine/headache days (MMD/MHD) at weeks 45–48 versus baseline. Secondary endpoints were changes in MMD/MHD, monthly analgesic intake (MAI), pain intensity (assessed using the numeric rating scale [NRS]), migraine-related disability and impact (assessed using the Headache Impact Test–6 [HIT-6], Migraine Disability Assessment [MIDAS], the Migraine Interictal Burden Scale–4 [MIBS-4]), patient-reported global treatment response (assessed using the Patient Global Impression of Change [PGI-C] questionnaire), and 100% response. Exploratory analyses assessed dose escalation, prior anti-calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) treatment failures, responders without adverse events, ≥ 30% reduction in the NRS during residual attacks, and clinically complex subgroups.

Results: Among the 261 patients (safety population) included in the study, 124 completed ≥ 48 weeks of treatment with eptinezumab. At week 48, the response rates for ≥ 50%, ≥ 75%, and 100% were 82.3%, 51.6%, and 9.7%, respectively. All secondary endpoints improved significantly ($p < 0.001$), with significant reductions from baseline: MMD/MHD, − 15.5; MAI, − 14.9; NRS, − 3.3; HIT-6, − 20.6; MIDAS, − 74; and MIBS-4, − 4.3. Also, 94.8% of patients reported PGI-C improvement. Dose escalation occurred in 69.4% of patients. Patients receiving ≥ 3 doses of 300 mg eptinezumab achieved outcomes comparable to responders receiving 100 mg. Among patients with prior anti-CGRP mAb treatment failures (51.6%), ≥ 50% and 100% responders were similar to mAb-naïve patients, whereas ≥ 75% response was lower (37.5%; $p = 0.002$). Response rates of ≥ 50%, ≥ 75% and 100% were achieved by 81.2%, 50.4%, and 8.5%, respectively, in patients without adverse events; 85.7%, 51.4%, and 8.6% in patients with psychiatric comorbidities; 87.8%, 54.9%, and 7.3% in patients with CM with medication overuse; and 89.2%, 50.0%, and 7.1% in patients with CM with both conditions.

Conclusions: Eptinezumab demonstrated sustained 48-week effectiveness, with high response rates of ≥ 75% and 100% in a difficult-to-treat population. Effectiveness was preserved in patients with prior anti-CGRP mAb failures after 300 mg escalation and in clinically complex subgroups. Many patients achieved ≥ 30% reduction in NRS during residual migraine attacks.

Trial Registration: ClinicalTrials.gov: NCT05570149.

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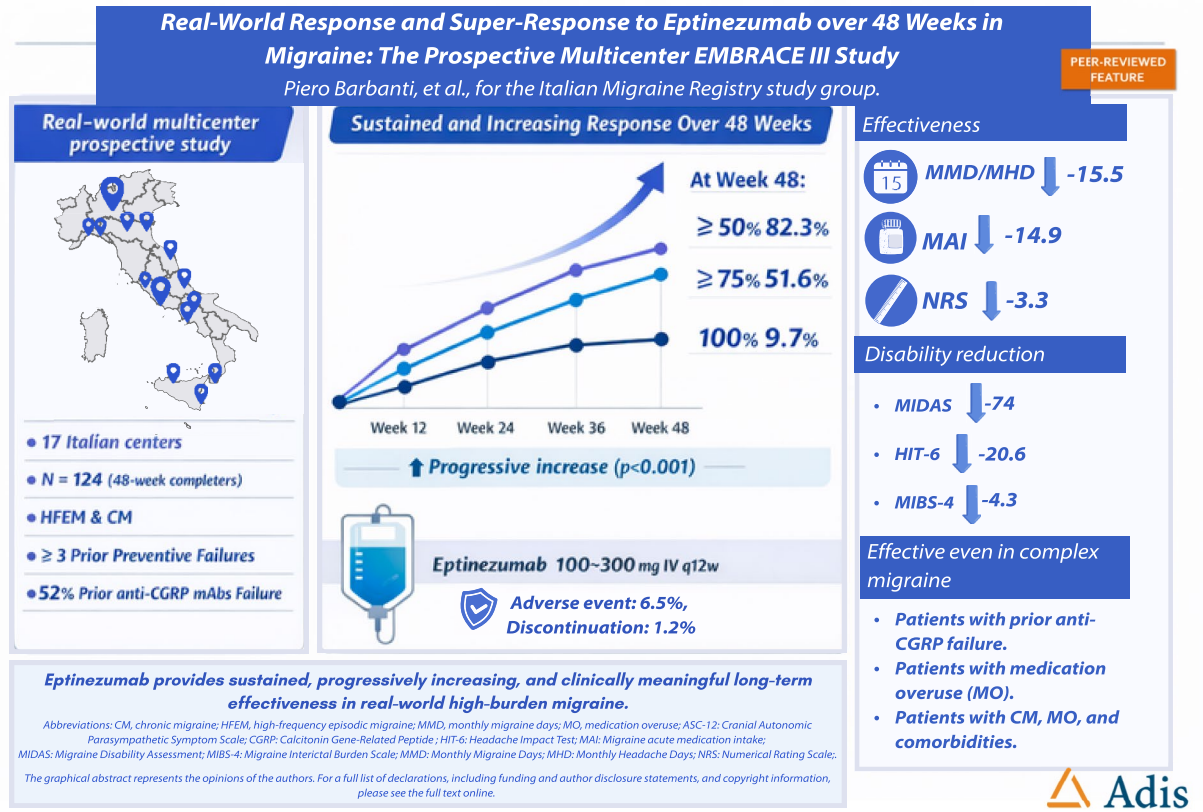
Graphical Abstract:



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Keywords: Eptinezumab; Migraine; CGRP; Treatment; Real-world; Disability

Key Summary Points

Why carry out this study?

Long-term real-world evidence on the effectiveness of eptinezumab in high-frequency episodic and chronic migraine, particularly in patients with multiple preventive treatment failures, is scarce

There is an unmet need to assess sustained treatment response (≥ 50% reduction) and super-response (≥ 75% reduction) in clinically complex populations treated in routine practice

We assessed whether eptinezumab provides sustained, clinically meaningful effectiveness, including response and super-response rates, over 48 weeks in a real-world population with difficult-to-treat migraine

What was learned from the study?

At 48 weeks, the ≥ 50%, ≥ 75%, and 100% response rates were 82.3%, 51.6%, and 9.7%, respectively, with significant improvements across all clinical outcomes, low adverse event rates, and a high proportion of responders free from adverse events

Eptinezumab demonstrated sustained and progressively increasing effectiveness over time, including in patients with prior anti-calcitonin gene-related peptide monoclonal antibody (CGRP mAb) failures and in clinically complex subgroups (e.g., psychiatric comorbidities, medication overuse)

A ≥ 75% response threshold may better discriminate treatment effects across patient subgroups

DIGITAL FEATURES

Graphical abstract available for this article https://doi.org/10.6084/m9.figshare.32300433.

INTRODUCTION

For nearly six decades, migraine preventive therapy has relied on non-specific pharmacological agents originally developed for other indications [1]. This approach has been characterized by modest efficacy and suboptimal tolerability, resulting in high treatment discontinuation rates due to adverse events, insufficient effectiveness, or both [2]. The introduction of therapies targeting the calcitonin gene–related peptide (CGRP) pathway, including monoclonal antibodies (mAbs) and gepants, represents a major paradigm shift in migraine prevention. These agents have demonstrated efficacy across a wide range of migraine subtypes—including chronic migraine (CM), patients with medication overuse, and those with relevant comorbidities—together with a rapid onset of action and a safety and tolerability profile suitable for long-term use [3].

Eptinezumab shares with other anti-CGRP mAbs robust evidence of efficacy and tolerability from 12-week randomized controlled trials (RCTs), including patients with prior preventive treatment failures [4–6]. Eptinezumab is uniquely characterized by the intravenous administration and by its ability to provide rapid relief of headache and associated symptoms when administered during an active migraine attack [7].

Despite the strength of RCT evidence, real-world data remain essential to evaluate the effectiveness of eptinezumab in unselected and clinically complex migraine populations. This approach also allows for evaluation of its performance in routine clinical practice, across longer treatment periods and the investigation of clinically relevant outcomes that may not be fully captured in controlled trial settings. Prospective, multicenter, real-world studies conducted over 12 weeks (EMBRACE) and 24 weeks (EMBRACE II) have shown that eptinezumab is effective, safe, and well tolerated in clinical practice, even among patients with difficult-to-treat migraine and a history of multiple preventive treatment failures, including prior exposure to anti-CGRP mAbs, with benefits emerging as early as the first treatment week [8]. Approximately one third of

patients in these studies required dose escalation to 300 mg at week 12, an adjustment which was associated with a further reduction in migraine-related disability [9].

In the last few years, expectations for migraine prevention have progressively evolved, with the International Headache Society now encouraging clinicians to pursue the highest achievable treatment outcomes [10]. This shift moves beyond conventional response thresholds toward more ambitious goals, including super-response (≥ 75% reduction in migraine frequency)—which captures both patients' aspiration and more profound effects on migraine pathophysiology—as well as sustained response over time. In this context of pursuing optimal migraine control and, in selected cases, freedom from disease [10], evidence on the long-term real-world effectiveness of eptinezumab beyond 24 weeks remains limited.

Accordingly, the present study aimed to evaluate both response (≥ 50% reduction in migraine frequency) and super-response to eptinezumab over 48 weeks in a large real-world population. In addition, we explored patterns and clinical correlates of dose escalation to 300 mg, as well as treatment outcomes in particularly challenging subgroups, including patients with prior failures to anti-CGRP mAbs and those with complex comorbidities.

METHODS

Study Design

EMBRACE III (EptinezuMaB in ReAl-world evidenCE) is a prospective, multicenter, observational real-world study conducted across 17 Italian headache centers based on routine clinical practice. The study started on 22 March 2023 and is currently ongoing. It is registered on ClinicalTrials.gov (identifier: NCT05570149) [11]. The study was designed to assess the real-world effectiveness, safety, and tolerability of eptinezumab administered according to standard clinical practice in patients with high-frequency episodic migraine (HFEM; 8–14 days per month) and CM (≥ 15 days per month).

Ethical Approval

The study was conducted in accordance with principles outlined in the Declaration of Helsinki. The study protocol received approval by the Lazio Area 5 Review Board (No. 177/SR/24) and was mutually recognized by other local Institutional Review Boards. All copyrighted scales used in this study (HIT-6, MIDAS, MIBS-4, ASC-12) were administered with the appropriate permission from the respective copyright holders. Eligible participants provided informed consent to participate in the study and were subsequently enrolled.

Patient Enrollment and Treatment

All consecutive adult patients eligible for eptinezumab treatment according to national reimbursement criteria were invited to participate. Eligibility required a documented diagnosis of HFEM or CM and an insufficient response to at least three prior preventive treatments, including beta-blockers, tricyclic antidepressants, and antiepileptic drugs, or onabotulinumtoxinA in the case of CM, in accordance with the Italian Medicines Agency (AIFA) regulations [12].

Eptinezumab was administered intravenously at a starting dose of 100 mg every 12 weeks, in line with approved prescribing recommendations. The planned treatment duration was 48 weeks, with clinical evaluations performed at each infusion visit. After the first treatment cycle (12 weeks), dose escalation from 100 to 300 mg was permitted based on clinical response and in accordance with shared decision-making between the physician and the patient.

Data Collection

Clinical and demographic data were collected prospectively by headache specialists using a structured electronic case report form. Baseline variables included age, sex, migraine history,

comorbidities, prior preventive treatments, and concomitant medications.

Patients were instructed to maintain paper or electronic headache diaries to record monthly migraine days (MMD) in patients with HFEM or monthly headache days (MHD) in patients with CM, along with monthly analgesic intake (MAI) and pain intensity, assessed using the Numerical Rating Scale (NRS). We used MMD in HFEM to capture discrete migraine attacks, whereas MHD were used in CM to better reflect overall headache burden, given the overlap of migraine-like and tension-type-like features and the early modification of symptoms by analgesic use before full migraine expression. All data were collected consistently with the methodology adopted in the EMBRACE and EMBRACE II studies [13, 14].

Migraine-related disability and impact were assessed using the Headache Impact Test–6 (HIT-6), Migraine Disability Assessment (MIDAS), and the Migraine Interictal Burden Scale–4 (MIBS-4). Patient-reported global treatment response was evaluated using the Patient Global Impression of Change (PGI-C). Safety data were collected at each visit through open-ended questioning and spontaneous adverse event reporting.

Study Endpoints

- Co-primary endpoints were the proportions of patients achieving ≥ 50% and ≥ 75% reductions from baseline in MMD (HFEM) or MHD (CM) at weeks 45–48.
- Secondary endpoints included changes from baseline to week 48 in MMD/MHD, NRS, MAI, HIT-6, MIDAS, and MIBS-4 scores, PGI-C ratings, and the proportion of patients achieving 100% response (weeks 45–48 versus baseline). Safety endpoints comprised the incidence, type, and severity of adverse events, classified per the Hartwig scale [15].
- Exploratory endpoints at weeks 45–48 versus baseline included: (i) ≥ 50%, ≥ 75%, and 100% responders among dose-escalated patients; (2) ≥ 50%, ≥ 75%, and 100% responders among patients with prior failures to anti-CGRP mAbs; (3) ≥ 50%, ≥ 75%, and 100% responders without adverse events; (4) ≥ 50% and ≥ 75% responders achieving ≥ 30% reduction in NRS score; and (5) ≥ 50%, ≥ 75%, and 100% responses in predefined subgroups including CM, psychiatric comorbidities, and medication overuse.

Statistical Methods

Baseline demographic and clinical characteristics were summarized using mean ± standard deviation for continuous variables and absolute frequencies with percentages for categorical variables. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Between-group comparisons were performed using the independent samples Student's t-test for normally distributed variables. When the assumption of normality was violated, the Mann–Whitney U-test was used. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate, based on the expected cell frequencies. For variables with > 2 categories, an overall group comparison was first performed and, if significant, followed by post hoc pairwise 2×2 analyses. To account for multiple post hoc comparisons within the same contingency table, *p*-values were adjusted using the Bonferroni correction. Temporal variation in responder rates, defined as ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days compared with baseline, was analyzed using Cochran's *Q* test, which accounts for correlated binary outcomes measured across multiple time points within the same subjects. When the global test was statistically significant, pairwise comparisons between time points were performed using McNemar tests. Adjustment for multiple comparisons was applied using the Bonferroni correction.

Changes over time in continuous clinical variables and disability scores were analyzed using the Friedman test for repeated measures. When a significant overall difference was detected, post hoc pairwise comparisons between time points were conducted using Wilcoxon signed-rank tests, with *p*-values adjusted according to the Bonferroni method. To assess whether the findings derived from the completer population (those who reached 48 weeks of treatment) were

affected by attrition or selection bias, a sensitivity analysis was performed. All statistical tests were two-tailed. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using the R environment (version 4.5; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

As of 1 September 2025, 261 subjects had received at least one dose of eptinezumab and were included in the safety population (Electronic Supplementary Material [ESM] Table S1). Of these, 124 patients had received at least four doses of eptinezumab and were included in the effectiveness analysis (females/males: 94/30; mean age: 48.8 years; HFEM: 21; CM: 103) (Fig. 1; Table 1).

Patients with CM, when compared to those with HFEM, showed significantly higher MAI ($p<0.001$), greater ictal allodynia ($p=0.003$), and higher migraine-related disability, as assessed by HIT-6 ($p=0.020$) and MIDAS ($p=0.014$).

Among the 124 patients treated for at least 48 weeks, 64 (51.6%) had previously failed treatment with other anti-CGRP mAbs (ESM Table S2). These patients, as compared to anti-CGRP mAbs–naïve subjects, were younger at migraine onset ($p=0.004$), showed higher MMD ($p=0.038$), a greater number of prior treatment failures ($p=0.041$), including onabotulinumtoxinA ($p=<0.001$), and a higher MIDAS score ($p=0.001$). The increase in NRS ($p=0.053$) and HIT-6 scores ($p=0.057$) was borderline significant.

Thirty-eight patients (30.6%) received eptinezumab 100 mg every 12 weeks throughout the entire treatment period, while 86 patients, following the 100 mg infusion at baseline escalated

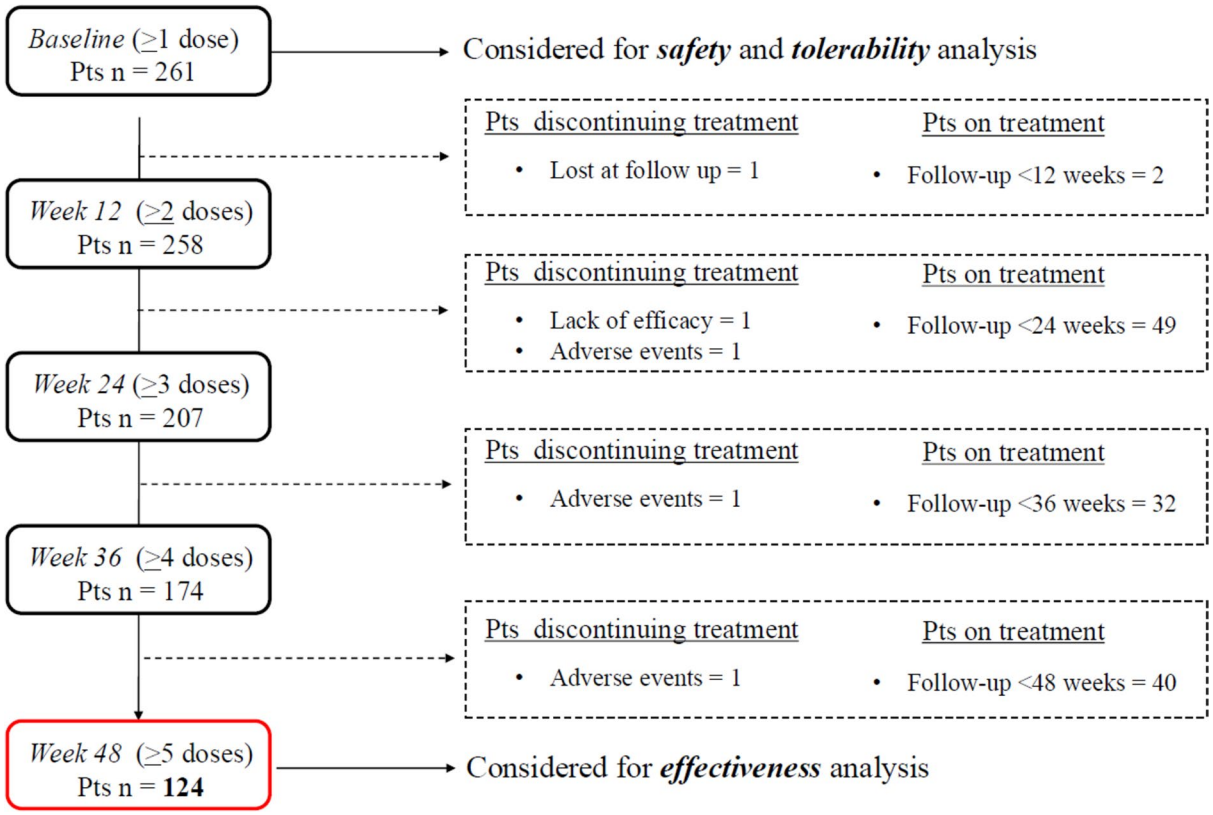

Fig. 1 Disposition of patients. Note that the shorter follow-up (< 48 weeks) observed in 137 patients was due to a later treatment initiation. *Pts* Patients

Table 1 Baseline demographic and clinical characteristics of the 124 patients with migraine who completed the 48-week follow-up

Variables	Number (%) or mean ± SD			
	All	HFEM	CM	*p*-value
Patients	124	21	103	
Age, years	48.8 ± 12.2	50.7 ± 12.6	48.4 ± 12.2	0.461
Females	94 (75.8%)	19 (90.5%)	75 (72.8%)	0.149
BMI, kg/m^2	23.6 ± 4.2	22.6 ± 4.0	23.8 ± 4.2	0.259
Age at onset, years	17.8 ± 9.7	18.1 ± 11.6	17.7 ± 9.3	0.862
MMD	–	11.9 ± 2.0	–	–
MHD	–	–	24.3 ± 5.4	–
NRS score	8.2 ± 1.1	8.2 ± 0.8	8.2 ± 1.2	0.806
Medication overuse	–	–	82 (79.6%)	–
Medication overuse duration, years	–	–	8.7 ± 9.1	–
MAI	26.4 ± 27.4	11.2 ± 4.3	29.5 ± 29.1	< 0.001
Unilateral pain	74 (59.7%)	59 (57.3%)	15 (71.4%)	0.554
UAS	50 (40.3%)	10 (47.6%)	40 (38.8%)	0.614
CAPS score	1.1 ± 1.7	1.3 ± 1.3	1.0 ± 1.7	0.457
Ictal allodynia	36 (29.0%)	0	36 (35.0%)	0.003
Interictal allodynia	5 (4.0%)	0	5 (4.9%)	0.588
ASC-12 score	2.4 ± 4.2	2.2 ± 4.4	2.4 ± 4.1	0.873
Dopaminergic symptoms	62 (50%)	7 (33.3%)	55 (53.4%)	0.151
Concomitant prophylaxis, pts	37 (29.8%)	4 (19.0%)	33 (32.0%)	0.355
Prior treatment failures	4.6 ± 1.8	4.6 ± 1.9	4.3 ± 1.4	0.413
Prior anti-CGRP mAb failures[a], pts	64 (51.6%)	13 (61.9%)	51 (49.5%)	0.426
Prior BONT-A failure[b], pts	52 (41.9%)	7 (33.3%)	45 (54.4%)	0.507
≥ 1 comorbidity, pts	70 (56.5%)	12 (57.1%)	58 (56.3%)	1.000
Psychiatric comorbidities, pts	35 (28.2%)	3 (14.3%)	32 (31.1%)	0.197
HIT-6 score	67.3 ± 5.3	64.9 ± 5.3	67.8 ± 5.3	0.020
MIDAS score	96.7 ± 57.5	75.5 ± 36.6	101 ± 60.2	0.014
MIBS-4 score	6.10 (3.3%)	5.38 (2.8%)	6.24 (3.4%)	0.222
None (0)	3 (2.4%)	0 (0.0%)	3 (2.9%)	0.231
Mild (1–2)	8 (6.5%)	1 (4.8%)	7 (6.9%)	
Moderate (3–4)	31 (25.0%)	9 (42.9%)	22 (21.4%)	
Severe (> 4)	82 (66.1%)	11 (52.4%)	71 (68.8%)	

Table 1 continued

All overall migraine population, *HFEM* high-frequency episodic migraine, *CM* chronic migraine, *BMI* Body Mass Index, *MHD* monthly headache days, *MMD* monthly migraine days, *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, *MAI* analgesic doses taken per month, *BoNT-A* OnabotulinumtoxinA, *HIT-6* Headache Impact Test-6, *MIDAS* Migraine Disability Assessment Scale, *MIBS-4* Migraine Interictal Burden Scale-4

[a]Of the 124 patients, 63 had failed treatment with a single anti-CGRP mAb (erenumab, $n = 62$; galcanezumab, $n = 1$), while 1 patient had failed two agents (erenumab and galcanezumab, $n = 1$)

[b]Proportion calculated based on the total number of subjects treated with OnabotulinumtoxinA

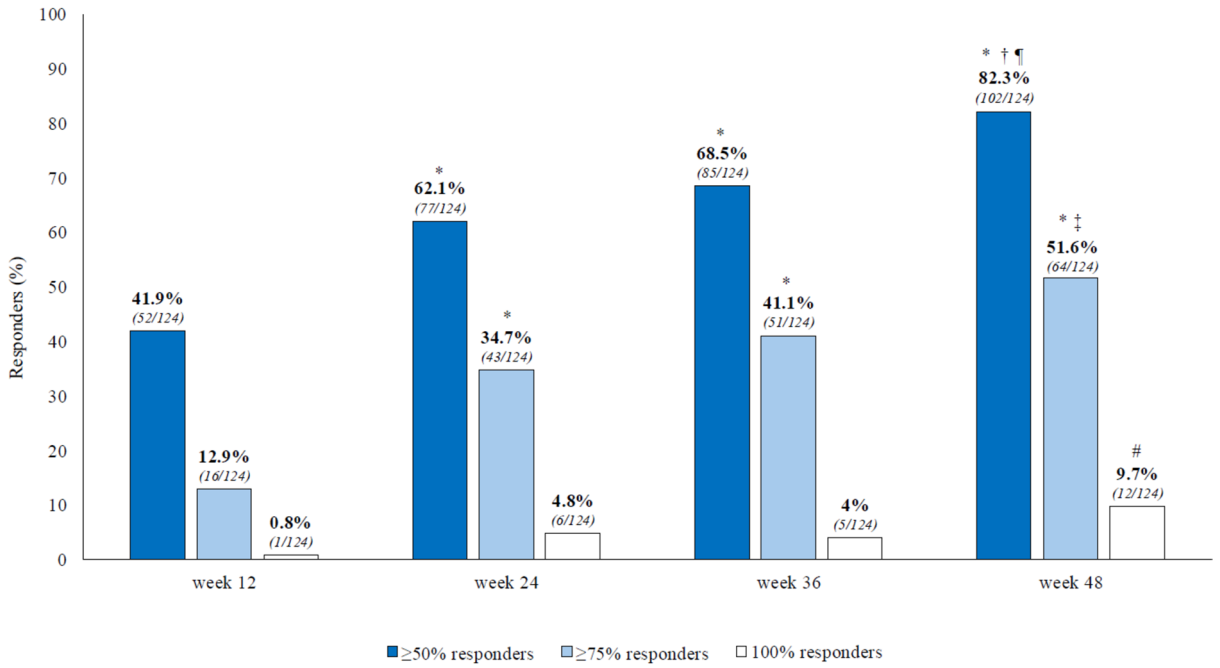

Fig. 2 Responders at weeks 12, 24, 36 and 48 in the overall patient population. ≥ 50% responders: proportion of patients with a ≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥ 75% responders: proportion of patients with a ≥ 75% reduction in monthly migraine/headache days compared to baseline; 100% responders: proportion of patients with a 100% reduction in monthly migraine/headache days compared to baseline. $^{*}p < 0.001$ vs week 12; $^{\dagger}p < 0.001$ vs week 24; $^{\ddagger}p < 0.01$ vs week 24; $^{\P}p < 0.05$ vs week 36; $^{\#}p < 0.05$ vs week 12

to 300 mg for one administration (23 patients, 18.6%), two administrations (34 patients, 27.4%), or three administrations (29 patients, 23.4%). Patients who escalated to the 300 mg dose at least once at baseline had higher MHD ($p = 0.026$), higher NRS scores ($p = 0.039$), greater MAI ($p = 0.003$), and a greater number of prior treatment failures ($p = 0.007$), including failures to anti-CGRP mAbs ($p = 0.006$) (ESM Table S3).

Potential attrition bias was assessed through a sensitivity analysis comparing 12-, 24-, and 36-week response rates between patients who completed 48 weeks of treatment and those who had not yet reached week 48 at data cut-off. The analysis was restricted to patients with

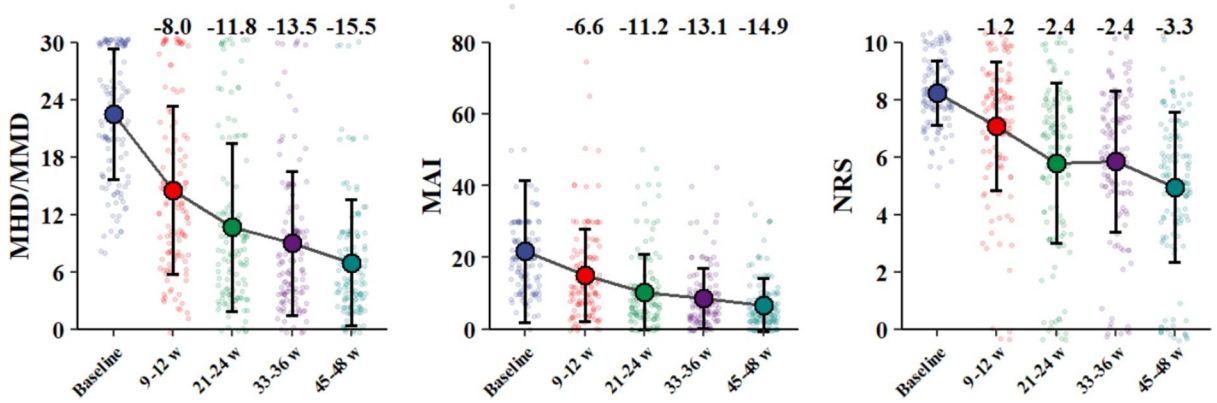

Fig. 3 Longitudinal clinical outcomes of monthly migraine/headache days (*MMD/MHD*), monthly analgesic intake (*MAI*), and numerical rating scale (*NRS*) across the study period. Solid points and error bars represent mean values and standard deviation, respectively; background jittered dots represent individual patients. Friedman's test shows significant improvement over time across all parameters ($p < 0.001$). Values reported above each time point indicate the mean change relative to baseline; as detailed in the Electronic Supplementary Material, all post-hoc comparisons against baseline reached statistical significance ($p < 0.001$). *w* weeks of treatment

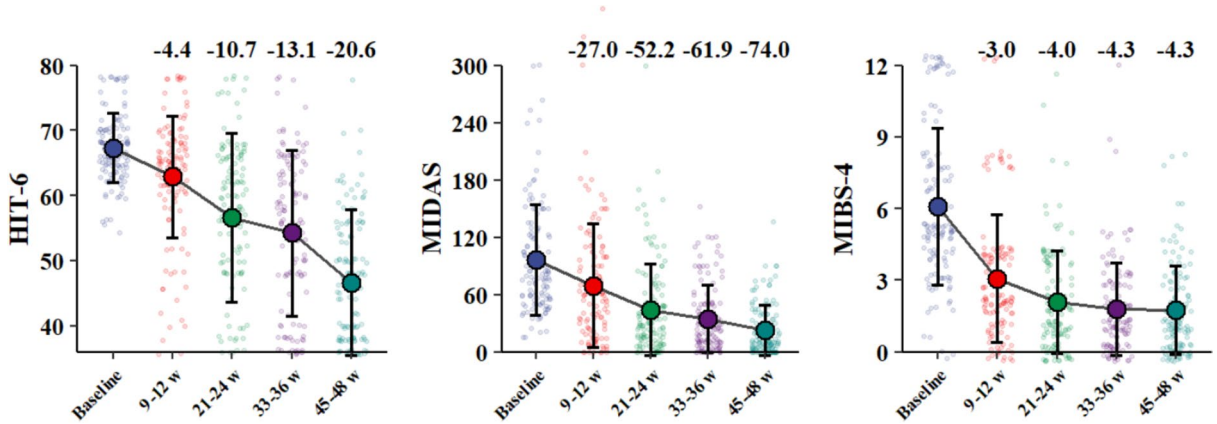

Fig. 4 Longitudinal clinical outcomes of Headache Impact Test–6 (*HIT-6*), Migraine Disability Assessment Scale (*MIDAS),* and Migraine Interictal Burden Scale–4 (*MIBS-4*) of the overall population across the study period. Solid points and error bars represent mean values and standard deviation, respectively; background jittered dots represent individual patients. Friedman's test shows significant improvement over time across all parameters ($p < 0.001$). Values reported above each time point indicate the mean change relative to baseline; as detailed in the Electronic Supplementary Material, all post-hoc comparisons against baseline reached statistical significance ($p < 0.001$). *w* weeks of treatment

available data at each time point. Across all response thresholds (≥ 50%, ≥ 75%, and 100%), response rates were comparable or lower in non-completers than in completers, arguing against selective dropout of poor responders and suggesting that attrition did not meaningfully bias long-term effectiveness estimates (ESM Table S4).

Co-primary Endpoints

At week 48, the ≥ 50% and ≥ 75% response rates were 82.3% and 51.6%, respectively (Fig. 2), with corresponding rates of 66.7% and 33.3% in patients with HFEM and 85.4% and 53.3%

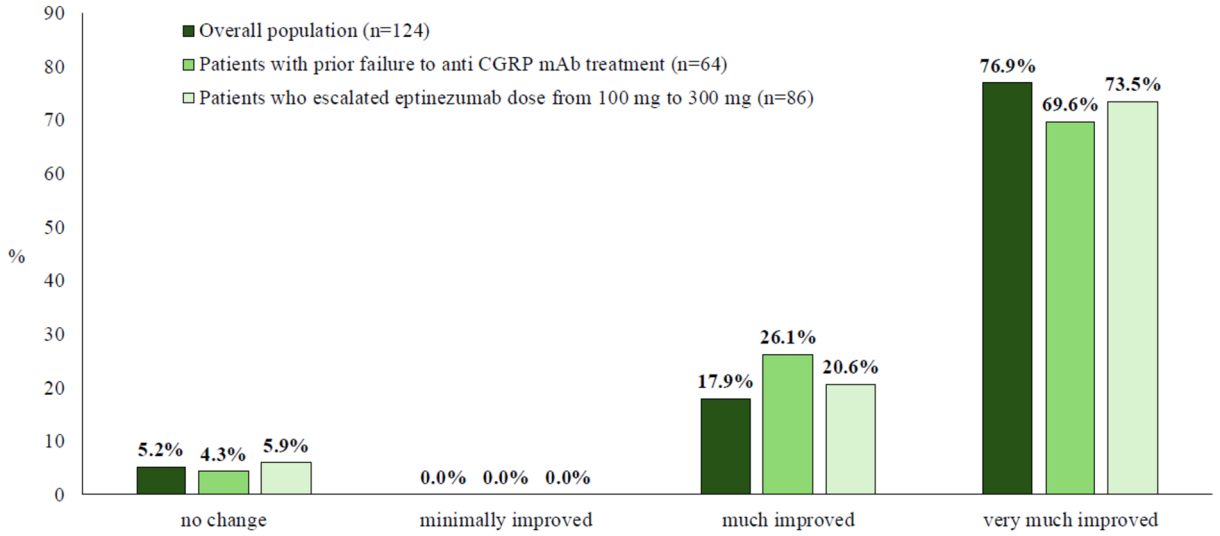

Fig. 5 Patient Global Impression of Change (PGIC) score at week 48. *anti-CGRP* mAbs Calcitonin gene-related peptide monoclonal antibody, *w* weeks

in patients with CM (data not shown). In the overall population, responder rates increased progressively over time across all response thresholds (Fig. 2). For the ≥ 50% response, rates increased from 41.9% at week 12 to 62.1% at week 24, 68.5% at week 36, and 82.3% at week 48 (overall $p<0.001$), with post hoc analyses showing significantly higher response rates at each subsequent visit compared with the first follow-up. A similar trend was observed for the ≥ 75% response, which increased from 12.9% to 34.7%, 41.1%, and 51.6% across the same time points ($p<0.001$).

Complete response (100% reduction in MMD) was observed in 0.8%, 4.8%, 4.0%, and 9.7% of patients at weeks 12, 24, 36, and 48, respectively ($p=0.002$). Overall, these data indicate a sustained and clinically meaningful increase in treatment response over the 48-week follow-up, with maximal benefit observed at the final evaluation.

Secondary Endpoints

In the overall migraine population, at week 48, significant reductions from baseline were observed in MMD/MHD (– 15.5), MAI (– 14.9), NRS (– 3.3), HIT-6 (– 20.6), MIDAS (– 74), and MIBS-4 (– 4.3) scores (all $p<0.001$) (Figs. 3, 4; ESM Table S5). Statistically significant improvements were also observed at the same time points across these secondary endpoints in both patient subgroups (HFEM and CM) and in the overall migraine population at weeks 45–48 compared with weeks 21–24 (ESM Table S7). Absolute responders (100% response) at week 48 accounted for 9.7% of the overall population (HFEM: 14.3%; CM: 8.7). (Fig. 2). At week 48, 94.8% of patients reported improvement in the PGIC with eptinezumab treatment, with 17.9% reporting "much improved" and 76.9% "very much improved," while 5.2% reported no change (Fig. 5).

Adverse events were reported in 6.5% of patients (17/261). The most frequently reported events were rhinorrhea, paresthesias, erythema, nausea, and constipation (each 0.8%), followed by hair effluvium, nasal dryness, pruritus, somnolence, asthenia, hyposmia, and extrasystole (each 0.4%). Most events were mild, with 14 out of 17 (82.3%) classified as grade I. One event of nausea was classified as grade II, while nasal dryness and erythema were each classified as grade III (Table 2). Treatment discontinuation due to adverse events occurred in three patients (1.2%), all during infusion (nausea, nasal dryness, and erythema).

Table 2 Treatment-emergent adverse events (TEAEs) among the 261 subjects enrolled (safety population)

	N (%)	Grade[a]		
Patients with TEAEs	17 (6.5)	I	II	III
Rhinorrhea	2 (0.8)	2		
Paraesthesias	2 (0.8)	2		
Erythema	2 (0.8)	1		1
Nausea during the administration	2 (0.8)	1	1	
Constipation	2 (0.8)	2		
Effluvium	1 (0.4)	1		
Nasal dryness	1 (0.4)			1
Itch	1 (0.4)	1		
Excessive daytime somnolence	1 (0.4)	1		
Asthenia	1 (0.4)	1		
Hyposmia	1 (0.4)	1		
Extrasystole	1 (0.4)	1		
Discontinuation due to TEAs	3 (1.1)[b]			

[a]Grade (according to Hartwig et al. [15]) *I*, the adverse event occurs without requiring any adjustment to the current pharmacological therapy; *II*, the adverse event necessitates discontinuation of the drug or adjustment of its dosage. No supplementary treatment or antidote is required; *III*, the adverse event necessitates discontinuation of the suspected drug, whether by interruption, suspension, or modification of the therapeutic regimen, and may warrant the administration of a specific antidote

[b]Two subjects discontinued the treatment due to the occurrence of erythema and severe nausea during the eptinezumab administration and one subject discontinued for rhinorrhea and severe nasal dryness, which were considered treatment related

Exploratory Endpoints

Among dose-escalated patients, the ≥ 50%, ≥ 75%, and 100% response rates varied according to the number of 300 mg doses received, with patients receiving a single 300 mg dose having response rates at 48 weeks of 86.9%, 30.4%, and 0%, respectively, with no significant difference compared with those consistently treated with the 100 mg dose. In patients receiving two 300 mg doses, the ≥ 50%, ≥ 75%, and 100% response rates were 73.5%, 38.2%, and 8.8%, respectively, which were significantly lower than the corresponding rates in the consistently 100 mg-treated group ($p = 0.005$). Patients receiving three 300 mg doses had ≥ 50%, ≥ 75%, and 100% response rates of 82.8%, 58.6%, and 6.9%, respectively, again showing no significant difference compared with patients consistently treated with the 100 mg dose (Fig. 6).

Among patients with prior failures to anti-CGRP mAbs, the proportions of ≥ 50% and 100% responders (76.6% and 14.0%, respectively) did not differ from those observed in anti-CGRP mAbs–naïve patients, whereas the proportion of ≥ 75% responders was significantly lower (37.5%, $p = 0.002$) (Fig. 7).

Responses of ≥ 50%, ≥ 75%, and 100% without adverse events were observed in 81.2%, 50.4%, and 8.5% of patients, respectively (Fig. 8). The proportions of ≥ 50% and ≥ 75% responders also achieving ≥ 30% reduction in NRS score were 34.7% and 14.5%, respectively (Fig. 9).

Lastly, ≥ 50%, ≥ 75%, and 100% response rates in patients with migraine affected by psychiatric comorbidities were 85.7%, 51.4%, and 8.6%. The ≥ 50%, ≥ 75%, and 100% response rates in patients with CM and medication overuse were 87.8%, 54.9%, and 7.3%; in patients with CM, medication overuse, and psychiatric comorbidities, the ≥ 50%, ≥ 75%, and 100% response rates were 89.2%, 50.0%, and 7.1%, respectively (Fig. 10).

DISCUSSION

In this large real-world cohort, EMBRACE III extends previous evidence by demonstrating that the clinical benefits of eptinezumab are sustained over 48 weeks in both patients with HFEM and those with CM, despite substantial disease burden and multiple prior preventive treatment failures, including anti-CGRP mAbs. More than 80% of patients achieved a ≥ 50% reduction in migraine frequency, more than 50% achieved a ≥ 75% reduction, and approximately 10% attained a complete response. Beyond high

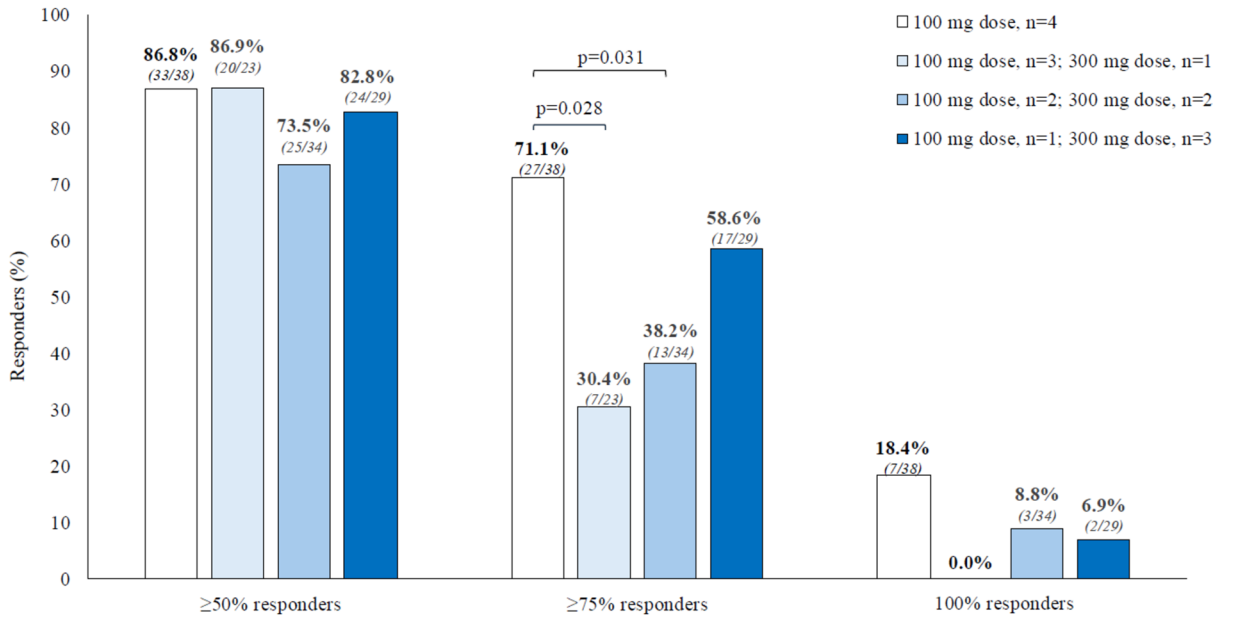

Fig. 6 Responder rates at week 48 across eptinezumab dosage groups. Bars represent the proportion of patients achieving ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine/headache days (MMD/MHD) relative to baseline. Groups include patients consistently treated with 100 mg and those escalating once, twice, or three times to 300 mg. Chi-square analysis reveals significant differences between groups, specifically within the ≥ 75% responder category. Where shown, *p*-values indicate significant post-hoc pairwise comparisons

responder and super-responders' rates, patients experienced significant improvements across all core migraine domains, including migraine frequency, acute medication use, pain intensity, and both ictal and interictal disability.

Notably, treatment benefits were sustained and appeared to further increase over time, with significant improvements in both primary and secondary endpoints at weeks 45–48 compared with weeks 21–24. In this non-randomized, real-world context, dose escalation to 300 mg occurred in the majority of patients (69.4%) and may have contributed to the progressive improvement, particularly among those receiving three 300-mg doses over the 48-week study period. However, this interpretation warrants caution, as dose-escalated patients exhibited greater clinical disability and a suboptimal response to the initial 100 mg regimen. Moreover, the study was not designed to formally compare the efficacy of different dosing regimens. Accordingly, dose escalation alone is unlikely to fully explain the progressive improvement observed. A complementary explanation is an ultra-late response to eptinezumab, as previously reported for other anti-CGRP mAbs, suggesting that both dose optimization and time-dependent treatment effects contribute to the observed longitudinal benefit [16, 17].

Another relevant observation is that prior failure to anti-CGRP mAbs did not affect the likelihood of achieving a ≥ 50% or 100% response with eptinezumab, whereas the probability of attaining a super-response (≥ 75%) was significantly lower in this subgroup. This finding suggests that switching from subcutaneous to intravenous anti-CGRP mAbs may be beneficial in selected patients, although the potential contribution of carry-over effects and regression to the mean cannot be excluded [18]. Importantly, the results of the present study suggest that a ≥ 75% response—rather than a ≥ 50% response—may represent a more informative cutoff for distinguishing patient subgroups. Patients with prior failure to anti-CGRP mAbs showed ≥ 50% responder rates that were comparable to those of treatment-naïve patients (76.6% vs 88.3%; $p = 0.139$), but significantly

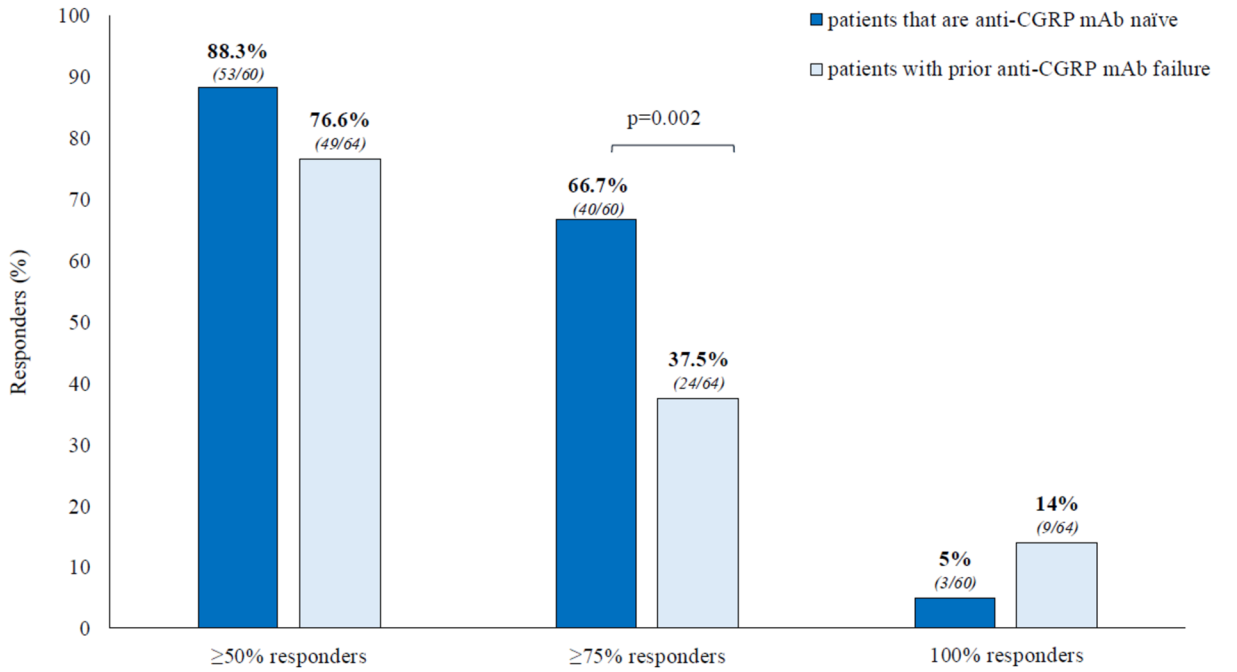

Fig. 7 Responder rates at week 48 according to prior anti-calcitonin gene-related peptide monoclonal antibody (*anti-CGRP mAb*) exposure. Bars represent the proportion of patients achieving ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine/headache days (MMD/MHD) relative to baseline. Comparisons distinguish between patients that are anti-CGRP mAb-naive ($n = 60$) and those with prior anti-CGRP mAb treatment failure ($n = 64$). Chi-square analysis reveals a significant difference between groups, specifically within the ≥ 75% responder category ($p = 0.002$); no significant differences were observed in the ≥ 50% and 100% categories

fewer ≥ 75% responder rates (37.5% vs 66.7%, respectively; $p = 0.002$). Similarly, patients escalating to 300 mg at least once did not differ in ≥ 50% response from those remaining on 100 mg ($p = 0.489$), but the former did exhibit significantly fewer ≥ 75% response after one or two 300-mg doses (one dose: $p = 0.028$; two doses: $p = 0.031$), reaching comparability only after three 300-mg doses. Collectively, these findings support raising the therapeutic response threshold in migraine research to better capture clinically meaningful differences across treatment strategies [10].

EMBRACE III also confirmed that eptinezumab is well tolerated, with adverse events, predominantly mild, occurring in 6.5% of patients and a low-rate discontinuation treatment due to adverse events (1.1%), supporting its safety and tolerability in patients with migraine with complex clinical scenarios and comorbidities. Additional clinically relevant insights include the characterization of responders without adverse events, a particularly desirable outcome from the patient perspective. The proportions of ≥ 50%, ≥ 75%, and 100% responders without adverse events (81.2%, 50.4%, and 8.5%, respectively) closely mirrored those observed in the overall population, underscoring a favorable efficacy–tolerability profile among eptinezumab responders. It should also be noted that approximately one third of ≥ 50% responders (34.7%) and one sixth of ≥ 75% responders (14.5%) achieved also a clinically meaningful reduction in residual pain intensity (≥ 30%) on remaining migraine days, an outcome of high relevance that is often underappreciated in routine

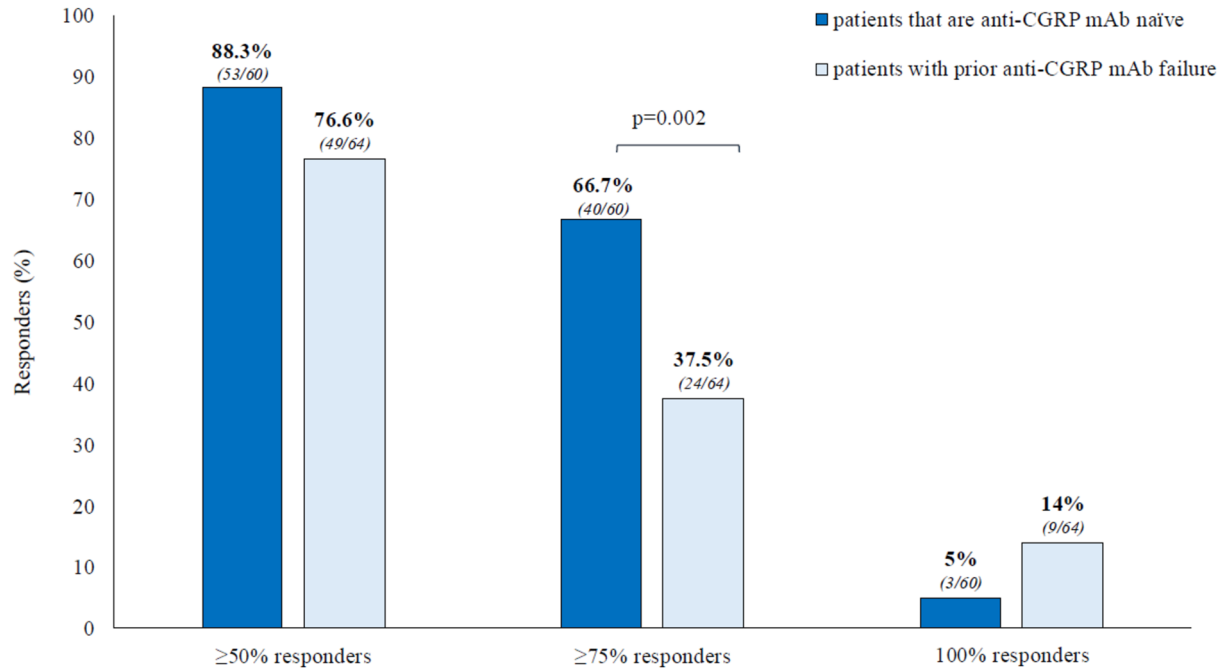

Fig. 8 Responder rates at week 48 in patients without adverse events. Bars represent the proportion of patients achieving ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine/headache days (MMD/MHD) relative to baseline among those reporting no adverse events. Data are shown for the total population (*All*, $n = 117$) and stratified by diagnosis: high-frequency episodic migraine (*HFEM*, $n = 19$) and chronic migraine (*CM*, $n = 98$). Chi-square analysis reveals a significant difference between the HFEM and CM groups, specifically within the ≥ 50% responder category ($p = 0.049$); no significant differences were observed in the other categories

clinical assessment. Taken together, these findings suggest that the benefits of eptinezumab may extend beyond migraine frequency reduction, contributing to broader patient-centered improvement, although whether similar effects occur with subcutaneous anti-CGRP mAbs remains to be established.

As a final result, the present study shows remarkably high response rates (e.g., ≥ 50% response: > 85%) even among highly clinically burdened migraine subgroups—namely, patients with psychiatric comorbidities, those with CM and medication overuse, and those with the combination of CM, medication overuse, and psychiatric comorbidities—traditionally regarded as hard-to-treat patients. Although this finding may appear unexpected, it is consistent with real-world versus RCT comparisons, suggesting that greater clinical complexity does not necessarily translate into poorer outcomes [19]. In our experience with real-world populations, the most complex patients achieved ≥ 50% response with rates comparable to, or even higher than that of less complex patients, potentially reflecting both contextual factors (e.g., stronger therapeutic alliance and placebo effects) and biological factors, including higher CGRP activity, which may enhance responsiveness to anti-CGRP treatments.

This study shares the inherent limitations of real-world, non-interventional investigations. In this context, it should be noted that the 48-week effectiveness and super-response rates reflect a completer population. While responder rates in patients who remain on treatment for a full year may be higher than those expected in an intention-to-treat analysis, our sensitivity analysis showed that response rates were comparable or lower in non-completers than in completers at earlier time points. This suggests that attrition did not meaningfully bias the long-term effectiveness estimates. In particular,

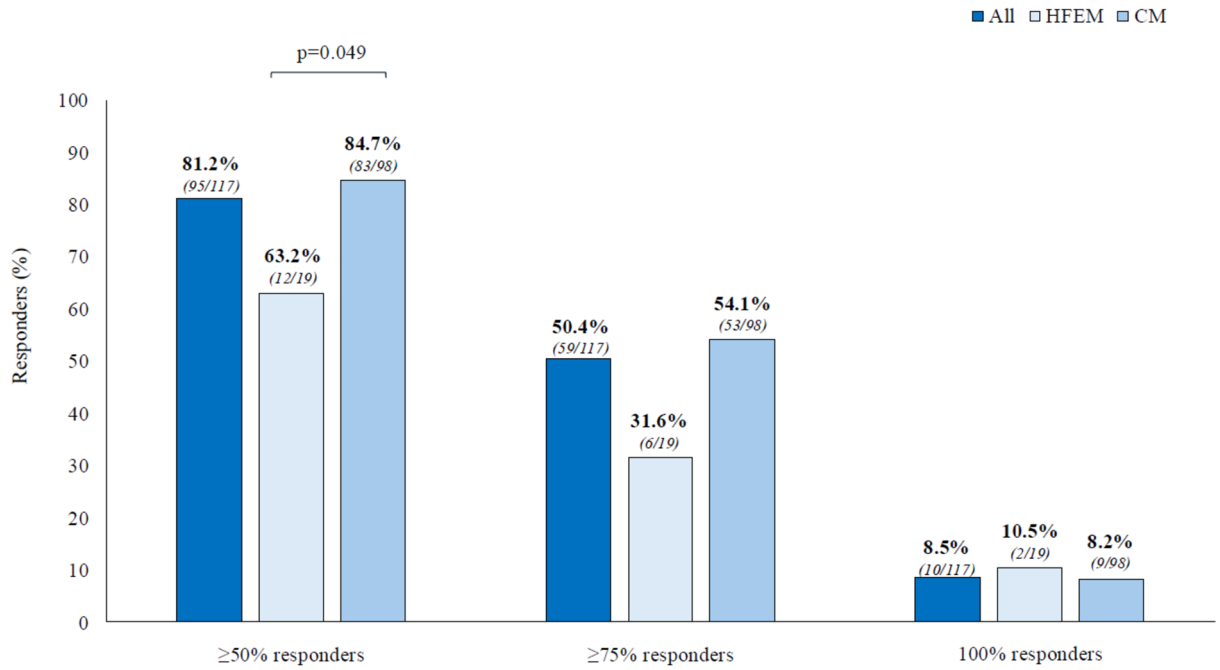

Fig. 9 Proportion of responders achieving ≥ 30% reduction in numerical rating scale (*NRS*) score during residual attacks at week 48. Bars represent the percentage of patients within the ≥ 50% and ≥ 75% responder categories who also experienced a significant reduction in pain intensity (NRS ≥ 30%) for remaining attacks. Data are presented for the total population (*All*, $n = 124$) and stratified by diagnosis: high-frequency episodic migraine (*HFEM*, $n = 21$) and chronic migraine (*CM*, $n = 103$). Chi-square analysis shows no significant differences between HFEM and CM groups for these combined outcomes

the contribution of features difficult to evaluate, like placebo effects and the therapeutic alliance between headache specialists and patients, may have amplified the observed effectiveness of eptinezumab. Moreover, the interpretation of treatment effectiveness in patients who escalated to the 300-mg dose is limited by treatment heterogeneity, as some patients escalated once, whereas others escalated twice or three times. In addition, dose escalation was not predefined but implemented after 12 weeks at the participating center's discretion, with decisions made jointly by physicians and patients and generally based on treatment response during the preceding 12 weeks. Finally, all patients had experienced at least three prior preventive treatment failures and had a baseline migraine frequency of at least 8 MMD. Therefore, these findings may not be readily generalizable to patients with lower migraine frequencies or < 3 prior treatment failures.

The main strengths of the study include the large sample size and the recruitment of patients across a wide network of centers representing northern, central, and southern Italy. In addition, patients were carefully characterized by headache specialists using a shared, predefined, web-based semi-structured questionnaire. Lastly, data quality was ensured through continuous centralized monitoring by the data management team of the Italian Migraine Registry.

CONCLUSION

In conclusion, the EMBRACE III study suggests that eptinezumab provides sustained effectiveness and good tolerability over 48 weeks of treatment in patients with HFEM and CM. A substantial proportion of patients achieved responder, super-responder, and absolute responder status,

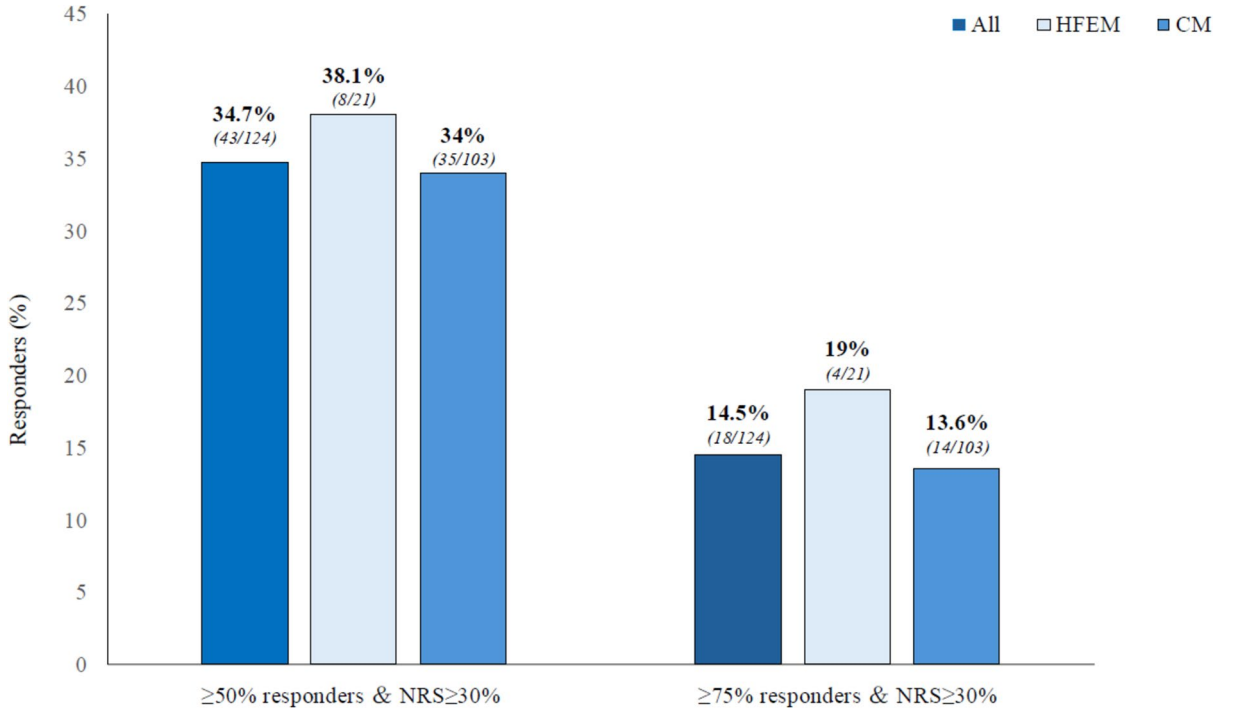

Fig. 10 Responder rates at week 48 across complex patient subgroups. Bars represent the proportion of patients achieving ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine/headache days (MMD/MHD) relative to baseline. The analysis includes three high-burden cohorts: patients with psychiatric comorbidities ($n = 35$); patients with chronic migraine and medication overuse ($CM + MO$, $n = 82$); and patients with the triple combination of CM, MO, and psychiatric comorbidities ($n = 28$)

including those who had experienced prior failure of anti-CGRP mAbs treatment, psychiatric comorbidities, and medication overuse. Dose escalation to 300 mg after week 12 was frequently required and was associated with higher response and super-response rates when the 300-mg dose was maintained at subsequent time points; dose escalation should therefore be considered in clinical practice in cases of insufficient response or reduced patient satisfaction. In addition, only a small proportion of responders, super-responders, and absolute responders reported adverse events, emphasizing that in a meaningful subset of patients, this treatment achieves a favorable balance between clinical effectiveness and tolerability—a highly desirable outcome for both clinicians and patients.

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

Declarations

Conflict of Interest. Piero Barbanti has received travel grants and honoraria for advisory boards, speaker panels or clinical investigation studies from Abbvie, Alder, Angelini, Assosalute, Biohaven, DOC Pharma, Eli-Lilly, Fondazione Ricerca e Salute, GSK, Lundbeck, Noema Pharma, Organon, Orion Pharma, Pfizer, Teva, Viatris, Visufarma, and serves as President with Italian Association of Headache Sufferers. Cinzia Aurilia has received travel grants from Eli-Lilly, Teva and Pfizer, honoraria from Teva. Massimo Filippi is Editor-in-Chief of the *Journal of Neurology*; has received compensation for consulting services and/or speaking activities from Bayer, Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme, Takeda, and Teva; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). Alberto Doretti has received travel grants and honoraria from Eli Lilly, Zambon, Teva, Abbvie, Neopharmed Gentili, and Lundbeck. Florindo d'Onofrio has received travel grants, honoraria as a speaker or for participating in advisory boards from Novartis, Teva, Neopharmed Gentili, Qbgroup srl, K link srl and Eli-Lilly. Roberta Messina received honoraria for speaker activities and for participating in advisory boards from Abbvie, Biomedia, Eli Lilly, Lundbeck, Organon, Pfizer and Teva. Angelo Ranieri has received honoraria for speaker activities and advisory boards, consulting, editorial contributions, and travel grants from Novartis, Teva, Eli-Lilly, VyvaMed Srl, CPM Srl, CTP SrlK link srl, Lundbeck, AIM Education Srl, and Momento Medico Srl. Paola Torelli has received travel grant and honoraria as a speaker or for

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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 (No. 177/SR/24) and mutually recognized by other local Institutional Review Boards. All copyrighted scales used in this study (HIT-6, MIDAS, MIBS-4, ASC-12) were administered with appropriate permission from the respective copyright holders. Eligible participants provided informed consent to participate in the study and were subsequently enrolled.

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