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Responders and super-responders to atogepant after 24 weeks of treatment in migraine: real-world evidence from the GIANT-2 study

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Abstract

Background Real-world evidence on atogepant remains limited. GIANT2 explores the 24-week real-life effectiveness of atogepant in patients with high-frequency episodic migraine (HFEM) or chronic migraine (CM) under routine clinical conditions.

Methods GIANT2 is a 24-week, prospective, multicenter, real-world, study including consecutive patients with HFEM or CM with ≥3 preventive treatment failures, treated with atogepant 60 mg once daily. Co-primary endpoints: proportions achieving ≥50% and ≥75% reductions in monthly migraine days for HFEM or monthly headache days for CM at weeks 21–24 versus baseline. Secondary endpoints: changes in migraine/headache days, analgesic intake, pain intensity, disability, patient global impression of change, 100% response rates, tolerability and safety. Response rates at weeks 21–24 were also evaluated in patients with prioranti-CGRP mAb failure. Exploratory analyses: proportion of ≥50% responders achieving ≥30% reduction in NRS scores and response rates in subgroups combining psychiatric comorbidities, CM, and medication overuse headache (MOH).

Results Of 233 patients enrolled, 156 completed ≥24 weeks of treatment, with 37.2% having failed prior anti-CGRP mAbs. At weeks 21–24, 76.9% achieved a ≥ 50% response and 45.5% a ≥ 75% response, with ≥50% response more frequent in HFEM than CM ($p = 0.005$). A 100% response occurred in 5.1% of patients. All secondary endpoints

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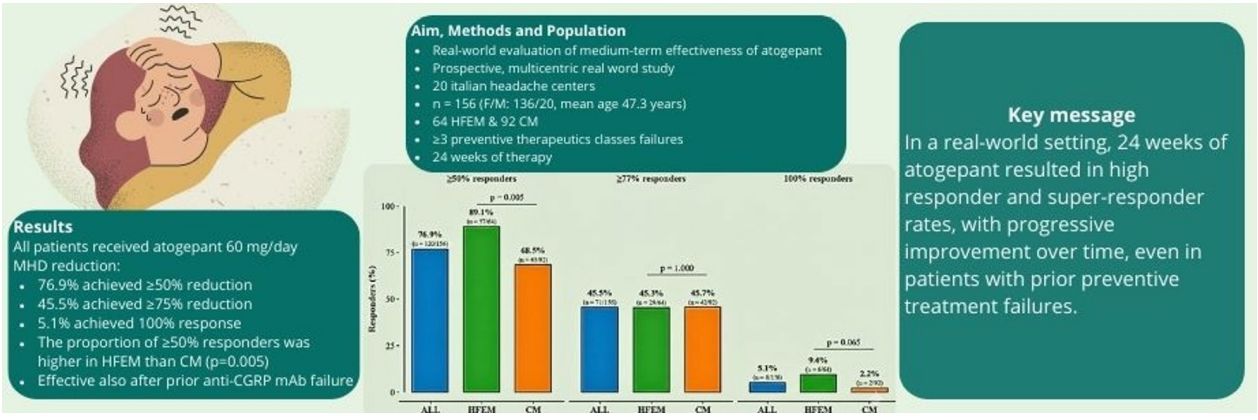
improved significantly ($p < 0.001$) with greater benefits at week 24 than week 12. No difference in effectiveness was observed between mAb-naïve patients and those with prior mAb failures, who achieved ≥50% and ≥75% response rates of 70.7% and 39.7%. A combined ≥50% frequency reduction and ≥30% pain reduction was achieved by 54.5% of patients. Among patients with psychiatric comorbidities, 63.0% were ≥50% responders, while among CM patients rates were 62.1% in those with MOH and 40.0% in those with both psychiatric comorbidities and MOH (≥75% responder rates 42.4%, 37.0%, and 28.0%). Adverse events occurred in 11.2% of patients and led to discontinuation in 1.3%.

Conclusions GIANT2 shows that atogepant effectiveness increases from week 12 to 24 with a high proportion of responders and super-responders regardless of prior anti-CGRP mAb failure and reduces pain intensity in residual headaches in most patients. It is also effective in migraine subgroups combining psychiatric comorbidities, CM and MOH.

Trial registration NCT06136442.

Keywords Atogepant, Migraine, CGRP, Treatment, Real-world, Disability

Graphical Abstract



Introduction

The advent of treatments targeting the calcitonin gene–related peptide (CGRP) pathway—both monoclonal antibodies (mAbs) and small-molecules antagonists (gepants)—has revolutionized migraine prevention. These treatments demonstrate high efficacy across diverse migraine subtypes and comorbidities, exibit excellent tolerability, and provide durable benefits even in patients with multiple prior preventive failures, enabling long-term disease control [1]. Moreover, CGRP-targeted therapies have contributed to redefining the benchmark for migraine prophylaxis, encouraging the pursuit of more stringent efficacy endpoints, such as ≥75% response rate (super-response), thereby raising the standards for preventive treatment [2].

Atogepant is the first gepant approved exclusively for migraine prevention [3]. Randomized controlled trials (RCT) have documented its efficacy, safety and tolerability in episodic migraine, chronic migraine (CM), and in patients with prior preventive treatment failures [4–6].

While RCTs provide essential evidence under controlled conditions, their generalizability to routine clinical practice is inherently limited by selective eligibility criteria and relatively short observation periods. Real-world evidence (RWE) is therefore crucial to evaluate treatment performance in broader patient populations characterized by heterogeneous phenotypes, comorbidities, and complex therapeutic histories [7]. RWE has been particularly informative for anti-CGRP mAbs, documenting late and ultra-late responders, clinically meaningful rates of super-response, putative response predictors and progressive benefits over time—phenomena only partially captured in RCT [8–12].

Comparable data for atogepant remain limited. The 12-week GIANT study provided preliminary real-world insights, reporting early clinical improvement, reductions in disability and attack severity, and effectiveness even in individuals with multiple preventive failures, including previous anti-CGRP mAb exposure [13].

The GIANT2 study is a 24-week, prospective, multicenter substudy of the Italian Migraine Registry (I-GRAINE) [14, 15], designed to extend these observations by evaluating the medium-term effectiveness of atogepant in a larger and more clinically representative population. By focusing on patients with advanced disease and high unmet preventive needs, GIANT2 aims to

clarify the real-world effectiveness profile of atogepant and inform its role in the contemporary management of difficult-to-treat migraine.

Methods

GIANT2 is a 24-week, prospective, multicenter, real-world study nested within the Italian Migraine Registry (I-GRAINE) [14, 15]. The study began on 9 April 2024 and is currently ongoing. It was pre-registered on ClinicalTrials.gov (ID: NCT06136442) [16].

All consecutive patients with high-frequency episodic migraine (HFEM, 8–14 days/month) or CM presenting to 20 headache centers across 8 Italian regions were enrolled. In accordance with the reimbursement criteria of the Italian Medicines Agency (AIFA) [17], all participants had failed at least three preventive therapeutic classes, including tricyclic antidepressants, beta-blockers, and antiepileptic drugs (or onabotulinumtoxinA in the case of CM). All patients received atogepant 60 mg once daily, typically after the evening meal, with a planned treatment duration of 12-month. The present analysis reports outcomes from the first 24 weeks of therapy.

Patients were evaluated by board-certified headache specialists who collected detailed sociodemographic, clinical, and therapeutic information through face-to-face interviews using a standardized, web-based semi-structured questionnaire previously described [18]. Clinical data were obtained from medical history, headache diaries, prescription records, and any available medical documentation.

Participants completed a paper-and-pencil diary to track migraine frequency, pain intensity according to the Numerical Rating Scale (NRS), and monthly intake of acute analgesics (MAI). Migraine-related disability was assessed using the Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS), while interictal burden was evaluated with the Migraine Interictal Burden Scale (MIBS-4). Treatment satisfaction was measured using the Patient Global Impression of Change (PGI-C). Adverse events were systematically collected at each visit using an open-ended question: 'Since the last visit, have you experienced any new or worsening symptoms or medical events?

The co-primary endpoints were the proportions of patients achieving ≥50% and ≥75% reductions in monthly migraine days (MMD) for HFEM and monthly headache days (MHD) for CM during weeks 21–24 compared with baseline. In CM, MHD were used as an inclusive measure capturing any headache day - whether migraine-like and tension-type–like - because, in real-world settings, distinguishing migraine from non-migraine headache days is often unreliable. A tension-type–like prodrome may precede a migraine attack and, when treated early with nonspecific acute medications, may ultimately be reported as a generic headache day.

Secondary endpoints, assessed at the same timepoints, included changes from baseline in MMD (HFEM), MHD (CM), MAI, NRS, HIT-6, MIDAS, and MIBS-4 scores, PGI-C responses, the proportion of 100% responders, and the occurrence of adverse events classified according to Hartwig [19]. In addition, the proportion of subjects achieving ≥50%, ≥75, and 100% response at weeks 21–24 among those with prior treatment failure to anti-CGRP mAbs was evaluated.

Exploratory endpoints included: (i) the proportion of ≥50% responders who also achieved a ≥ 30% reduction in NRS scores compared to baseline; (ii) ≥50%, ≥75, and 100% response rates in migraine patients with psychiatric comorbidities (identified on the basis of a documented specialist diagnosis or the ongoing use of antidepressants, anxiolytics, or other psychotropic medications prescribed for indications other than migraine); (iii) ≥50%, ≥75, and 100% response rates in patients with CM and medication overuse; and (iv) ≥50%, ≥75, and 100% response rates in patients with CM, medication overuse, and psychiatric comorbidities.

Statistical analysis

Descriptive statistics for continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as absolute frequencies and percentages (%). Comparisons between independent groups were performed using Student's t tests for normally distributed continuous variables, and Mann-Whitney U tests when normality was violated, assessed via the Shapiro-Wilk test. Categorical variables were compared using the Chi-square test or Fisher's exact test when expected cell counts were below five.

Longitudinal within-subject changes from baseline to weeks 12 and 24 for clinical outcomes, including MMD, MHD, MAI, NRS, HIT-6, and MIDAS, were analysed using the Friedman test due to non-normal distributions. When the global Friedman test was significant, pairwise post hoc comparisons between time points were performed using Wilcoxon signed-rank tests with Bonferroni correction for multiple comparisons.

Treatment-emergent adverse events were summarized descriptively by number and percentage, stratified by severity grade according to Hartwig's classification [18], without inferential testing. A sensitivity analysis assessed potential attrition bias by comparing patients who completed 24 weeks of treatment with those still undergoing treatment who had not yet reached this time point. All tests were two-sided, with a significance threshold of $p \leq 0.05$. Statistical analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

At the date of 12 August 2025, 233 patients had received at least one dose of atogepant 60 mg and were included in the safety population (Supplementary Table 1). A total of 156 patients completed ≥24 weeks of treatment and constituted the efficacy cohort (F/M: 136/20; mean age 47.3 years), comprising 64 individuals with HFEM and 92 with CM (Fig. 1). The mean number of prior preventive treatment failures was 4.1, and 37.2% of patients had previously failed anti-CGRP mAb therapy (Table 1). Compared with HFEM, CM patients had significantly higher MAI scores ($p < 0.001$), more frequent prior preventive treatment failures ($p < 0.001$), more frequent prior non-response to anti-CGRP mAbs ($p = 0.014$) and OnabotulinumtoxinA ($p = 0.002$), and a higher baseline burden, as reflected by worse HIT-6, MIDAS, and MIBS-4 scores (all $p < 0.001$).

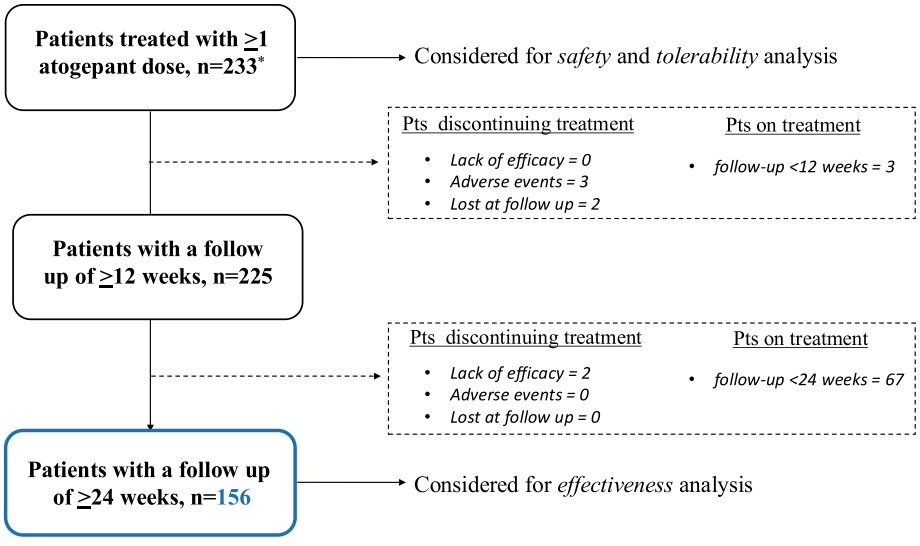
Potential attrition bias was evaluated through a sensitivity analysis. Specifically, 12-week response rates were compared between patients who subsequently completed 24 weeks of treatment and those who had not yet reached week 24 at the time of the data cut-off. To ensure comparability, the analysis was restricted to patients with available 12-week effectiveness data. Response rates at 12 weeks were equal or higher in non-completers compared with completers across all predefined thresholds, including responder, super-responder, and absolute-responder categories. These findings are not consistent with a selective loss of poor early responders and indicate that attrition between weeks 12 and 24 was unlikely to bias effectiveness estimates.

Primary endpoints

At weeks 21–24, 76.9% of patients achieved a ≥50% reduction in MMD/MHD and 45.5% reached a ≥75% reduction. In HFEM, response rates were 89.1% and 45.3%, and in CM 68.5% and 45.7%, respectively. The proportion of ≥50% responders was higher in HFEM than CM ($p = 0.005$) (Fig. 2). Patients achieving ≥50% response had a more favorable baseline profile than non-responders (< 50%), including lower migraine frequency ($p = 0.002$), less frequent and shorter medication overuse ($p = 0.001$ and $p = 0.048$), fewer dopaminergic symptoms ($p = 0.027$), fewer prior preventive failures ($p = 0.031$), lower rates of OnabotulinumtoxinA failure ($p = 0.013$), fewer psychiatric comorbidities ($p = 0.017$) and lower HIT-6 ($p = 0.002$) and MIDAS ($p = 0.033$) scores, with a trend for lower MAI ($p = 0.052$) (Table 2). Patients with ≥75% response showed trends toward lower ASC-12 ($p = 0.057$) and fewer prior treatment failures ($p = 0.062$).

Secondary endpoints

At weeks 21–24, all secondary endpoints improved significantly from baseline (all $p < 0.001$). Mean changes in the overall cohort were: MMD in HFEM −7.3±0.4; MHD in CM −12.3±1.8; MAI −12.1±5.4; NRS −3.1±1.3; HIT-6 -15.1±2.6; MIDAS −66.9±43.7; and MIBS-4 -4.7±0.9. Within subgroups, HFEM patients showed reductions in MMD (−7.3 ± 0.4), MAI (−7.3 ± 0.4), NRS (−3.8 ± 0.5), HIT-6 (−17.0 ± 0.5), MIDAS (−53.7 ± 50.2), and MIBS-4 (−4.4 ± 0.6), and CM patients MHD (−12.3 ± 1.8), MAI (−15.2 ± 5.5), NRS (−2.6 ± 1.1), HIT-6 (−13.9 ± 4.6), MIDAS (−76.7 ± 42.2), and MIBS-4 (−4.9 ± 0.8) (all $p < 0.001$). Improvements at weeks 21–24 were significantly greater than those observed at weeks 9–12, overall



**These patients are still on atogepant treatment. The reason for a shorter follow up (<12 weeks) is due the a later treatment start*

Fig. 1 Patients' disposition

Table 1 Demographic and clinical features of the 156 patients who completed the 24-weeks follow-up

Variables	Number (%) or mean ± SD			*p*-value
	All	HFEM	CM	
Patients	**156**	**64**	**92**	
Age, *yrs*	47.3±13.0	47.3±13.5	47.3±12.8	0.997
Females	136 (87.2)	53 (82.8)	83 (90.2)	0.264
BMI, kg/m2	23.2±3.5	22.9±3.2	23.5±3.7	0.360
Age at onset, *yrs*	15.8±7.1	15.5±6.2	16.1±7.66	0.587
MMD	-	10.6±1.9	-	-
MHD	-	-	21.8±6.0	-
NRS	8.1±0.9	8.1±0.8	8.1±1.0	0.909
Medication overuse	68 (72.3)	-	68 (72.3)	-
Medication overuse duration, *yrs*	7.3±12.3	-	7.3±12.3	-
Unilateral pain	67 (42.9)	26 (40.6)	41 (44.6)	0.745
UAS	60 (38.5)	23 (35.9)	37 (40.2)	0.709
CAPS	1.1±1.7	1.0±1.5	1.2±1.9	0.528
Allodynia	37 (23.7)	10 (15.6)	27 (29.3)	0.073
ASC-12	2.6±4.1	2.7±4.5	2.6±3.8	0.860
Dopaminergic symptoms	56 (35.9)	19 (29.7)	37 (40.2)	0.238
MAI	17.6±11.9	10.4±3.1	22.7±13.2	< 0.001
Concomitant prophylaxis, *pts*	64 (41.0)	30 (46.9)	34 (37.0)	0.283
Prior treatment failures	4.1±2.0	3.5±0.9	4.5±2.4	< 0.001
Prior anti-CGRP mAb failures*	58 (37.2)	16 (25.0)	42 (45.7)	0.014
Prior BoNT-A failure	35 (22.4)	6 (9.4)	29 (31.5)	0.002
≥1 comorbidity, *pts*	95 (60.9)	38 (59.4)	57 (62.0)	0.874
Psychiatric comorbidities, *pts*	46 (29.5)	14 (21.9)	32 (34.8)	0.119
HIT-6	66.5±8.1	63.6±9.7	68.6±5.9	< 0.001
MIDAS	84.7±75.0	59.0±58.8	103±80.1	< 0.001
MIBS-4	7.6±3.0	7.5±3.1	7.6±3.2	< 0.001

Abbreviations: *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

*Of the 58 patients, 54 had failed treatment with a single anti-CGRP mAb (erenumab, $n=47$; galcanezumab, $n=6$; fremanezumab, $n=1$), while 4 had failed two agents (erenumab and galcanezumab, $n=3$; fremanezumab and galcanezumab, $n=1$)

and within subgroups (Table 3). At weeks 21–24, 5.1% of patients achieved a 100% response (HFEM: 9.4%; CM: 2.2%) with a non-significant trend toward higher rates in HFEM ($p=0.065$) (Fig. 2). Overall, 61.6% of participants rated themselves as either *much improved* (47.4%) or *very much improved* (41%) (Fig. 3). Adverse events occurred in 11.2% of the safety population (26/233), most commonly constipation (5.6%), nausea (1.7%) and combined constipation and nausea (1.3%). Three patients (1.3%) discontinued treatment, two due to treatment-related adverse events (Table 4).

Among 58 patients with prior anti-CGRP mAb failure, baseline characteristics differed from treatment-naïve patients ($n=98$), including higher proportion of CM ($p=0.014$), younger age at migraine onset ($p=0.036$), higher migraine frequency ($p=0.003$), more frequent allodynia ($p=0.003$), higher MAI ($p=0.048$), more prior preventive failures ($p<0.001$), and higher MIDAS scores ($p=0.007$), with a trend toward higher HIT-6 ($p=0.066$) (Supplementary Table 3). At weeks 21–24, response rates were 70.7% for ≥50% reduction, 39.7% for ≥75%, and 1.7% for 100% reduction (Fig. 4). Substantial improvements were observed in migraine frequency (–10.5±0.1), NRS (–2.8±1.2), MAI (–12.8±3.9), HIT-6 (–15.3±4.4), MIDAS (–82.6±52.9), and MIBS-4 (–5.4±1.1), all significantly greater than changes at weeks 9–12 ($p<0.001$ for migraine frequency, NRS, HIT-6, MIDAS; $p=0.005$ for MAI) (Table 5).

Exploratory endpoints

At weeks 21–24, 54.5% of patients (85/156) achieved the composite endpoint of ≥50% reduction in migraine frequency combined with ≥30% reduction in NRS (HFEM: 68.8%; CM: 44.6%), and 37.2% met the stricter composite of ≥75% reduction plus ≥30% NRS reduction (HFEM: 40.6%; CM: 34.8%) (Fig. 5).

When stratified by comorbidity profile, ≥50% responder rates were 63% in patients with psychiatric comorbidities, 62.1% in CM with medication overuse, and 40% in CM with both psychiatric comorbidities and medication overuse. The corresponding ≥75% responder rates were 37%, 42.4, and 28%, while 100% responder rates were 0%, 3.0, and 0%, respectively (Fig. 6).

Discussion

This prospective, multicenter, real-world study shows that, in patients with HFEM or CM and at least three prior preventive treatment failures—including anti-CGRP mAbs in approximately one third of cases—6 months of atogepant treatment resulted in ≥50% and ≥75% response rates of 76.9% and 45.5%, respectively. Higher response—but not super-response—rates were observed in HFEM. Response and super-response rates did not differ between patients with prior anti-CGRP mAbs failure and anti-CGRP–naïve patients. Notably, the 86.5% of patients with prior anti-CGRP mAb failure reported being much improved or very much improved on the PGI-C.

In addition, residual migraine pain intensity, a patient-reported outcome rarely assessed in real-world studies, was also reduced by at least 30% in 54.5% of responders and 37.2% of super-responders.

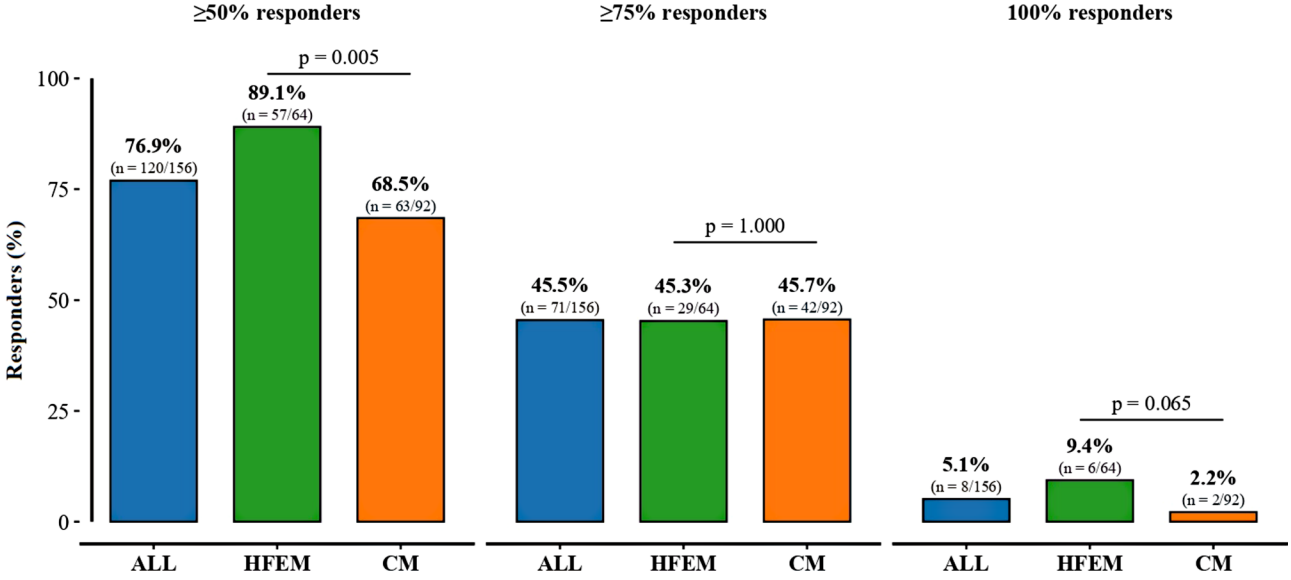


Fig. 2 Response rates at weeks 21–24. All: total patient population; HFEM: patients with high-frequency episodic migraine; CM: patients with chronic migraine. ≥50% responders: proportion of patients with a ≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥75% responders: proportion 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

This exploratory measure, assessed for the first time in a real-world setting, captures therapeutic effects beyond mere reduction in migraine frequency, with atogepant reducing both attack frequency and intensity on residual headache days in responders, thereby more accurately reflecting overall clinical benefit.

At week 24, atogepant was associated with statistically significant reduction of migraine frequency, analgesic intake, pain severity, and both ictal and interictal disability compared with week 12, supporting the notion that, despite their rapid onset of action, CGRP pathway–targeting therapies may continue to confer additional therapeutic benefits over time [8–10].

Subjects with psychiatric comorbidities and, in CM patients, those with medication overuse were responders in more than 60% of cases and super-responders in nearly 40%. Patients combining CM with both medication overuse and psychiatric comorbidities were still responders in 40% of cases and super-responders in 28%, highlighting the potential for a beneficial atogepant response even in more disabled and complex migraine scenarios. However, although atogepant demonstrated effectiveness even in clinically complex patients, responder status was more frequent among individuals with a less severe baseline profile, while super-response tended to occur in individuals with fewer prior preventive failures (Table 2). Cautiously, this pattern may suggest that earlier use of atogepant could increase the likelihood of achieving better clinical responses, while retaining efficacy in difficult-to-treat cases, in line with the observations from the Eureka study on anti-CGRP mAbs [20].

Bearing in mind the limitations inherent to indirect comparisons across real-world studies, the GIANT2 study documents a substantial proportion of super-responders to atogepant, particularly among patients with HFEM (45.3%). This rate is numerically higher than those reported with erenumab after 48 weeks (31.6%) and with galcanezumab (32.4%), fremanezumab (30.8%), and eptinezumab (17%) after 24 weeks. However, differences in study design, patient populations, and follow-up duration preclude direct comparison.

In patients with CM, the proportion of super-responders observed with atogepant at 24 weeks (45.7%) exceeded that reported with galcanezumab (37.8%) and was within the range of proportions reported with fremanezumab (44.8%), eptinezumab (43.5%), and erenumab after 48 weeks (44.5%) [21–24].

Atogepant was generally well tolerated in this real-world cohort, with adverse events reported in 11.2% of patients and predominantly of mild to moderate severity. Gastrointestinal symptoms, mainly constipation and nausea, were the most frequently observed and accounted for the few treatment discontinuations. The proportion of adverse events in the present study was substantially lower than that reported (44.3%) in another Italian 12-week real-world study, which systematically assessed specific symptoms, including weight changes [25]. In our study, adverse events were collected as typically done in clinical practice, by asking patients about any newly perceived symptoms without targeted questioning, to preserve the observational nature of the study. Compared with our previous 12-week GIANT study, the slightly

Table 2 Comparison of clinical and demographic features in the 156 patients who completed the 24-week follow-up stratified by ≥50% and ≥75% response rate

Variables	Number (%) or mean±SD		p-value	Number (%) or mean±SD		p-value
	<50% RR	≥50% RR		<75% RR	≥75% RR	
Patients	**36**	**120**		**85**	**71**	
Age, *yrs*	49.1±14.1	46.8±12.7	0.390	47.3±13.6	47.3±12.4	0.999
Females	30 (83.3)	106 (88.3)	0.408	73 (85.9)	63 (88.7)	0.772
BMI, *kg/m2*	23.3±4.0	23.2±3.3	0.868	23.1±3.5	23.4±3.6	0.555
Age at onset, *yrs*	35.2±14.1	34.1±12.2	0.777	33.8±13.2	35.3±12.5	0.653
MMD/MHD	20.8±7.64	16.2±6.9	0.002	17.5±7.43	16.9±7.2	0.617
NRS	8.1±1.0	8.1±0.9	0.721	8.1±1.03	8.2±0.9	0.720
Medication overuse	25 (69.4)	44 (36.7)	0.001	41 (48.2)	28 (39.4)	0.347
Medication overuse duration, *yrs*	7.8±11.9	3.4±9.2	0.048	5.2±11.4	3.5±8.2	0.280
Unilateral pain	14 (38.9)	53 (44.2)	0.712	37 (43.5)	30 (42.3)	1.000
UAS	16 (44.4)	44 (36.7)	0.518	32 (37.6)	28 (39.4)	0.949
CAPS	1.2±1.6	1.1±1.8	0.873	1.1±1.6	1.2±2.0	0.834
Allodynia	11 (30.6)	26 (21.7)	0.381	21 (24.7)	16 (22.5)	0.898
ASC-12	3.0±4.2	2.5±4.1	0.482	3.2±4.4	1.9±3.6	0.057
Dopaminergic symptoms	19 (52.8)	37 (30.8)	0.027	34 (40.0)	22 (31.0)	0.317
MAI	20.5±8.7	16.8±12.7	0.052	17.2±9.2	18.2±14.6	0.628
Concomitant prophylaxis, *pts*	15 (41.7)	46 (38.3)	0.869	36 (42.4)	25 (35.2)	0.456
Prior treatment failures	4.9±2.8	3.8±1.6	0.031	4.3±2.2	3.8±1.6	0.062
Prior anti-CGRP mAb failures	17 (47.2)	40 (33.3)	0.187	35 (41.2)	22 (31.0)	0.250
Prior BoNT-A failure	14 (38.9)	21 (17.5)	0.013	24 (28.2)	11 (15.5)	0.088
≥1 comorbidity, *pts*	26 (72.2)	68 (56.7)	0.139	54 (63.5)	40 (56.3)	0.453
Psychiatric comorbidities, *pts*	0.4±0.51	0.2±0.4	0.017	0.3±0.4	0.2±0.4	0.163
HIT-6	69.4±5.3	65.7±8.6	0.002	66.4±8.03	66.8±8.2	0.731
MIDAS	111±84.9	76.6±70.1	0.033	91.1±83.0	77.2±64.1	0.246
MIBS-4	7.3±3.0	7.6±3.2	0.586	7.4±3.2	7.7±3.1	0.624

Abbreviations: *RR*, response rate: reduction in migraine frequency from baseline to weeks 21–24; *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

Table 3 Change in clinical outcomes at weeks 9–12 and weeks 21–24 in the 156 patients who completed the 24-week follow-up

	Time point	MMD	MHD	MAI	NRS	HIT6	MIDAS	MIBS-4
ALL	Baseline	10.6±1.9	21.8±6.0	17.6±11.9	8.1±0.9	66.5±8.1	84.7±75.0	7.6±3.2
	Weeks 9–12	6.3±5.6*	14.2±9.4*	10.1±11.4*	5.9±2.4*	57.5±12.2*	47.2±67.4*	3.2±2.7*
	Δ	−4.3 ± 3.7	−7.6 ± 3.4	−7.5 ± 0.5	−2.2 ± 1.5	−9.0 ± 4.1	−37.5 ± 7.6	−4.4 ± 0.5
	Weeks 21–24	3.3±2.3*¶	9.5±7.8*¶	5.5±6.5*¶	5.0±2.2*¶	51.4±10.7*¶	17.8±31.3*¶	2.9±2.3*¶
	Δ	−7.3 ± 0.4	−12.3 ± 1.8	−12.1 ± 5.4	−3.1 ± 1.3	−15.1 ± 2.6	−66.9 ± 43.7	−4.7 ± 0.9
HFEM	Baseline	10.6±1.9	-	10.4±3.1	8.1±0.8	63.6±9.7	59.0±58.8	7.5±3.1
	Weeks 9–12	6.3±5.6*	-	5.6±5.9*	5.4±2.5*	54.2±12.7*	32.7±59.2*	3.3±2.6*
	Δ	−4.3 ± 3.7	-	−4.8 ± 2.8	−2.7 ± 1.7	−9.4 ± 3.0	−26.3 ± 0.4	−4.2 ± 0.5
	Weeks 21–24	3.3±2.3*¶	-	2.6±2.1*¶	4.3±2.0*¶	46.6±9.2*¶	5.3±8.6*¶	3.1±2.5*¶
	Δ	−7.3 ± 0.4	-	7.3±0.4	−3.8 ± 0.5	−17.0 ± 0.5	−53.7 ± 50.2	−4.4 ± 0.6
CM	Baseline	-	21.8±6.0	22.7±13.2	8.1±1.0	68.6±5.9	103.1±80.1	7.6±3.2
	Weeks 9–12	-	14.2±9.4*	13.3±13.2*	6.2±2.2*	59.8±11.3*	57.2±71.1*	3.2±2.7*
	Δ	-	−7.6 ± 3.4	−9.4 ± 0	−1.9 ± 1.2	−8.8 ± 5.4	−45.9 ± 9.0	−4.4 ± 0.5
	Weeks 21–24	-	9.5±7.8*¶	7.5±7.7*¶	5.5±2.1*¶	54.7±10.5*¶	26.4±37.9*¶	2.7±2.2*¶
	Δ	-	−12.3 ± 1.8	−15.2 ± 5.5	−2.6 ± 1.1	−13.9 ± 4.6	−76.7 ± 42.2	−4.9 ± 0.8

Abbreviations: *All*, overall migraine population; *HFEM*, high-frequency episodic migraine; *CM*, chronic migraine; *MMD*, monthly migraine days; *MHD*, monthly headache days; *MAI*, analgesic doses taken per month; NRS, Numerical Rating Scale; *HIT-6*, Headache Impact Test-6; MIDAS, Migraine Disability Assessment Scale; *Δ* difference vs. baseline

*$p < 0.001$ (weeks 9–12 vs baseline; weeks 21–24 vs baseline)

¶$p < 0.001$ (comparison between weeks 21–24 and weeks 9–12)

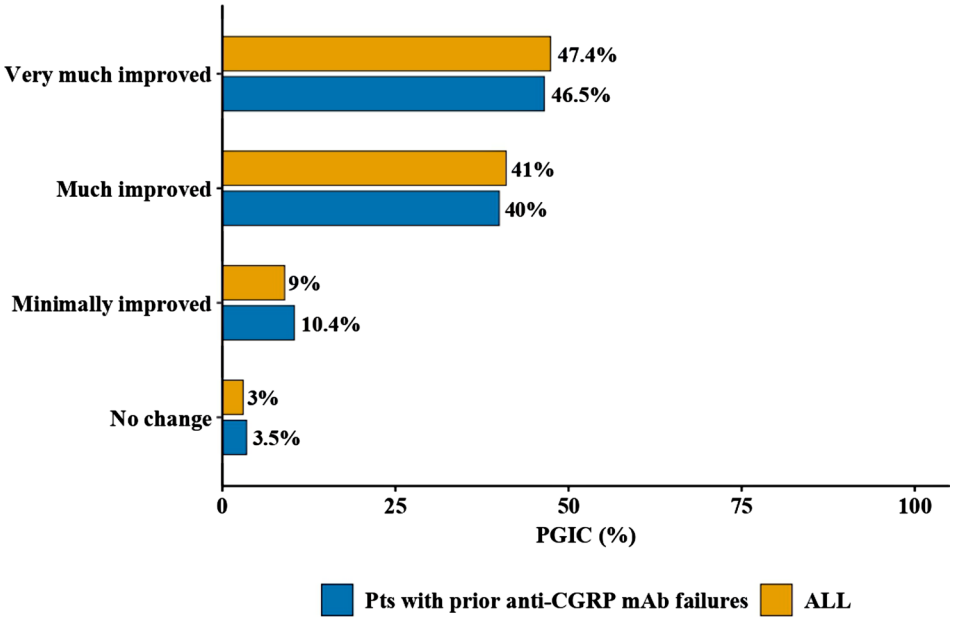


Fig. 3 Patient global impression of change (PGIC) at weeks 21–24 in the overall patient population (all patients; *n* = 156, gray bars), in patients with prior failure to monoclonal antibodies targeting CGRP pathway (anti-CGRP mAbs; *n* = 58, blue bars)

Table 4 Treatment-emergent adverse events (TEAEs) among the 233 subjects enrolled (safety population)

	N (%)	Grade[a]		
Patients with TEAEs	**26 (11.2)**	**I**	**II**	**III**
- *Constipation*	13 (5.6)	7	6	
- *Nausea*	4 (1.7)	1	3	
- *Constipation and nausea*	3 (1.3)		1	2
- *Lack of appetite*	2 (0.9)		2	
- *Hypertension*	1 (0.4)	1		
- *Renal colic*	1 (0.4)		1	
- *Insomnia*	1 (0.4)	1		
Vertigo	1 (0.4)	1		
Discontinuations due to TEAEs	3 (1.3)[b]			

[a]Grade (according to Hartwig SC, et al. [19]: *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]Three subjects discontinued the treatment. Two individuals discontinued because of severe nausea and constipation, both events judged to be treatment related. One patient discontinued due to hypertension, which was considered unrelated to the study medication

higher frequency of adverse events observed here may reflect the longer treatment exposure and differences in baseline patient characteristics, including prior experience with preventive therapies.

The limitations of the present study are those inherent to real-world investigations, including the lack of a placebo control and the potential for recall bias. Furthermore, due to Italian Medicine Agency regulations, our data refer to patients with at ≥ 8 migraine days per month and ≥3 prior treatment failures, which may limit generalizability to patients with lower migraine frequency or fewer prior treatment failures. Patients did not use electronic diaries, and, as in all I-GRAINE pharmacological studies, MHD were used to assess CM patients, potentially limiting comparability with studies using also migraine-day–based definitions. Finally, exploratory endpoints should be interpreted cautiously, as they were not powered for formal testing or adjusted for multiplicity and were intended for hypothesis generation rather than causal inference. Strengths include the large sample of patients prospectively recruited across 20 headache centers in 8 regions of northern, central, and southern Italy. Further strengths are represented by the exploratory endpoints, designed to capture the overall effectiveness of the drug by considering composite efficacy measures (concomitant reduction in both frequency and intensity) and evaluating subgroups of clinically complex patients. Lastly, as GIANT2 is a substudy of the Italian Migraine Registry (I-GRAINE), fully compliant with EU GDPR and the Italian Data Protection Authority, the quality of clinical data is ensured by an integrated, standardized process for data collection, storage, and analysis.

In conclusion, the GIANT2 study shows that 24 weeks of atogepant treatment are associated with high

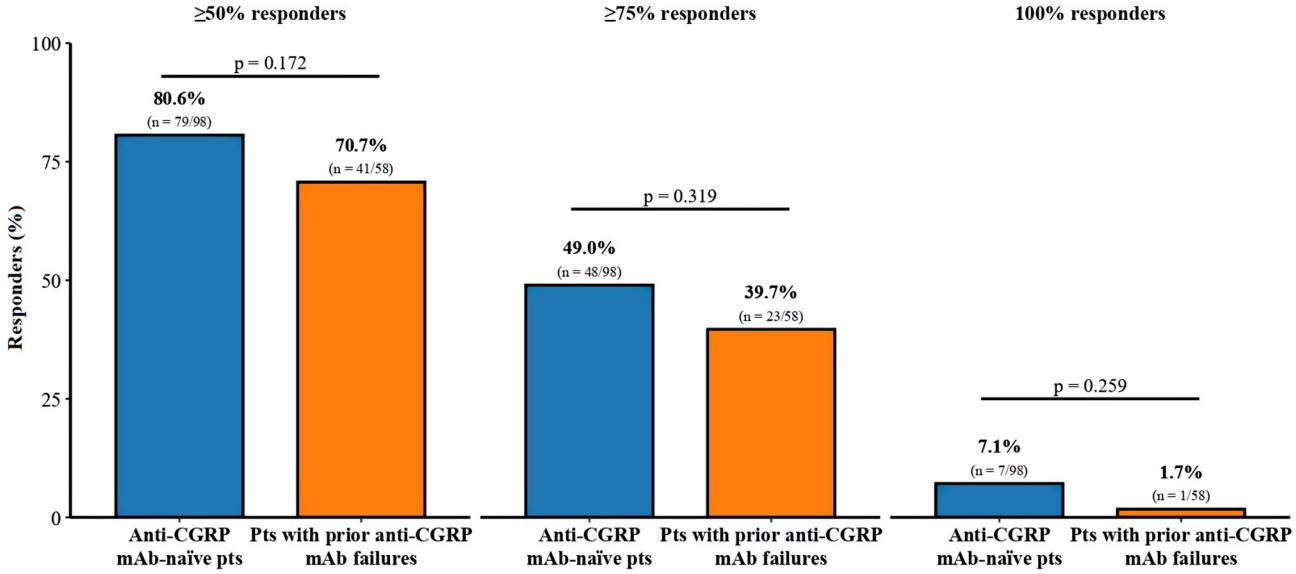


Fig. 4 Response rates at weeks 21–24 in patients naïve to anti-CGRP mAbs (blue bars, *n* = 98) and individuals with prior anti-CGRP mAb failures (orange bars, *n* = 58). ≥50% responders: proportion of patients with a ≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥75% responders: 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 5 Change in clinical outcomes from baseline to weeks 9–12 and 21–24 in 156 patients completing 24 weeks of follow-up, stratified by anti-CGRP mAb use (mAb-naïve vs prior mAb failures)

Patients	Time	MMD/MHD	NRS	MAI	HIT6	MIDAS	MIBS-4
Anti-CGRP mAbs-naïve	Baseline	16.0±6.7	8.1±1.0	16.4±12.0	65.7±8.7	71.3±57.3	7.3±3.1
	Week 9–12	10.0±8.7*	5.9±2.4*	9.3±12.0*	57.5±11.9*	43.1±57.9*	3.6±2.8*
	Δ	−6.0±2.0	−2.2±1.4	−7.1±0	−8.2±3.2	−28.2±0.6	−3.7±0.3
	Week 21–24	6.0±6.2*#	4.8±2.2*	4.6±5.6*#	50.6±10.5*#	14.0±23.5*	3.0±2.4*
	Δ	−10.0±0.5	−3.3±1.1	−11.8±6.4	−15.1±1.4	−57.3±33.8	−4.3±0.7
Prior failure to anti-CGRP mAbs	Baseline	19.3±7.8	8.1±0.8	19.8±11.5	68.0±6.6	106.9±93.8	8.0±3.2
	Week 9–12	12.8±9.1*	5.9±2.3*	11.7±10.3*	57.5±12.7*	54.3±81.4*	2.6±2.4*
	Δ	−6.5±1.3	−2.2±1.5	−8.1±1.2	−10.5±6.1	−52.6±12.4	−5.4±1.2
	Week 21–24	8.8±7.7*¶	5.3±2.0*¶	7.0±7.6*§	52.7±11.0*¶	24.3±40.9*¶	2.6±2.1*
	Δ	−10.5±0.1	−2.8±1.2	−12.8±3.9	−15.3±4.4	−82.6±52.9	−5.4±1.1

Abbreviations: *Δ* difference vs. baseline, *MMD*, monthly migraine days; *MHD*, monthly headache days; *MAI*, analgesic doses taken per month; NRS, Numerical Rating Scale; *HIT-6*, Headache Impact Test-6; MIDAS, Migraine Disability Assessment Scale

*$p < 0.001$ (weeks 9–12 vs baseline; weeks 21–24 vs baseline)

¶$p < 0.001$ (weeks 21–24 vs weeks 9–12). #$p < 0.05$ (weeks 21–24 vs weeks 9–12)

§$p = 0.005$ (weeks 21–24 vs weeks 9–12)

responder and super-responder rates in patients with HFEM or CM, irrespective of prior anti-CGRP mAb failure. While encouraging, these results should be interpreted cautiously, considering the inherent features and limitations of real-world studies, and should not be taken as evidence of atogepant's superiority over anti-CGRP mAbs. Effectiveness increased between weeks 12 to 24 and was observed even in clinically complex patient subgroups. A substantial proportion of patients experienced a concomitant reduction in pain intensity, in addition to the reduction in migraine frequency. Atogepant was generally well tolerated with a low incidence of adverse events. These findings support atogepant as an effective and safe preventive option across a broad clinical spectrum of migraine, with potential added benefit when introduced earlier in the treatment course.

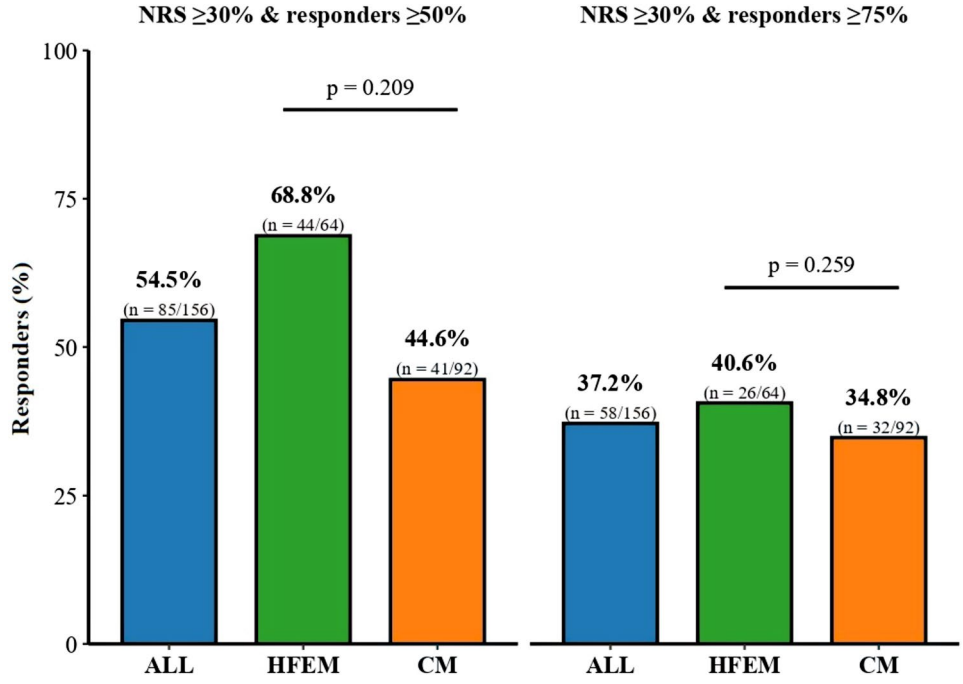


Fig. 5 Proportion of patients achieving the composite endpoints of a ≥ 50% or ≥75% reduction in migraine frequency combined with a ≥ 30% reduction in NRS score, compared with baseline. All: total patient population; HFEM: patients with high-frequency episodic migraine; CM: patients with chronic migraine

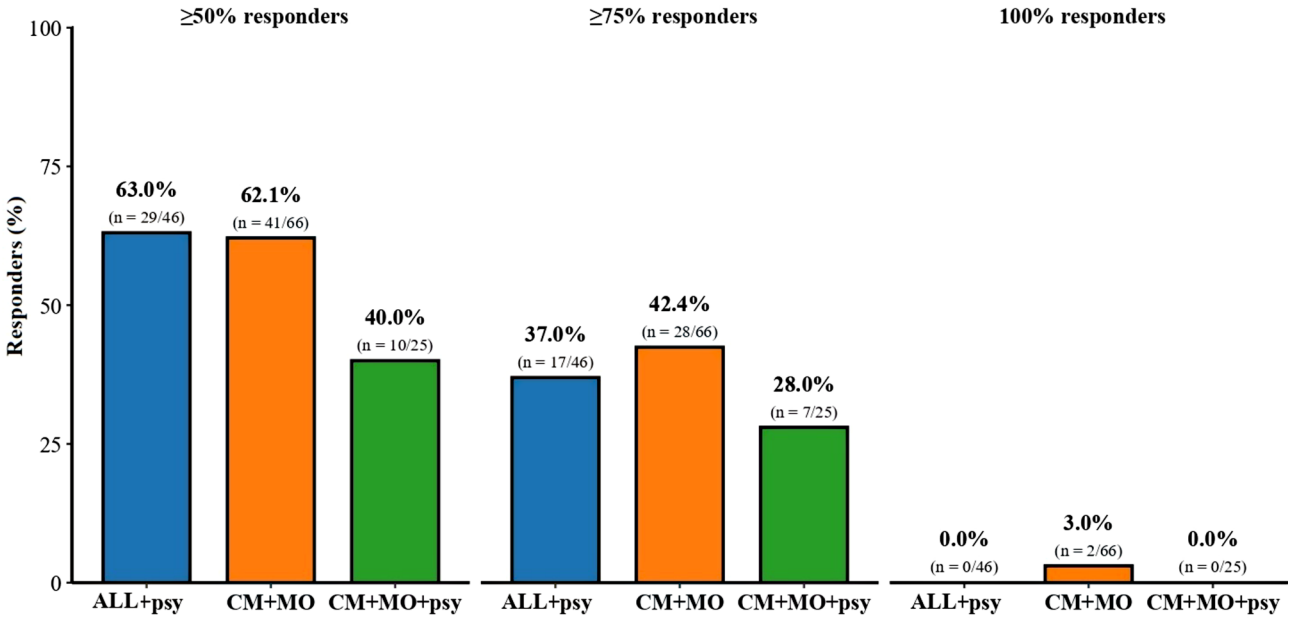


Fig. 6 Proportion of patients achieving a ≥ 50%, ≥75%, or 100% reduction in migraine frequency compared with baseline among patients with psychiatric comorbidities (blue bars), patients with chronic migraine (CM) and medication overuse (orange bars), and patients with CM, medication overuse, and psychiatric comorbidities (green bars)

Supplementary Information

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Supplementary Material 1

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Author contributions
PB, GE, PT and AP designed the study, PB and GE drafted the manuscript, AP and SB carried out data analysis, GE, AD, FP, SR, SS, CA, PS, MA, AS, AG, RA, SM, CZ, PB, CC, FdO, VI, AR, FB, JSdS, AC, LDC, MZ, MLBDP, LV, LB, GF, RV, VD, PT, MA and Italian Migraine Registry (I-GRAINE) study group performed data collection, PB, GE, CT and SB revised the manuscript. The author(s) read and approved the final manuscript.

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Data availability
Anonymized data will be shared by request from any qualified investigator.

Declarations

Consent for publication
Not applicable

Competing interests
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