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ORIGINAL COMMUNICATION

# Super- and absolute responders to anti-cgrp monoclonal antibodies in migraine: A one-year multicenter, prospective, observational study

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## Abstract

**Aim** To assess the frequency of *super-responders* (≥75% reduction in migraine frequency) and *absolute responders* (100% reduction) to monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) after one year of treatment in individuals with high frequency (HFEM) or chronic migraine (CM).

**Methods** This multicenter ($n=16$), prospective, real-life study, involved consecutive adults with HFEM or CM and ≥3 prior preventive failures, receiving subcutaneous anti-CGRP mAbs for ≥12 months. Co-primary endpoints were the 12-month rates of *super-* and *absolute responders*. Secondary endpoints included subgroup analyses by migraine type and timing of response, categorized as early (≤3 months), late (>3–6 month), or ultra-late (>6–12 month).

**Results** 572 patients completed 12 months of treatment: 70.0% achieved super-response (HFEM: 64.9%; CM: 71.8%) and 23.4% absolute response (HFEM: 29.9%; CM: 21.0%). Both outcomes exhibited a time-dependent progression. Among *super-responders* ($n=400$), 29.4% were early, 22.6% late, and 18.0% ultra-late. Among *absolute responders* ($n=134$), 3.1% responded early, 3.7% late, and 16.6% ultra-late.

**Conclusion** One year of anti-CGRP mAbs therapy yields a ≥75% response in over two-thirds and a 100% response in nearly one-quarter of patients with HFEM or CM and prior treatment failures. Most *super-* and *absolute responses* emerge after six months, supporting long-term continuation treatment.

**Keywords** Migraine · Anti-CGRP mAbs · Super-response · Absolute response · Real-life

## Introduction

Migraine is a highly prevalent and disabling neurological disorder that may follow a progressive course, particularly when preventive treatment is delayed or suboptimal [1, 2]. Early and sustained use of effective prophylaxis is therefore essential to reduce disease burden, prevent chronification, and improve long-term outcomes [3, 4].

Traditionally, a ≥50% reduction in monthly migraine days (MMD) has served as a benchmark for therapeutic efficacy in both clinical trials and practice, with a ≥30% reduction deemed acceptable in patients with chronic migraine (CM) [5–7]. Although clinically meaningful, these thresholds may fall short of the expectations and lived experience of patients—many of whom aspire not merely to partial improvement, but to near-complete remission of attacks [8]. For these individuals, a super-response (≥75% reduction in MMD) or an absolute response (100% reduction)

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represents the true clinical ideal, typically associated with a marked improvement in quality of life and functional status. However, such profound responses have historically been rare with conventional preventive agents, owing to their limited efficacy, delayed onset, and poor tolerability, all of which undermine long-term adherence [9, 10].The advent of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway has refined the treatment landscape [11, 12]. These agents offer a favorable efficacy–tolerability balance across randomized controlled trials and real-world studies, including in patients with high-frequency episodic migraine (HFEM: 8–14 MMD) and CM [13–15] Compared to traditional prophylactics such as topiramate, propranolol, and onabotulinumtoxinA, anti-CGRP mAbs consistently demonstrate a superior benefit–risk profile—reflected not only in improved adherence, but also in a more favorable likelihood to be helped or harmed (LHH) ratio, which further underscores their clinical utility [16].

Importantly, accumulating real-world evidence suggests that a substantial proportion of patients treated with anti-CGRP mAbs not only reach the conventional 50% response threshold, but also achieve super-response or absolute response rates—previously considered exceptional [15]. This observation raises questions about the continued adequacy of the 50% reduction as a universal marker of therapeutic success [17]. In the current era of mechanism-based and patient-centered care, it may be time to redefine treatment endpoints, recognizing that that profound responses are not only desirable, but increasingly attainable [18].

Moreover, while often early, the therapeutic response to anti-CGRP mAbs may also occur in a delayed or ultra-delayed fashion in a considerable subset of patients [19, 20]. This highlights the need to pursue higher treatment goals while extending evaluation periods beyond the usual 3–6 months—ideally up to 12 months—to fully capture therapeutic potential.

This prospective, multicenter, real-world study investigates 12-month rates of super- and absolute response to subcutaneous anti-CGRP mAbs in patients with HFEM and CM. By exploring the prevalence and clinical correlates of such outcomes, this work aims to support a shift toward more ambitious and patient-relevant therapeutic goals in migraine prevention.

## Methods

This multicenter, prospective, observational study involved 16 headache centers across seven Italian regions—Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, and Piedmont—representing Northern, Central, and Southern Italy. The study is part of the I-NEED (Italian NEw migrainE Drugs database) project (NCT07103694), conducted within the framework of the Italian Migraine Registry (I-GRAINE; NCT07163416).

After providing written informed, we included all consecutive adult patients diagnosed with HFEM or CM, who had failed at least three distinct classes of preventive medications and had a Migraine Disability Assessment Scale (MIDAS) score $\geq 11$, according to the criteria defined by the Italian Medicines Agency [21]. Patients were required to had been treated with erenumab (70 mg or 140 mg every 28 days), galcanezumab (120 mg monthly following a 240 mg loading dose), or fremanezumab (either 225 mg every 30 days or 675 mg every 90 days) for at least 12 consecutive months to be included in the analysis. The choice of agent and dosing regimen was based on drug availability, physician's clinical judgment, and/or patient preference. As eptinezumab became availble in Italy at a later stage, no patient had completed 12 months of treatment with this agent during the study period; therefore, individuals treated with eptinezumab were excluded from the present analysis.

Exclusion criteria included prior exposure to CGRP -targeted preventive treatments, use of onabotulinumtoxinA within 3 months, relevant cardiovascular comorbidities, or any other clinically significant condition as judged by the treating investigator.

No additional preventive treatments were introduced during the follow-up. The study was approved by the IRCCS San Raffaele Roma Ethics Committee (approval No. 11/2018) and by local ethics committees of all participating sites. The study was funded by IRCCS San Raffaele, Rome, until 26/03/2024, and thereafter by San Raffaele University, Rome.

Patients were instructed to complete a paper-based headache diary during a 28-day run-in period (baseline) and throughout the study. The diary captured the following information: migraine frequency (MMD in subjects with HFEM, and monthly headache days [MHD] in those with CM); monthly analgesic intake; pain intensity (numerical rating scale, NRS); pain side; unilateral cranial autonomic symptoms; allodynia; dopaminergic symptoms; and migraine-related disability, assessed with both the MIDAS and the Headache Impact Test (HIT-6) questionnaires.

In line with our previous prospective real-world studies, in individuals with CM, the term 'headache day' was used to indicate any day with headache, including both migraine-like and tension-type headaches [15]. This approach reflects real-world patient behavior, as individuals with CM frequently initiate acute treatment at headache onset, even when symptoms are not yet classifiable as a migraine attack—thereby potentially confounding the classification of migraine episodes. Data were collected during in-person assessments at baseline and at 3, 6, and 12 months of treatment.

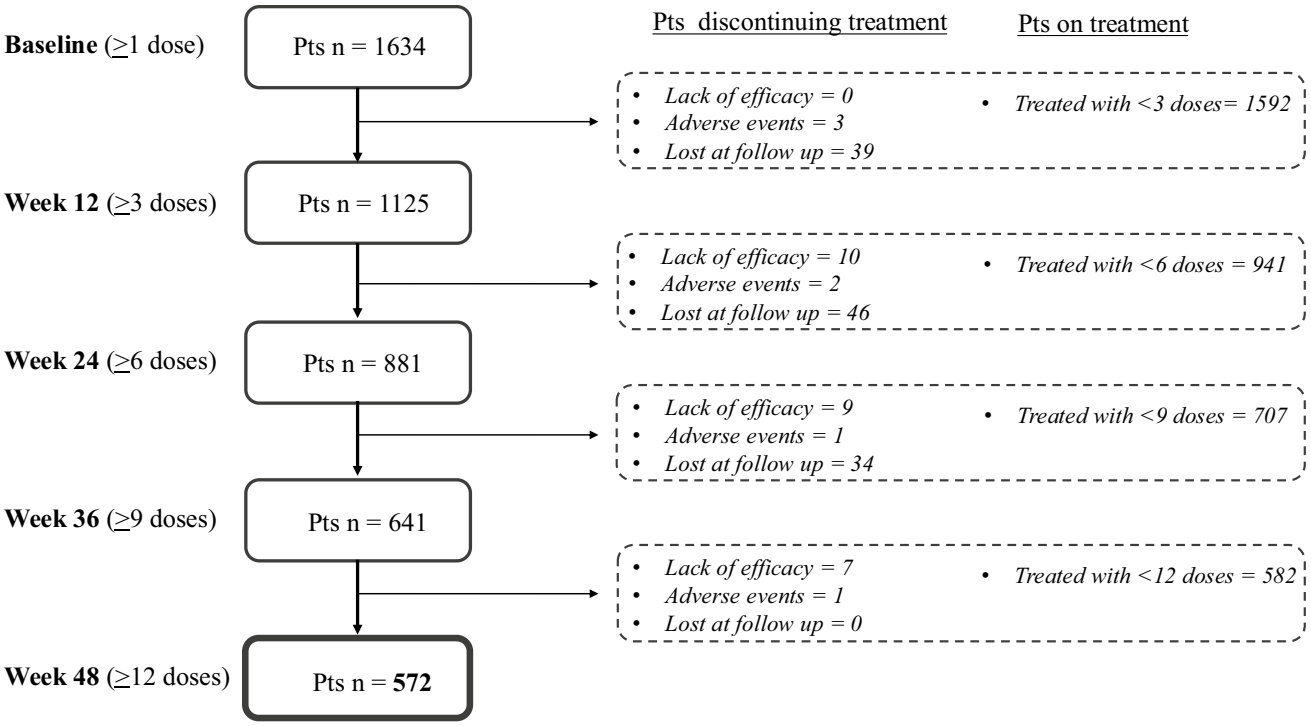


**Fig. 1** Patients' disposition

Responders were defined as patients achieving a ≥ 50% reduction in migraine frequency—MMD for HFEM or MHD for CM—during weeks 45–48 of treatment compared to baseline. Super-responders were those with a ≥ 75% reduction, and absolute responders were those with a 100% reduction in migraine frequency, according to the same criteria.

Each response category (response, super-response, and absolute response) was further stratified based on the time of onset as early (≤ 3 months), late (> 3 to ≤ 6 months), or ultra-late (> 6 to ≤ 12 months).

The co-primary endpoints were the proportions of super-responders and absolute responders at 12 months. Secondary endpoints included: (1) subgroup analyses based on migraine type (HFEM vs CM); and (2) timing of onset of super- and absolute response, classified as early, late, or ultra-late, as defined above.

## Statistical methods

Convenience sampling was used, including only patients treated with anti-CGRP mAbs for ≥ 12 months. Previous studies from the same registry showed as this sample size allowed a reliable estimation of response and comparison of response subclasses. Continuous variables are reported as mean ± standard deviation (SD) for normally distributed data, or as median and interquartile range (IQR) for non-normally distributed data. Between groups comparisons were performed using one-way ANOVA for normally distributed variables, and the Kruskal–Wallis test for non-parametric data, as appropriate. Categorical variables are expressed as counts and percentages. Group comparisons were conducted using the Chi-square test or Fisher's exact test when expected cell counts were < 5. Given the exploratory nature of the study, no corrections for multiple comparison were applied. To assess whether the study findings based on the sub-sample of patients who completed 12 months of treatment (out of the 1,634 who initiated treatment) might be affected by selection bias, a sensitivity analysis was planned to compare the main clinical characteristics of the two groups. All statistical analyses were performed using R software (version 4.3.0). A $p$-value < 0.05 was considered statistically significant.

## Results

As of March 31, 2023, a total of 1,634 patients had received at least one dose of subcutaneous anti-CGRP mAbs. Among them, 572 patients (75.5% female; mean age 48.2 ± 10.6 years) had completed ≥ 12 consecutive months of treatment with erenumab (n = 527), galcanezumab ($n$ = 5), or fremanezumab ($n$ = 40) and were therefore included in the effectiveness analysis (Fig. 1).

Among the remaining 1,062 patients, treatment discontinuation due to adverse events occurred in 3 patients before week 12, 2 before week 24, 1 before week 36, and 1

before week 48. Additionally, 39, 46, and 34 patients were lost to follow-up before weeks 12, 24, and 36, respectively. All other patient had not yet reached the 12-month treatment time point due solely to later treatment initiation with no evidence of early discontinuation or selective drop-out (Fig. 1).

The risk of selection or attrition bias was addressed and excluded. A sensitivity analysis comparing the 572 patients with ≥ 12 months of treatment to those with shorter follow-up showed no significant differences in baseline clinical features or in the distribution of non-responders, responders, super-responders, and absolute responders (Supplementary Table). These findings confirm that the exclusion of patients with shorter exposure was attributable exclusively to calendar time and not to treatment discontinuation or differential response patterns.

Within the 572-patient cohort, 154 (26.9%) were diagnosed with HFEM and 418 (73.1%) with CM; overall, 64.7% met criteria for medication overuse. Baseline clinical characteristics were as follows: mean age at migraine onset 17.7 ± 8.8 years; MMD 10.3 ± 2.3; MHD 23.4 ± 5.6; prior preventive treatment failures 4.9 ± 1.9; MIDAS 81.6 ± 56.6; HIT-6 65.7 ± 10.0. No treatment switching occurred due to national reimbursement restrictions. Subjects with CM differed from those with HFEM in several baseline parameters: they had a higher BMI ($p = 0.022$), greater monthly analgesic intake ($p < 0.001$), more frequent unilateral cranial autonomic symptoms ($p = 0.018$), higher HIT-6 and MIDAS scores ($p = 0.026$, and $p = 0.030$, respectively), and greater number of prior preventive treatments failures ($p < 0.001$).A summary of socio-demographic and clinical characteristics is provided in Table 1.

At month 12, 70.0% (400/572) of patients were classified as *super-responders*, including 64.9% (100/154) of those with HFEM and 71.8% (300/418) of those with CM (Fig. 2). *Absolute responders* accounted for 23.4% (134/572) of the entire cohort: 29.9% (46/154) in HFEM and 21.1% (88/418) in CM (Fig. 3).

The temporal onset of super-response varied substantially: 29.4% (168/572) were early *super-responders* (≤ 3 months), 22.6% (129/572) were late *super-responders* (> 3–6 months), and 18.0% (103/572) were ultra-late *super-responders* (> 6–12 months) (Fig. 2). In the HFEM subgroup, the proportions of early, late, and ultra-late *super-responders* constituted 23.4% (36/154), 21.4% (33/154), and 20.1% (31/154), respectively; in CM, they were 31.6% (132/418), 23.0% (96/418), and 17.2% (72/418) (Fig. 4).

Similarly, absolute response emerged progressively over time: 3.1% (18/572) were early, 3.7% (21/572) late, and 16.6% (95/572) ultra-late *absolute responders* (Fig. 3). Among patients with HFEM, early, late, and ultra-late *absolute responders* accounted for 5.2% (8/154), 5.2% (8/154), and 19.5% (30/154), respectively. In the CM subgroup, the corresponding figures were 2.4% (10/418), 3.1% (13/418), and 15.6% (65/418) (Fig. 5).

Comparative analysis revealed significant differences among subgroups (Table 2). Within the *super-responder* group, patients classified as ultra-late *super-responders* reported lower baseline pain intensity on the NRS ($p = 0.019$) and a lower prevalence of unilateral cranial autonomic symptoms, either isolated ($p = 0.014$) or in combination with unilateral pain and ictal allodynia ($p = 0.041$).

In the *absolute responder* subgroup, a non-significant trend toward higher baseline MIDAS scores was observed ($p = 0.057$). Compared to the remaining *super-responders*, *absolute responders* were characterized by a higher HFEM-to-CM ratio ($p = 0.002$), lower baseline MHD in CM subgroup ($p = 0.001$), more frequent dopaminergic symptoms ($p = 0.045$), lower HIT-6 scores ($p = 0.005$), greated overall comorbidity burden ($p = 0.012$), and a higher proportion with ≥ 1 comorbidity ($p = 0.036$) (Table 2).

## Discussion

Super- and absolute responses to anti-CGRP mAbs align with patients' core expectations from migraine prophylaxis: a substantial and sustained reduction in attack frequency and associated disability [8]. Furthermore, achieving a super- or absolute response—rather than the conventional ≥ 50% response rate—may more effectively reduce avoidant behaviors and cephalalgiaphobia, both closely linked to attack frequency and known contributors to migraine interictal burden [22].

This study provides robust real-world evidence that one year treatment with anti-CGRP mAbs leads to super-response in 70% and absolute response in 23.4% of patients with HFEM or CM, despite a history of multiple prophylactic failures. These effects unfolded progressively over time: while 29.4% of patients were early *super-responders*, an additional 22.6% and 18% qualified as late and ultra-late *super-responders*, respectively. Absolute responses followed an even more delayed trajectory: only 3.1% emerged as early *absolute responders*, 3.7% as late *absolute responders*, and 16.8% as ultra-late *absolute responders*.

These findings confirm that anti-CGRP mAbs can elicit profound therapeutic benefits extending well beyond the conventional 50% response threshold, particularly with prolonged exposure. They reinforce the concept of a time-dependent maturation of responsiveness to anti-CGRP mAbs, which involves not only ≥ 50% response—already reported by our group—but also the progressive attainment of super- and absolute responses [20]. Consequently, they call into question the adequacy of the standard 3–6-month evaluation window to capture high-magnitude outcomes [23].

**Table 1** Demographic and clinical features of patients with high-frequency episodic migraine (HFEM) or chronic migraine (CM)

| | All patients | HFEM | CM | *p*-value |
|---|---|---|---|---|
| Patients | 572 | 154 | 418 | – |
| Age, years | 48.2 ± 10.6 | 49.0 ± 10.6 | 47.9 ± 10.7 | 0.252 |
| Females | 432 (75.5) | 116 (75.3) | 316 (75.6) | 1.000 |
| BMI | 23.2 ± 3.6 | 22.6 ± 2.7 | 23.4 ± 3.8 | **0.022** |
| Age at disease onset | 17.7 ± 8.8 | 18.3 ± 10.2 | 17.5 ± 8.3 | 0.313 |
| MMDs at baseline | – | 10.3 ± 2.3 | | – |
| MHDs at baseline | – | | 23.4 ± 5.6 | – |
| Monthly analgesic medications | 23.9 ± 20.1 | 12.9 ± 6.4 | 28.0 ± 21.9 | **< 0.001** |
| Medication overuse | 370 (64.7) | – | 370 (88.5) | – |
| NRS score | 7.6 ± 1.3 | 7.4 ± 1.5 | 7.6 ± 1.3 | 0.075 |
| Unilateral pain | 325 (56.9) | 95 (62.1) | 230 (55.0) | 0.157 |
| UAS | 301 (52.6) | 68 (44.2) | 233 (44.7) | **0.018** |
| Allodynia | 331 (57.9) | 81 (52.6) | 250 (59.8) | 0.146 |
| Dopaminergic symptoms | 379 (66.3) | 107 (69.5) | 272 (65.1) | 0.374 |
| Unilateral pain + UAS | 185 (32.3) | 46 (29.9) | 139 (33.2) | 0.471 |
| Unilateral pain + allodynia | 191 (33.5) | 51 (33.1) | 140 (33.5) | 0.971 |
| Unilateral pain + UAS + allodynia | 135 (23.6) | 31 (20.1) | 104 (24.9) | 0.250 |
| HIT-6 score | 65.7 ± 10.0 | 64.1 ± 10.9 | 66.3 ± 9.6 | **0.026** |
| MIDAS | 81.6 ± 56.6 | 57.6 ± 56.2 | 91.7 ± 54.3 | **0.030** |
| Previous treatment failures | 4.9 ± 1.9 | 4.3 ± 1.7 | 5.2 ± 1.9 | **< 0.001** |
| *1–2* | 42 (7.4) | 21 (13.8) | 21 (5.1) | **< 0.001** |
| *3–4* | 183 (32.4) | 62 (40.8) | 121 (29.3) | |
| *≥ 5* | 340 (60.2) | 69 (45.4) | 271 (65.6) | |
| Pts using concomitant prophylaxis | 298 (52.1) | 80 (51.9) | 218 (52.2) | 1.000 |
| Comorbidities | 1.0 ± 1.1 | 1.1 ± 1.2 | 1.0 ± 1.1 | 0.245 |
| Pts with ≥ 1 comorbidity | 347 (60.7) | 97 (63.0) | 250 (59.8) | 0.553 |
| Pts with psychiatric comorbidities | 185 (32.3) | 48 (31.2) | 137 (32.8) | 0.792 |
| Erenumab | 527 (92.1) | 138 (89.6) | 389 (93.1) | – |
| Galcanezumab | 5 (0.8) | 2 (1.3) | 3 (0.7) | – |
| Fremanezumab | 40 (7.0) | 14 (9.1) | 26 (6.2) | – |

BMI, Body Mass Index; MMD, Monthly Migraine Day; MHD, Monthly Headache Day; NRS, Numerical Rating Scale; UAS, Unilateral cranial autonomic symptoms; HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment Scale; NSAIDs, Non-Steroidal Anti-inflammatory Drugs

Values are expressed as mean ± SD or n (%) unless otherwise stated

Values in bold indicate statistical significance ($p < 0.05$)

Importantly, this study offers novel insights into the temporal dynamics of clinical response to anti-CGRP mAbs in migraine, revealing that both the ≥ 75% and 100% response rates tend to emerge progressively over time. In particular, absolute response is predominantly observed as an ultra-late outcome, typically beyond six months of therapy. This delayed yet robust clinical improvement likely reflects the gradual neurobiological remodeling within the trigemino-vascular system, including processes of synaptic plasticity and neurotransmitter adaptations [2]. Taken toghether, these findings underscore the critical importance of long-term treatment to fully realize the therapeutic potential of anti-CGRP mAbs in the preventive management of migraine. Notably, while treatment discontinuation after 12 month is ofern followed by an increase in migraine frequency, this effect appears to be attenuated by repetitive migraine treatment cycles, suggesting that prolonged exposure to anti-CGRP therapies may contribute to favorably modify migraine course [23].

Phenotypically, *absolute responders* were characterized by a delayed onset of therapeutic response and, paradoxically, by lower baseline headache frequency and disability compared to other *super-responders* (75–99%), despite a higher burden of comorbidities. Notably, ultra-late *super-responders* displayed clinical features suggestive of lower baseline trigeminal sensitization, including reduced pain intensity, less frequent ictal allodynia, and fewer signs of trigemino-autonomic reflex activation. These traits align

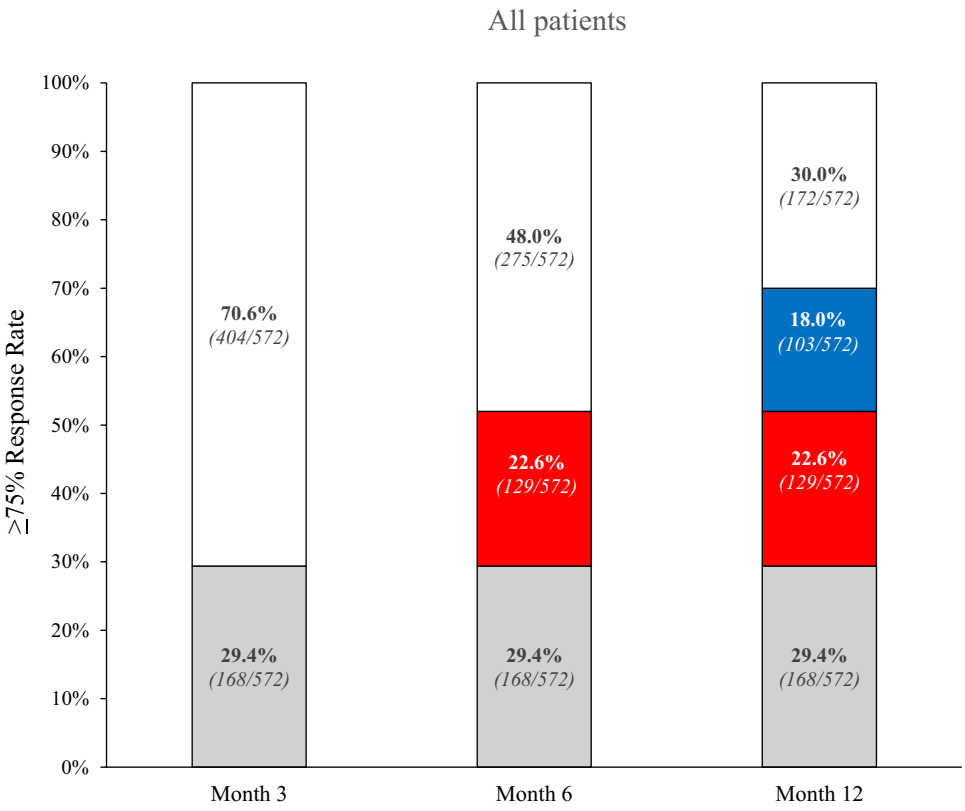


**Fig. 2** Proportion of all migraine patients achieving a ≥ 75% reduction in monthly migraine/headache days from baseline during treatment with anti-CGRP mAbs. Light grey bars represent *early* super-responders (≥ 75% reduction within 3 months), red bars *late* super-responders (> 3 to ≤ 6 months), and blue bars *ultra-late* super-responders (> 6 to ≤ 12 months). White bars represent individuals who had not yet achieved a ≥ 75% reduction at the corresponding time point

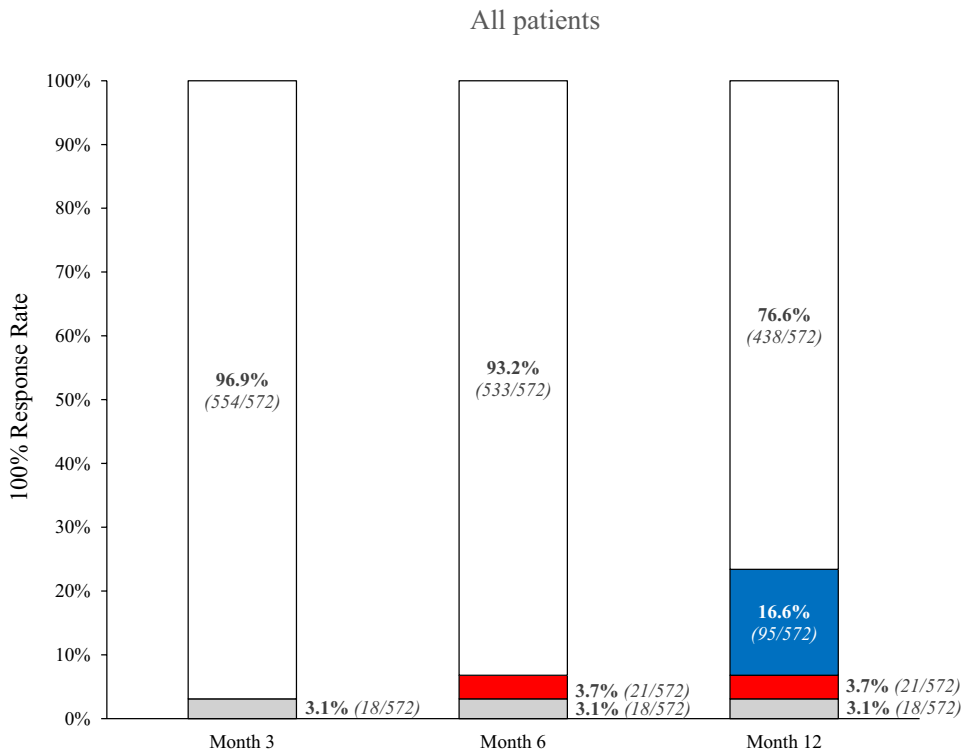


**Fig. 3** Proportion of all migraine patients achieving a 100% reduction in monthly migraine/headache days from baseline during treatment with anti-CGRP mAbs. Light grey bars represent *early* absolute responders (100% reduction within 3 months), red bars *late* absolute responders (> 3 to ≤ 6 months), and blue bars *ultra-late* absolute responders (> 6 to ≤ 12 months). White bars represent individuals who had not yet achieved a 100% reduction at the corresponding time point

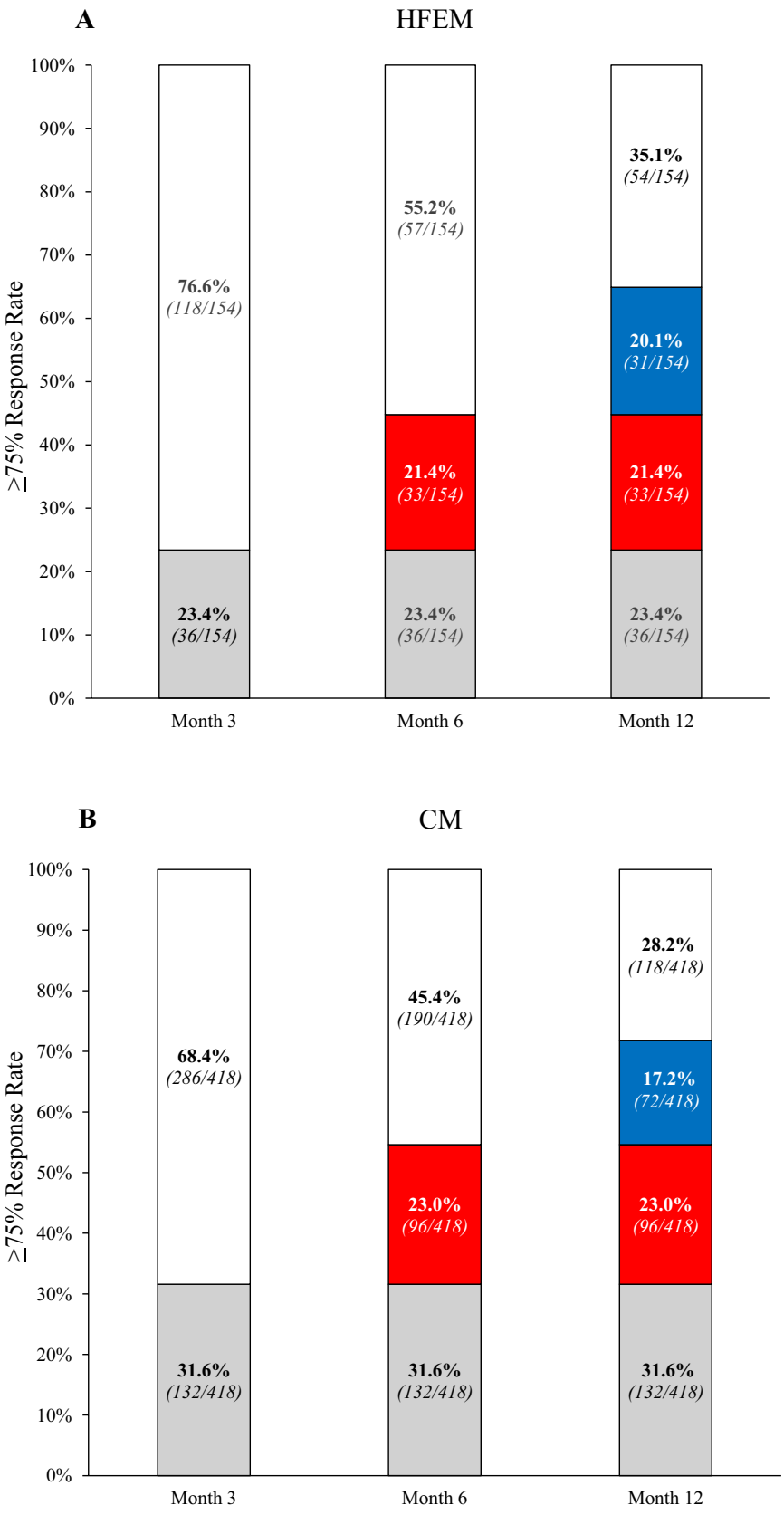


**Fig. 4** Proportion of patients with high-frequency episodic migraine (HFEM, panel A) or chronic migraine (CM, panel B) achieving a ≥ 75% reduction in monthly migraine/headache days from baseline during treatment with anti-CGRP mAbs. Light grey bars represent *early* super-responders (≥ 75% reduction within 3 months), red bars *late* super-responders (> 3 to ≤ 6 months), and blue bars *ultra-late* super-responders (> 6 to ≤ 12 months). White bars represent individuals who had not yet achieved a ≥ 75% reduction at the corresponding time point

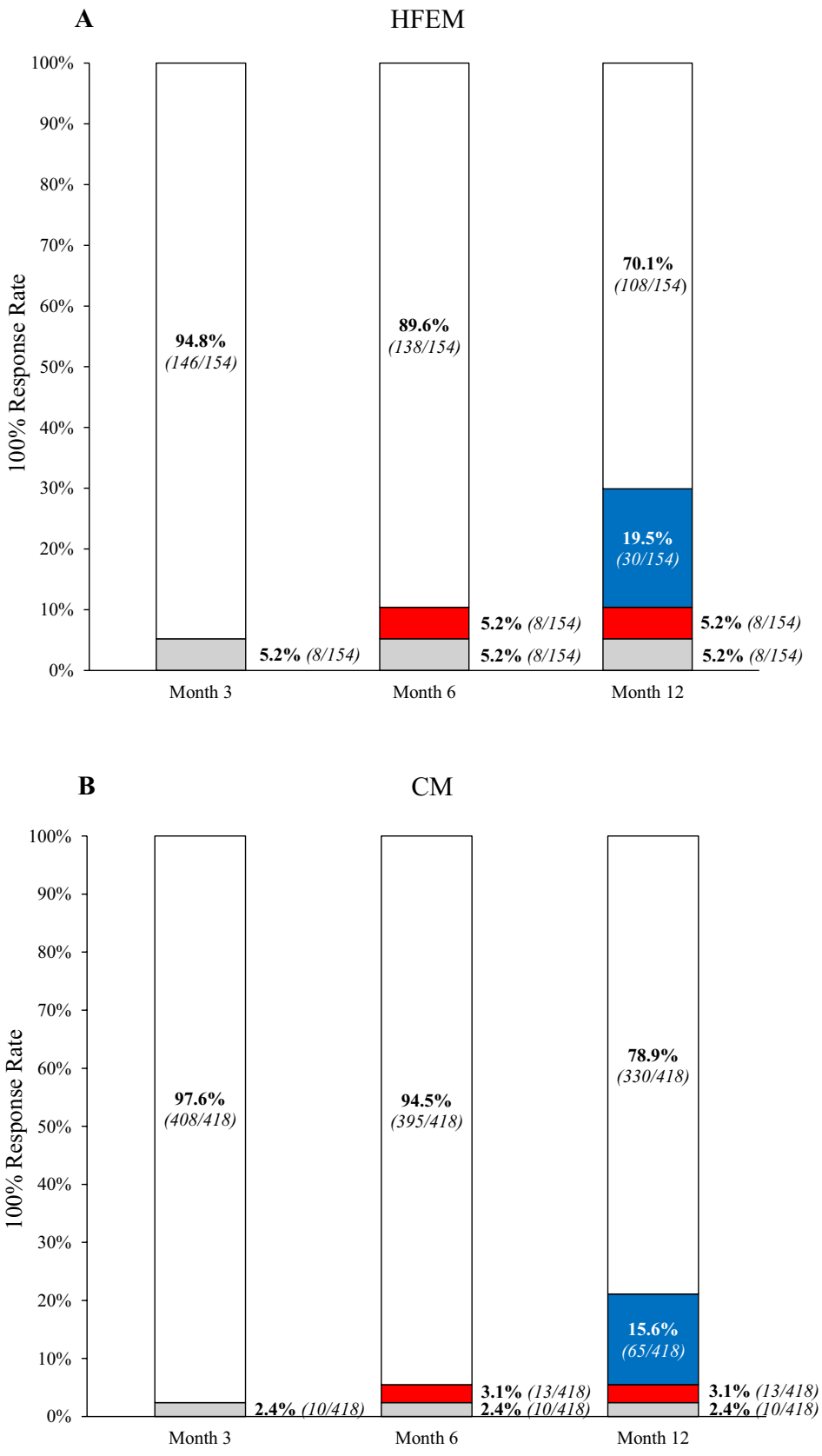


**Fig. 5** Proportion of patients with high-frequency episodic migraine (HFEM, panel A) or chronic migraine (CM, panel B) achieving a 100% reduction in monthly migraine/headache days from baseline during treatment with anti-CGRP mAbs. Light grey bars represent *early* absolute responders (100% reduction within 3 months), red bars *late* absolute responders (> 3 to ≤ 6 months), and blue bars *ultra-late* absolute responders (> 6 to ≤ 12 months). White bars represent individuals who had not yet achieved a 100% reduction at the corresponding time point

**Table 2** Comparison of demographic and clinical characteristics among *early* (≤3 months), *late* (>3 to ≤6 months), and *ultra-late* (>6 to ≤12 months) responders within the super-responder group (≥75% reduction from baseline migraine frequency) and the absolute-responder group (100% reduction)

| | Super-responders ($n=400$) | | | | Absolute-responders ($n=134$) | | | |
|---|---|---|---|---|---|---|---|---|
| | *Early* responders | *Late* responders | *Ultra-late* responders | *p*-value | *Early* responders | *Late* responders | *Ultra-late* responders | *p*-value |
| Patients | 168 (29.4) | 129 (22.6) | 103 (18) | - | 18 (3.1) | 21 (3.7) | 95 (16.6) | - |
| HFEM | 36 (23.4) | 33 (21.4) | 31 (20.1) | 0.273 | 8 (5.2) | 8 (5.2) | 30 (19.5) | 0.576 |
| CM | 132 (31.6) | 96 (23) | 72 (17.2) | | 10 (2.4) | 13 (3.1) | 65 (15.6) | |
| Females | 129 (76.8) | 97 (75.2) | 87 (84.5) | 0.196 | 12 (66.7) | 19 (90.5) | 75 (78.9) | 0.193 |
| Age, yrs | 48.0 ± 10.5 | 47.1 ± 10.8 | 48.9 ± 11.4 | 0.529 | 49.3 ± 7.3 | 49.9 ± 11.9 | 48.7 ± 11.7 | 0.898 |
| BMI | 22.9 ± 3.0 | 23.5 ± 4.0 | 22.9 ± 9.3 | 0.271 | 23.1 ± 3.2 | 24.0 ± 5.1 | 23.4 ± 4.2 | 0.777 |
| Age at onset | 18.0 ± 8.5 | 16.9 ± 8.1 | 18.2 ± 9.3 | 0.392 | 18.0 ± 8.9 | 17.8 ± 8.8 | 18.1 ± 9.1 | 0.994 |
| MMD at baseline | 17.5 ± 7.1 | 18.2 ± 6.9 | 16.9 ± 7.8 | 0.250 | 15.9 ± 7.3 | 15.9 ± 7.3 | 17 ± 7.6 | 0.785 |
| MHD at baseline | 21.1 ± 6.8 | 20.8 ± 7.2 | 19.4 ± 8.0 | 0.233 | 17.7 ± 7.0 | 18.6 ± 6.8 | 19.2 ± 7.7 | 0.774 |
| Analgesics per month | 22.3 ± 21.4 | 21.9 ± 15.2 | 24.5 ± 16.7 | 0.508 | 20.3 ± 16.7 | 24.4 ± 21.4 | 22.4 ± 18.7 | 0.801 |
| Medication overuse | 109 (82.6) | 85 (88.5) | 65 (90.3) | 0.232 | 7 (70.0) | 10 (76.9) | 57 (87.7) | 0.271 |
| Medication overuse duration, months[a] | 3.5 (0.0–12.7) | 7.0 (1.0–60.0) | 3.0 (1.0–33.0) | 0.373 | 5.0 (0.0–10.5) | 72.0 (0.0–222.0) | 8.0 (2.0–54.0) | 0.373 |
| NRS score at baseline | 7.8 ± 1.2 | 7.7 ± 1.3 | 7.3 ± 1.3 | **0.019** | 8.2 ± 1.1 | 7.6 ± 1.1 | 7.5 ± 1.3 | 0.072 |
| Unilateral pain | 109 (64.9) | 81 (62.8) | 53 (61.5) | 0.076 | 13 (72.2) | 13 (61.9) | 53 (55.8) | 0.433 |
| UAS | 90 (53.6) | 80 (62.0) | 44 (42.7) | **0.014** | 8 (44.4) | 10 (47.6) | 49 (51.6) | 0.859 |
| Allodynia | 110 (65.5) | 78 (60.5) | 63 (61.2) | 0.627 | 12 (66.7) | 12 (57.1) | 56 (58.9) | 0.786 |
| Unilateral pain + UAS | 63 (37.5) | 53 (41.1) | 28 (27.2) | 0.079 | 7 (38.9) | 5 (23.8) | 32 (33.7) | 0.581 |
| Unilateral pain + allodynia | 72 (42.9) | 47 (36.4) | 32 (31.1) | 0.141 | 9 (50.0) | 5 (23.8.3) | 29 (30.5) | 0.181 |
| Unilateral pain + UAS + allodynia | 51 (30.4) | 39 (30.2) | 18 (17.5) | **0.041** | 7 (38.9) | 3 (14.3) | 22 (23.2) | 0.190 |
| Dopaminergic symptoms | 105 (62.5) | 81 (62.8) | 72 (69.9) | 0.412 | 13 (72.2) | 13 (61.9) | 70 (73.7) | 0.555 |
| HIT-6 score at baseline | 67.2 ± 6.2 | 65.9 ± 10.2 | 64.6 ± 12.6 | 0.094 | 66.2 ± 5.9 | 63.7 ± 6.6 | 64.0 ± 12.6 | 0.735 |
| MIDAS score at baseline | 75.1 ± 61.1 | 108.6 ± 71.0 | 61.7 ± 44.1 | 0.420 | 10.0 ± 14.1 | 63.3 ± 38.2 | 119.2 ± 77.1 | 0.131 |
| Triptan responders | 108 (75.0) | 91 (80.5) | 58 (67.4) | 0.108 | 11 (78.6) | 16 (84.2) | 59 (75.6) | 0.721 |
| Prior treatment failures | 4.6 ± 1.8 | 4.9 ± 1.8 | 4.9 ± 2.1 | 0.233 | 4.5 ± 3.0 | 5.1 ± 1.7 | 4.9 ± 2.5 | 0.715 |
| *1–2* | 18 (10.8) | 11 (8.6) | 8 (7.9) | | 4 (22.2) | 2 (9.5) | 11 (11.8) | 0.579 |
| *3–4* | 64 (38.3) | 39 (30.5) | 35 (34.7) | 0.506 | 4 (22.2) | 5 (23.8) | 31 (33.4) | |
| *≥5* | 85 (50.9) | 78 (60.9) | 58 (57.4) | | 10 (55.6) | 14 (66.7) | 51 (54.8) | |
| Pts using concomitant prophylaxis | 84 (50.0) | 66 (51.2) | 62 (60.2) | 0.232 | 9 (50.0) | 14 (66.7) | 55 (57.9) | 0.571 |
| Comorbidities | 0.9 ± 1.0 | 1.0 ± 1.2 | 1.1 ± 1.1 | 0.359 | 0.9 ± 0.9 | 1.5 ± 1.4 | 1.1 ± 1.1 | 0.203 |
| Pts with ≥ 1 comorbidity | 93 (55.4) | 69 (53.5) | 67 (65.0) | 0.169 | 11 (61.1) | 14 (66.7) | 62 (65.3) | 0.929 |
| Pts with psychiatric comorbidities | 45 (26.8) | 37 (28.7) | 33 (32.0) | 0.650 | 6 (33.3) | 9 (42.9) | 30 (31.6) | 0.612 |
| Onabotulinumtoxin A responders[b] | 5 (9.1) | 4 (6.3) | 1 (11.1) | 0.337 | 1 (20.0) | 1 (7.7) | 2 (4.8) | 0.568 |
| Erenumab | 144 (85.7) | 121 (87.0) | 99 (96.1) | – | 17 (94.4) | 18 (85.7) | 90 (94.7) | – |
| Galcanezumab | 3 (1.8) | – | 1 (1.0) | – | – | 1 (4.8) | – | – |

**Table 2** (continued)

| | Super-responders ($n=400$) | | | | Absolute-responders ($n=134$) | | | |
|---|---|---|---|---|---|---|---|---|
| | *Early* responders | *Late* responders | *Ultra-late* responders | *p*-value | *Early* responders | *Late* responders | *Ultra-late* responders | *p*-value |
| Fremanezumab | 21 (12.5) | 8 (13.0) | 3 (2.9) | – | 1 (5.6) | 2 (9.5) | 5 (5.2) | – |

*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; *HIT-6*, Headache Impact Test-6, *MIDAS*, Migraine Disability Assessment Scale

Values are expressed as mean ± SD or n (%) unless otherwise stated;

[a]Median (IQR);

[b]Proportion calculated on the 165 subjects who were treated with OnabotulinumtoxinA

Values in bold indicate statistical significance ($p < 0.05$)

with previously identified predictors of delayed ≥ 50% response to anti-CGRP mAbs, supporting the hypothesis that individuals with limited clinical expression of trigeminal sensitization may require a longer duration of treatment to achieve fulltherapeutic benefit [19, 20, 24].

Several limitations warrant consideration. First, the study population did not include individuals with low-frequency episodic migraine, thereby limiting the generalizability of findings to this subgroup. Second, only subcutaneous anti-CGRP monoclonal antibodies were evaluated, with a marked predominance of erenumab—reflecting its earlier market availability in Italy—thus potentially introducing a treatment-related bias. Third, it cannot be ruled out that the progressive increase in super- and absolute-response rates over time may partly reflect, beyond the pharmacological effects of anti-CGRP monoclonal antibodies, concurrent improvements in quality of life, reduced stress levels, and enhanced psychological well-being. Fourth, in patients with CM, we combined both migraine-like and tension-type-like days under the definition of MHD to better reflect real-world clinical practice and to avoid underestimating the number of migraine days. Lastly, treatment allocation was not randomized, and while real-world in nature, the observational design cannot fully exclude unmeasured confounding factors that may have influenced treatment outcomes.

Despite these limitations, the study is supported by several methodological strengths. These include a large and clinically well-characterized patient cohort, a prospective multicenter design mirroring routine clinical practice across tertiary headache centers within a national migraine registry, and systematic, in-person neurological assessments performed at predefined intervals. Collectively, these features enhance both the internal validity and the real-world relevance of our findings, providing robust evidence on the temporal dynamics of response to anti-CGRP mAbs in patients with HFEM and CM.

In summary, one year of anti-CGRP mAbs therapy leads to a ≥ 75% response in more than two-thirds of patients with HFEM or CM and prior prophylactic failures, and to a 100% response in nearly one-quarter.

The considerable proportion of late and ultra-late responders highlights the importance of therapeutic persistence and extended follow-up to fully capture the treatment's potential. These findingd support the adoption of super-response and absolute response as clinically meaningful endpoints and reinforce the hypothesis that sustained anti-CGRP mAbs therapy may favorably modulate migraine pathophysiological circuits, ultimately translating into robust clinical improvement and enhanced patient quality of life.

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Stefania Proietti, Stefano Bonassi, Sabina Cevoli; Drafting of the manuscript: Piero Barbanti, Cinzia Aurilia, Stefano Bonassi; Revising it for intellectual content: Piero Barbanti, Cinzia Aurilia, Davide Mascarella, Stefania Proietti, Stefano Bonassi, Paola Torelli, Sabina Cevoli; Final approval of the completed manuscript: Piero Barbanti, Cinzia Aurilia, Giulia Fiorentini, Gabriella Egeo, Davide Mascarella, Stefania Proietti, Roberta Messina, Massimo Filippi, Stefano Bonassi, Paola Torelli, Sabina Cevoli.

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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, 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 received travel grants from Eli-Lilly, Teva and Pfizer, honoraria from Teva; Giulia Fiorentini have no disclosures to declare, Gabriella Egeo received travel grants and honoraria from Eli-Lilly, TEVA and Lundbeck. Davide Mascarella received travel grants Abbvie, Organon, Teva and educational grant from Eli Lilly and Organon; Stefania Proietti have no disclosures to declare; 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 Editor-in-Chief of the Journal of Neurology; 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); Stefano Bonassi have no disclosures to declare; Paola Torelli received travel grant, honoraria as a speaker, or for participating in advisory boards from Teva, Eli Lilly, Allergan, Organon, Pfizer, Lundbeck and Abbvie; Sabina Cevoli received honoraria for speaker panels from Teva, Abbvie and Organon.



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