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GIANT: a prospective, multicenter, real-world study on the effectiveness, safety, and tolerability of atogepant in migraine patients with multiple therapeutic failures

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Abstract

Background Atogepant, the first oral CGRP receptor antagonist approved for migraine prevention, has demonstrated efficacy and safety in randomized clinical trials (RCT). However, prospective real-world data are lacking.

Objective To explore the effectiveness, safety, and tolerability of atogepant 60 mg at week 12 in patients with high-frequency episodic (HFEM: 8-14 days/month) or chronic migraine (CM) with multiple therapeutic failures.

Methods This ongoing, multicenter ($n = 16$), prospective real-world study included consecutive adults with HFEM or CM who had failed ≥3 prior preventive treatments, according to AIFA criteria. Participants received atogepant 60 mg daily, with treatment planned for up to 12 months.

Primary endpoint: change from baseline to week 12 in monthly migraine days (MMD) for HFEM and monthly headache days (MHD) for CM. Secondary endpoints: changes in monthly analgesic intake (MAI), pain intensity (NRS), disability (HIT-6, MIDAS), interictal burden (MIBS-4), treatment satisfaction (PGIC), responder rates (≥ 50%, ≥ 75%, 100%), and changes in migraine frequency during the first treatment week compared to the last pre-treatment week. Adverse events were monitored throughout.

Results A total of 183 patients were enrolled and 82 completed ≥ 12 weeks of follow-up. Of these, 41.5% had previously failed anti-CGRP mAbs. At week 12, significant reductions ($p < 0.001$) were observed in MMD (–6.0) and MHD (–11.2). Secondary outcomes also improved significantly ($p < 0.001$): MAI (–10.9), NRS (–2.7), HIT-6 (–13.2), MIDAS (–61.1), and MIBS-4 (–5.4). Responder rates were 65.9% (≥ 50%), 36.6% (≥ 75%), and 6.1% (100%). PGIC documented

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high satisfaction (much/very much improved: 70.7%). A significant decrease ($p < 0.001$) in migraine frequency was already evident by week 1 (overall: −2.5 days, HFEM: −1.5, CM: −3.1). In the mAb-failure subgroup, ≥ 50% and ≥ 75% response rates were 52.9% and 23.5%, with significant improvements in all primary and secondary endpoints ($p < 0.001$). Adverse events occurred in 5.5% of patients, and 1.6% discontinued treatment.

Conclusion The GIANT study provides real-world evidence of atogepant's effectiveness, safety, and tolerability in patients with HFEM and CM with multiple therapeutic failures and comorbidities. It extends RCT data by showing rapid onset of action, meaningful reductions in pain intensity and interictal disability, high patient satisfaction, and effectiveness even in patients with anti-CGRP mAb failures.

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

Introduction

The introduction of calcitonin gene-related peptide (CGRP)-targeted therapies has marked a significant advancement in migraine prevention, offering a more precise and mechanism-based approach compared to conventional preventive treatments [1]. Among these, anti-CGRP monoclonal antibodies (mAbs) and CGRP receptor antagonists (gepants) represent two distinct pharmacological classes, each with specific pharmacokinetic properties and clinical applications. Monoclonal antibodies targeting the CGRP pathway (e.g., erenumab, fremanezumab, galcanezumab, and eptinezumab) are large molecules with an extended half-life, allowing for monthly or quarterly administration. Their favorable pharmacokinetic profile and minimal drug interactions make them a valuable option for migraine prevention. In contrast, gepants, such as atogepant, rimegepant, and ubrogepant, are small-molecule CGRP receptor antagonists that offer oral administration, a rapid onset of action, and the potential for both acute and preventive treatment [2, 3]. Gepants expand therapeutic opportunities for migraine patients, representing the first class of therapy that appears to bridge the gap between acute and preventive treatments [4]. Moreover, they can be used in patients with a history of ischemic cardiovascular or cerebrovascular events, further broadening their clinical applicability [5–7].

Atogepant, an orally administered, highly selective CGRP receptor antagonist, has demonstrated robust efficacy and safety in the prophylaxis of both episodic migraine and chronic migraine (CM) at the dose of 60 mg. Pivotal phase III randomized controlled trials (RCTs) have demonstrated clinically meaningful reductions in migraine frequency and improved response rates in patients with episodic migraine or CM, including those with multiple prior preventive treatment failures, while maintaining a favorable safety profile [8–10]. Further, in a long-term extension study, atogepant demonstrated sustained efficacy in migraine prevention, with a ≥ 50% reduction in migraine days observed in 84.2% of patients, a ≥ 75% reduction in 69.9%, and a 100% reduction in 48.4% by weeks 49–52 compared to baseline [11].

While RCTs are indispensable for establishing the efficacy and safety of atogepant under controlled conditions, their applicability to routine clinical practice is inherently limited. Real-world evidence is essential to complement RCT findings, offering a broader perspective on treatment outcomes in diverse patient populations over extended periods. Unlike RCTs, which often exclude patients with significant comorbidities or complex treatment regimens, real-world experience captures key aspects of real-life migraine management, including long-term adherence, safety in heterogeneous populations, and the impact of polypharmacy [12]. Integrating RCT and real-world data helps bridge the gap between clinical trials and everyday practice, optimizing therapeutic decision-making and ensuring that novel treatments like atogepant achieve their full potential in real-world settings.

To address this critical need, we designed the GIANT (atoGepant IN reAl life in iTaly) study, a prospective, multicenter, real-world investigation evaluating the effectiveness, safety, and tolerability of atogepant for the prophylaxis of high-frequency episodic migraine (HFEM, 8–14 days/month) and CM. By generating robust real-world insights, this study is aimed at refining the positioning of atogepant in personalized migraine management, facilitating its integration into routine clinical care.

Methods

This multicenter, prospective, real-world study was conducted across 16 headache centers in Italy, spanning 7 regions (Lazio, Sicily, Lombardy, Emilia-Romagna, Calabria, Campania, Abruzzo), and represents a substudy of the Italian Migraine Registry (I-GRAINE) [13]. The study was preregistered on ClinicalTrials.gov (ID: NCT06136442), commenced on 09 Apr 2024, and remains ongoing [14].

We enrolled all consecutive adults with HFEM or CM who provided informed consent and had failed ≥ 3 prior preventive treatments—at adequate doses and durations—among tricyclic antidepressants, beta-blockers and antieptileptics (or onabotulinumtoxinA for those with CM), according to Italian Medicines Agency (AIFA)

guidelines [15]. In line with AIFA requirements for reimbursement of CGRP-targeted therapies, patients prospectively recorded migraine characteristics using a paper diary prior to initiating atogepant treatment.

Eligible participants received atogepant 60 mg once daily, with treatment planned for up to 12 months. According to current AIFA regulations, continuation beyond 12 weeks is still permitted for responders who maintain their response through week 24.

At baseline, trained neurologists conducted a standardized assessment, including a comprehensive neurological and physical examination. A shared semi-structured questionnaire was used to collect detailed sociodemographic data, migraine characteristics, comorbidities, and current or past treatments, as previously described [16].

Patients were asked to use a paper–pencil headache diary to document migraine frequency, pain severity using the Numerical Rating Scale (NRS), and monthly analgesic intake (MAI). Migraine-related disability was assessed using the Headache Impact Test (HIT-6) and the Migraine Disability Assessment Scale (MIDAS), while interictal burden was evaluated with the Migraine Interictal Burden Scale (MIBS-4). Treatment satisfaction was measured via the Patient Global Impression of Change (PGIC). Adverse events were closely monitored throughout the study.

Follow-up visits took place at 12 weeks, during which data were collected on monthly migraine days (MMD) for HFEM, monthly headache days (MHD) for CM, NRS, MAI, HIT-6, MIDAS, PGIC scores, and adverse events.

The primary endpoint was the change in MMD for subjects with HFEM and in MHD for those with CM at weeks 9–12, compared to baseline. Secondary endpoints included changes in MAI, NRS, HIT-6, MIDAS, and MIBS-4 scores at the same timepoint, as well as PGIC at week 12. Additionally, we assessed the proportion of patients achieving ≥50%, ≥75%, and 100% reduction in migraine frequency from baseline to weeks 9–12, alongside changes in migraine frequency during the first treatment week compared to the last pre-treatment week.

Patients who had received anti-CGRP monoclonal antibodies within the previous five months or onabotulinumtoxinA within the last three months were excluded.

The study was approved by the Lazio 5 Institutional Review Board (n. 0003898) and was mutually recognized by all participating centers.

Statistical analysis

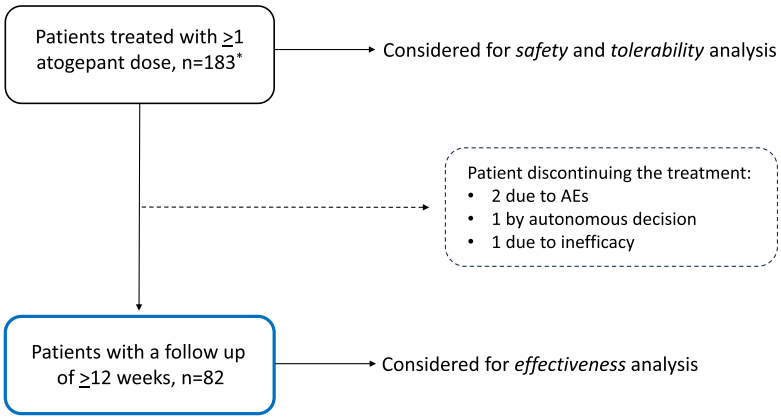
Baseline demographic and clinical characteristics of the study population were summarized with descriptive statistics. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the Student's T test or ANOVA test for normally distributed data, or the Mann–Whitney and Kruskall Wallis tests for non-normally distributed data. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Group comparisons of categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate. Changes in continuous clinical outcomes between baseline and follow-up (weeks 9–12) were evaluated using the Wilcoxon signed-rank test for paired samples. Response rates (RR ≥50%, RR ≥75%, and RR =100%) were analyzed at weeks 9–12 for the total sample and separately for the CM and HFEM subgroups. To assess the early effect of treatment on MMD and MHD, the response observed at the first week of treatment was compared with the last week before treatment. Univariate analyses on RR ≥50% were conducted to identify potential predictors of treatment response. A significance level of $p < 0.05$ was considered statistically significant in all analyses. Statistical analyses were performed using SPSS software (version 13, IBM Corp., Armonk, NY, USA).

Results

As of June 6, 2024, a total of 183 consecutive patients had been enrolled in the study and were considered as safety population (Supplementary Table 1). By January 5, 2025, 82 patients had completed at least 12 weeks of follow-up and were included in the effectiveness analysis. Among the remaining 101 patients, 97 had not yet reached the 12-week follow-up due to staggered enrollment and treatment initiation, while 4 discontinued treatment for various reasons. (Fig. 1).

A sensitivity analysis was conducted on the 82 patients who completed the 12-week follow-up to assess potential baseline differences compared to the 101 patients still undergoing treatment. No major baseline differences were observed, except for a higher proportion of females (92% vs. 78%; $p = 0.015$), higher prevalence of allodynia (17% vs. 7%; $p = 0.032$), and younger mean age at migraine onset (15.1 vs. 18.6 years; $p = 0.021$).

The baseline characteristics of patients who completed the 12-week follow-up are summarized in Table 1. Compared to patients with HFEM, those with CM were more often females ($p = 0.040$), had higher rates of UAS ($p = 0.041$), and scored significantly higher on the Cranial Autonomic Parasympathetic Symptom Scale (*CAPS*, $p = 0.029$) and Allodynia Symptom Checklist (ASC-12, $p = 0.034$). Individuals with CM had more frequent dopaminergic symptoms ($p = 0.002$), higher MAI ($p < 0.001$), and a trend toward a higher number of prior treatment failures ($p = 0.050$), including failures with anti-CGRP mAbs ($p = 0.012$). MIDAS score was also significantly higher in the CM subgroup ($p = 0.004$).



**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 82 patients who completed the 12-week follow-up

Variables	Number (%) or mean±SD			*p*-value
	All	HFEM	CM	
Patients	**82**	**35**	**47**	
Age, *yrs*	45.3±14.7	47.1±13.3	44.1±15.6	0.366
Females	75 (91.5)	29 (82.9)	46 (97.9)	0.040
BMI	23.4±3.8	23.2±3.2	23.4±3.5	0.866
Age at onset, *yrs*	15.1±6.4	16.0±6.0	14.4±6.7	0.276
MMD	10.2±2.7	10.2±2.7	-	-
MHD	22.7±5.6	-	22.7±5.6	-
NRS	8.0±1.0	8.1±1.0	8.0±1.0	0.892
Medication overuse	34 (41.5)	-	34 (72.3)	-
Medication overuse duration, *yrs*	5.5±5.4	-	5.5±5.4	-
Unilateral pain	11 (13.4)	4 (11.4)	7 (14.9)	0.649
UAS	29 (35.4)	8 (22.9)	21 (44.7)	0.041
CAPS	1.1±1.9	0.6±1.3	1.5±2.2	0.029
Allodynia	14 (17.1)	4 (11.4)	10 (21.3)	0.241
ASC-12	2.3±3.8	1.5±3.3	2.9±4.0	0.034
Dopaminergic symptoms	24 (29.3)	4 (11.4)	20 (42.6)	0.002
MAI	18.5±10.6	11.1±5.9	23.2±10.2	<0.001
Pts using concomitant prophylaxis	27 (33.0)	8 (22.9)	19 (40.4)	0.094
Prior treatment failures	4.4±2.4	3.5±2.0	5.0±2.9	0.050
Pts with prior treatment failures with anti-CGRP mAbs	34 (41.5)	9 (25.7)	25 (53.2)	0.012
Pts with prior treatment failure to OnabotulinumtoxinA	11 (13.4)	1 (2.9)	10 (21.3)	0.155
Pts with ≥1 comorbidity	48 (58.5)	20 (57.1)	28 (59.6)	0.825
Pts with psychiatric comorbidities	27 (32.9)	10 (28.6)	17 (36.2)	0.469
HIT-6	64.4±9.5	61.7±11.4	66.4±7.0	0.094
MIDAS	84.5±76.0	65.9±68.8	97.3±78.8	0.004
MIBS-4	9.2±3.4	9.0±3.2	9.3±3.6	0.553

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, *MAI* analgesic doses taken per month, *NRS* Numeric Rating Scale, *UAS* unilateral cranial autonomic symptoms, *CAPS* Cranial Autonomic Parasympathetic Symptom Scale, *ASC-12* Allodynia Symptom Checklist, *Dopaminergic symptoms*, presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis; *HIT-6* Headache Impact Test-6, *MIDAS* Migraine Disability Assessment Scale, *MIBS-4* Migraine Interictal Burden Scale-4

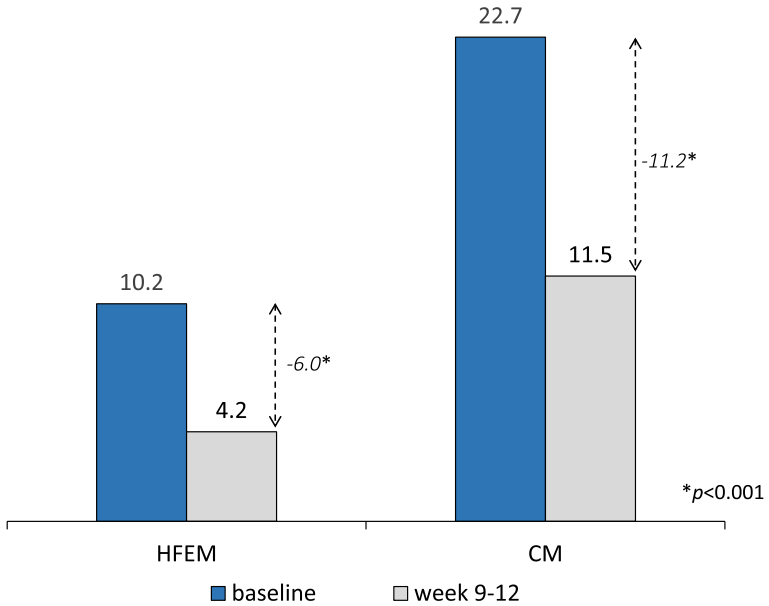


Fig. 2 Change in monthly migraine days (MMD) for subjects with patients with high-frequency episodic migraine (HFEM) and in monthly headache days (MHD) for those with chronic migraine (CM) at weeks 9–12, compared to baseline

Primary and secondary endpoints

From baseline to weeks 9–12, significant reductions were observed in MMD (−6.0, $p < 0.001$) and MHD (−11.2, $p < 0.001$) (primary endpoint) (Table 2 and Fig. 2). All secondary endpoints also significantly improved ($p < 0.001$), including MAI (−10.9), NRS (−2.7), HIT-6 (−13.2), MIDAS (−61.1), and MIBS-4 (−5.4) (Table 2). In the HFEM subgroup, meaningful reductions ($p < 0.001$) were noted in MAI (−6.8), NRS (−3.5), HIT-6 (−15.4), MIDAS (−56.8), and MIBS-4 (−7.5), while similar improvements were observed in the CM subgroup for MAI (−13.7), NRS (−2.3), HIT-6 (−11.8), MIDAS (−64.3), and MIBS-4 (−4.1). Figure 3 shows responder rates at weeks 9–12. Overall, 65.9% of patients achieved a ≥ 50% response rate, with higher rates in HFEM (80%) than CM (59.6%). A ≥ 75% response was observed in 36.6% of patients (HFEM: 40%; CM: 34%), while a 100% response 100% was achieved in 6.1% (HFEM: 14.3%; CM: 0%).

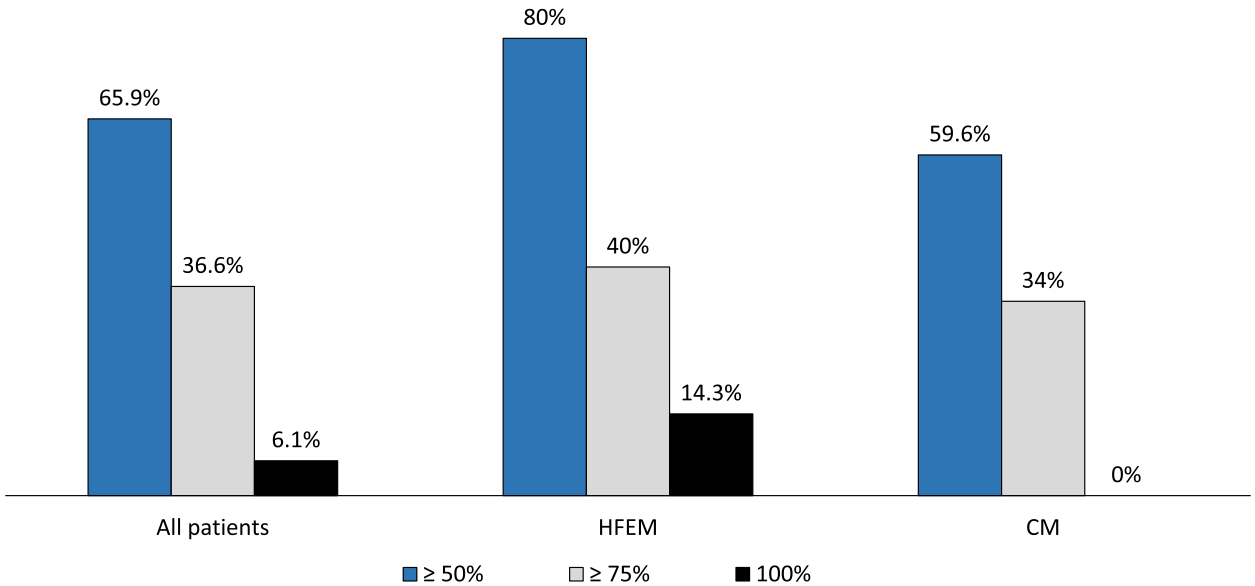


Fig. 3 Response rates at weeks 9–12. All: total patient population; HFEM: patients with high-frequency episodic migraine; CM: patients with chronic migraine. ≥ 50% responders: proportion of patients with a ≥ 50% reduction in monthly migraine/headache days compared to baseline; ≥ 75% responders: proportion of patients with a ≥ 75% reduction in monthly migraine/headache days compared to baseline; 100% responders: proportion of patients with a 100% reduction in monthly migraine/headache days compared to baseline

Table 2 Change in clinical outcomes from baseline to weeks 9-12 in the 82 patients who completed the 12-week follow-up

	All ($n = 82$)				**HFEM ($n = 35$)**				**CM ($n = 47$)**			
Clinical outcomes	**Baseline**	**Week 9-12**	**Δ**	***p*-value***	**Baseline**	**Week 9-12**	**Δ**	***p*-value***	**Baseline**	**Week 9-12**	**Δ**	***p*-value***
MMD	10.2±2.7	-	-	-	**10.2±2.7**	**4.2±4.1**	**-6.0±3.9**	**<0.001**	-		-	-
MHD	22.7±5.6	-	-	-	-	-	-	-	**22.7±5.6**	**11.5±8.7**	**-11.2±7.7**	**<0.001**
MAI	18.5±10.6	7.4±7.8	-10.9±9.7	<0.001	11.1±5.9	4.3±5.9	-6.8±5.3	<0.001	23.2±10.2	9.5±8.2	-13.7±10.9	<0.001
NRS	8.0±1.0	5.3±2.2	-2.7±2.4	<0.001	8.1±1.0	4.5±2.3	-3.5±2.7	<0.001	8.1±1.0	5.8±2.0	-2.3±1.9	<0.001
HIT-6	64.4±9.4	51.1±12.1	-13.2±12.6	<0.001	61.7±11.4	46.3±12.9	-15.4±15.3	<0.001	66.4±7.0	54.6±10.2	-11.8±10.3	<0.001
MIDAS	84.2±76.0	22.8±29.6	-61.1±68.9	<0.001	65.9±68.8	9.1±13.3	-56.8±73.6	<0.001	97.3±78.8	33.0±34.2	-64.3±65.8	<0.001
MIBS-4	9.2±3.4	3.8±3.8	-5.4±4.7	<0.001	9±3.2	1.5±2.3	-7.5±3.9	<0.001	9.3±3.6	5.2±3.9	-4.1±4.8	<0.001

Abbreviations: *All* overall migraine population, *HFEM* high-frequency episodic migraine, *CM* chronic migraine, Δ, difference between baseline and weeks 9–12, *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, *MIBS-4* Migraine Interictal Burden Scale

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

Primary endpoint is highlighted in bold.

According to the PGIC, 48.3% of patients rated themselves as "very much improved," 22.4% "much improved," 19% "minimally improved," and 10.3% reported no change (Fig. 4). By week 12, 72.3% (34/47) of patients initially classified as CM had transitioned to episodic migraine ($p = 0.004$). Furthermore, among CM patients with baseline medication overuse, 67.6% (23/34) no longer met criteria for medication overuse at follow-up ($p = 0.021$).

A significant decrease in migraine frequency was already evident as early as week 1, with mean decreases of 2.5 days in the overall population ($p < 0.001$), 1.5 days in the HFEM subgroup ($p < 0.001$), and 3.1 days in the CM subgroup ($p < 0.001$) (Table 3).

Univariate analysis

Patients who achieved a ≥ 50% reduction in migraine frequency were significantly less likely to have a history of prior anti-CGRP mAb failures ($p = 0.038$) and presented with fewer baseline comorbidities ($p = 0.029$), particularly psychiatric disorders ($p = 0.018$). Those achieving a ≥ 75% reduction in migraine frequency had a lower prevalence of previous treatment failures ($p = 0.001$)—including anti-CGRP mAbs ($p = 0.039$)—and fewer baseline comorbidities ($p = 0.010$), especially psychiatric disorders ($p = 0.004$) (Table 4). Among individuals with CM, a ≥ 50% response rate was associated with unilateral pain ($p = 0.032$), fewer prior anti-CGRP mAb failures ($p = 0.020$), fewer psychiatric comorbidities ($p = 0.011$), and lower baseline MIDAS scores ($p = 0.002$) (Supplementary Table 2).

Adverse events

Ten patients (5.5%) reported at least one treatment-emergent adverse event (Table 5), most commonly constipation or nausea, either alone or in combination. Two patients (1.6%) discontinued treatment due to nausea and constipation, which were considered treatment related. One patient discontinued due to hypertension, deemed unrelated to the treatment.

Patients with Prior Anti-CGRP mAb treatment failure: subgroup analysis

Among the 183 patients enrolled at baseline, 76 (41.5%) had previously failed treatment with anti-CGRP mAbs. Compared to the rest of the cohort, this subgroup had a lower HFEM-to-CM ratio ($p = 0.033$), younger age at onset ($p < 0.005$), higher baseline MMD ($p < 0.001$) and MHD ($p < 0.001$), more frequent medication overuse ($p < 0.021$), a higher number of prior treatment failures ($p < 0.001$) – including a trend toward significance for onabotulinumtoxinA ($p = 0.050$), and higher rates of psychiatric comorbidities ($p = 0.004$) (Supplementary Table 3). Of these 76 patients, 34 completed at least 12 weeks of follow-up (Supplementary Table 4). This subgroup showed statistically significant improvements (p

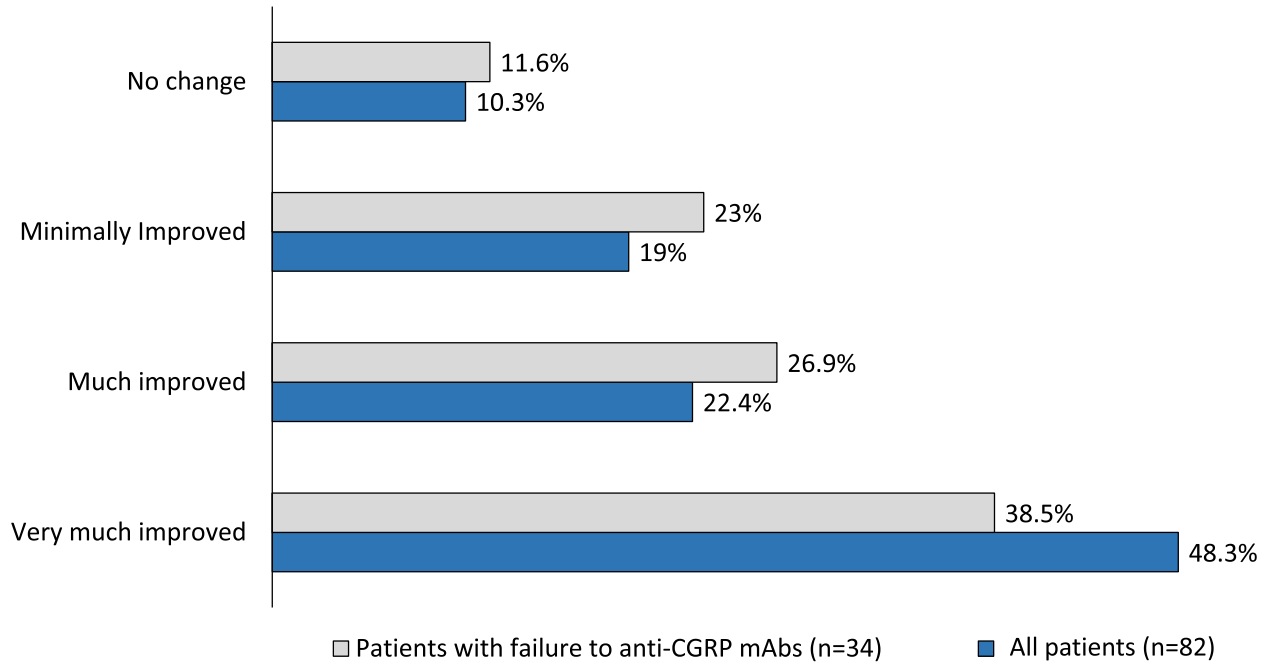


Fig. 4 Patient Global Impression of Change (PGIC) at weeks 9–12 in the overall patient population (all patients; $n = 82$, blue bars), in patients with prior failure to monoclonal antibodies targeting CGRP pathway (anti-CGRP mAbs; $n = 34$, gray bars)

Table 3 Change in migraine frequency during the first week of treatment versus the last week before treatment in the 82 patients who completed the 12-week follow-up

	All ($n = 82$)	HFEM ($n = 35$)	CM ($n = 47$)
Migraine days during last week before treatment	4.3 ±1.9	2.5±0.7	5.7±1.4
Migraine days during the first week of treatment	2.2±2.3	1.0±1.2	2.8 ±2.4
Δ	-2.5±2.0	-1.5±0.5	-3.1±2.1
p-value	<0.001	<0.001	<0.001

Abbreviations: *All* overall migraine population, *HFE* high-frequency episodic migraine, *CM* chronic migraine

* *p*-value of nonparametric test for two paired samples

<0.001) across all outcome measures, including reductions in MMD/MHD (−8.9 days), MAI (−9.8), NRS (−2.5), HIT-6 (−12.7), MIDAS (−68.9) and MIBS-4 (−4.8) (Table 6). The proportion of patients achieving ≥50%, ≥75% response rates were 52.9% and 23.5%, respectively, with higher values in the HFEM subgroup (88.9% and 33.3%) compared to CM (44.0% and 20.0%) (Fig. 5).

Discussion

The GIANT study provides the first real-world evidence on the effectiveness, safety and tolerability of atogepant for the prevention of HFEM and CM in a multicenter Italian cohort. These findings confirm and expand upon the efficacy and tolerability outcomes reported in RCTs, offering valuable insights into the drug's performance in clinical practice. The study population comprised patients with complex migraine

Table 4 Comparison of clinical and demographic features based on ≥50% and ≥75% response rates in the 82 patients who completed the 12-week follow-up

Variables	Number (%) or mean±SD			Number (%) or mean±SD		
	<50% RR	≥50% RR	*p*-value	<75% RR	≥75% RR	*p*-value
Patients	**28**	**54**		**52**	**30**	
Age, *yrs*	44.4±16.4	45.8±13.8	0.717	44.7±16.4	46.5±11.3	0.780
Females	27 (96.4)	48 (88.9)	0.247	48 (92.3)	27 (90.0)	0.719
BMI	23.5±3.4	233±3.3	0.899	23.5±3.4	23.1±3.3	0.622
Age at onset, *yrs*	14.1±5.2	15.7±6.9	0.518	15.2±6.5	14.9±6.5	0.843
Disease duration, *yrs*	30.3±15.7	30.0±13.9	0.996	29.5±16.0	31.1±11.5	0.767
MHD+MMD	19.5±8.6	16.3±7.1	0.073	18.5±8.1	15.4±6.8	0.105
NRS score	8±1.1	8.1±1.0	0.609	7.9±1.0	8.2±1.0	0.276
Unilateral pain	2 (7.1)	9 (16.7)	0.230	6 (54.5)	5 (16.7)	0.512
UAS	12 (43.0)	17 (31.5)	0.307	19 (36.5)	10 (33.3)	0.770
CAPS	1.3±1.6	1.1±2.0	0.426	1.0±5.4	1.3±2.4	0.935
Allodynia	4 (14.3)	10 (18.5)	0.629	9 (17.3)	5 (16.7)	0.941
ASC-12	2.5±3.6	2.1±3.8	0.498	2.7±3.7	1.7±3.9	0.071
Dopaminergic symptoms	11 (39.3)	13 (24.1)	0.15	19 (36.5)	5 (16.7)	0.057
MAI	19.6±10.4	17.9±10.7	0.361	18.9±11.4	17.8±8.8	0.792
Pts using concomitant prophylaxis	11 (39.3)	16 (29.6)	0.378	19 (36.5)	8 (26.7)	0.360
Prior treatment failures	4.9±2.5	4.1±2.3	0.087	4.9±2.6	3.3±1.7	0.001
Pts with prior treatment failures with CGRP-mAbs	16 (57.1)	18 (33.3)	0.038	28 (50.0)	8 (26.7)	0.039
Pts with prior treatment failure to OnabotulinumtoxinA	5 (62.5)	6 (66.7)	0.627	9 (64.3)	2 (66.7)	0.938
Pts with >1 comorbidity	21 (75.0)	27 (50.0)	0.029	36 (69.2)	12 (40.0)	0.010
Pts with psychiatric comorbidities	14 (50.0)	13 (24.1)	0.018	23 (44.2)	4 (13.3)	0.004
HIT-6	65.3±10.1	64.0±9.1	0.236	65.4±8.7	62.8±10.5	0.120
MIDAS	105.0±89.4	73.1±66.1	0.060	87.1±76.1	78.8±76.8	0.349
MIBS-4	9.5±3.7	9.0±3.3	0.387	9.3±3.4	8.9±3.6	0.606

Abbreviations: *RR* response rate: reduction in migraine frequency from baseline to weeks 9-12; *BMI* Body Mass Index, *MHD* monthly headache days, *MMD* monthly migraine days, *MAI* analgesic doses taken per month, *NRS* Numeric Rating Scale, *UAS* unilateral cranial autonomic symptoms, *CAPS* Cranial Autonomic Parasympathetic Symptom Scale, *ASC-12* Allodynia Symptom Checklist, *Dopaminergic symptoms*, presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis, *HIT-6* Headache Impact Test-6, *MIDAS* Migraine Disability Assessment Scale, *MIBS-4* Migraine Interictal Burden Scale-4

Table 5 Treatment-emergent adverse event (TEAEs) emerged among the 183 subjects enrolled (safety population

	N (%)	Grade[a] *(according to Hartwig SC, et al [17])*		
Patients with TEAEs	10/183 (5.5)	I	II	III
• *Constipation*	5 (2.7)	2	3	2
• *Nausea*	2 (1.1)	1	1	
• *Constipation and nausea*	2 (1.1)		1	
• *Hypertension*	1 (0.5)			
Discontinuations due to TEAEs	3 (1.6)[b]			

[a] Grade I: the adverse event occurs without requiring any adjustment to the current pharmacological therapy; Grade II: the adverse event necessitates discontinuation of the drug or adjustment of its dosage. No supplementary treatment or antidote is required; Grade 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 severe nausea and constipation, which were considered treatment-related. One patient discontinued due to hypertension, which was considered unrelated to the treatment

profiles, as reflected by a mean of 4.3 prior preventive treatment failures—often including anti-CGRP mAbs—frequent medication overuse (41.5%), and a high prevalence of psychiatric comorbidities (32.9%).

At 12 weeks, atogepant 60 mg once daily led to substantial reductions in migraine frequency (MMD: −58.8%; MHD: −49.3%), along with significant improvements in pain intensity (NRS: −33.8%), monthly acute medication use (−58.9%), ictal disability (HIT-6: −20.5%; MIDAS: −72.6%), and interictal burden (MIBS-4: −58.7%). Clinical benefit was already detectable within the first week of treatment, an attribute that may enhance adherence and patient engagement, especially in individuals with previous treatment failures. Patient-reported satisfaction was high, with 70.7% describing themselves as"much improved"or"very much improved"on the PGIC. Adverse events were uncommon (5.5%), primarily involving nausea and constipation, leading to treatment discontinuation in 1.6% of the cohort.

The ≥ 50% response rate observed in this real-world cohort (65.9%) exceeds that reported in the ELEVATE trial (51%) [10], despite the inclusion of a more challenging population. Notably, 41.5% of our patients had previously failed treatment with anti-CGRP mAbs—typically an exclusion criterion in RCTs—yet 52.9% of them still achieved a ≥ 50% response rate. Among those naïve to anti-CGRP mAbs, response rates were even more striking (≥ 50% in 75%, ≥ 75% in 45.8%, and 100% in 10%). This apparent superiority of real-world effectiveness compared to RCT efficacy—also observed for anti-CGRP mAbs—may reflect enhanced placebo responses or higher CGRP pathway activation in real-world populations [18].

Clinically relevant outcomes included also the reversion from CM to episodic migraine in nearly 75% of patients and the resolution of medication overuse in over two-thirds within 12 weeks. These findings support the role of atogepant in addressing factors such as central sensitization and maladaptive neuroplasticity that sustain migraine chronification. Finally, univariate analyses

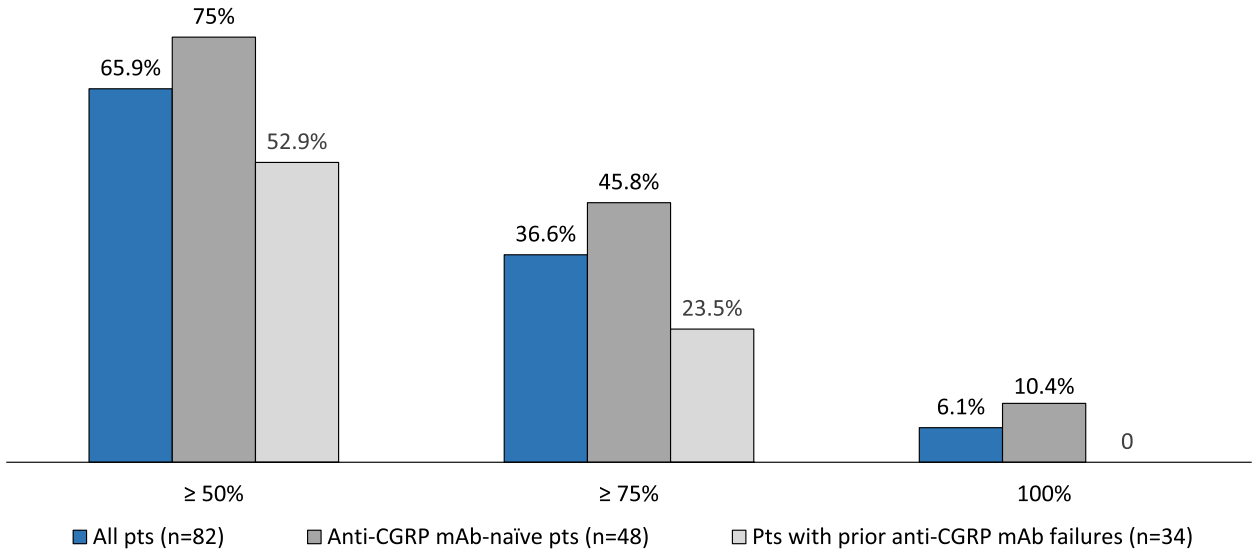


Fig. 5 Response rates at weeks 9–12 in the overall migraine population (all patients, *n* = 82), patients naïve to anti-CGRP mAbs (*n* = 48) and individuals with prior anti-CGRP mAb failures (*n* = 34). ≥ 50% responders: proportion of patients with a ≥ 50% reduction in monthly migraine/headache days 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 6 Change in clinical outcomes from baseline to weeks 9-12 in the 34 patients with prior anti-CGRP mAb treatment failure among the 82 who completed the 12-week follow-up

Clinical outcomes	Baseline	Week 9-12	Δ	*p*-value*
MMD/MHD	21.5±7.7	12.6±9.5	-8.9±7.3	<0.001
MAI	19.5±10.6	9.4±9.2	-9.8±9.7	<0.001
NRS	8.0±0.8	5.5±1.7	-2.5±1.9	<0.001
HIT-6	67.3±7.6	54.6±10.9	-12.7±11.8	<0.001
MIDAS	102.9±82.5	34.0±36.0	-68.9±64.8	<0.001
MIBS-4	9.5±3.4	4.7±3.8	-4.8±4.2	<0.001

Abbreviations: Δ, difference between baseline and weeks 9–12; *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, *MIBS-4* Migraine Interictal Burden Scale

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

identified prior treatment history and comorbidities, particularly psychiatric disorders, as key predictors of clinical response. Patients with fewer previous preventive failures and no psychiatric disorders showed higher odds of achieving ≥ 50% and ≥ 75% responses, highlighting the value of early, personalized intervention and integrated care strategies that address psychiatric burden.

The clinical benefit to atogepant in patients previously unresponsive to anti-CGRP mAbs should be interpreted with caution. Potential explanations include a carry-over effect or a late/ultra-late response to prior treatments [19]. Nevertheless, pooled RCT data indicate that atogepant demonstrates the highest therapeutic gain over placebo in patients with two to four prior preventive failures as regards ≥ 50% response rate (33%) compared to erenumab (16%), galcanezumab (24.4%), fremanezumab (25%) and eptinezumab (29%) [10, 20–23]. Atogepant also appears to have a numerically lower number needed to treat relative to other CGRP-pathway-targeting preventives, offering comparable efficacy to anti-CGRP mAbs [24].

The efficacy of atogepant in mAb-refractory patients may also reflect its distinct molecular mechanism [25]. Unlike ligand-binding mAbs, which neutralize extracellular CGRP, and differently from erenumab—which binds the CGRP receptor but is degraded after internalization—atogepant is co-internalized with the receptor and continues to block CGRP signaling within endosomes. This property may extend its inhibitory effect beyond surface receptor interaction and contribute to its therapeutic benefit in difficult-to-treat cases [26, 27].

The study's strengths include its prospective, multicenter design across Northern, Central, and Southern Italy, enhancing representativeness and generalizability of the findings. Consecutive patient enrollment minimized selection bias, and the use of a shared, platform-based electronic case report form ensured uniform data collection. Importantly, the dataset originates from a national headache registry, reinforcing its methodological rigor and real-world relevance. Lastly, we provide data on the effectiveness of atogepant in patients with prior failures to anti-CGRP mAbs, pain intensity and interictal disability, and on patients ' satisfaction, features non considered in RCTs.

However, some potential limitations should be acknowledged. First, the exclusion of patients with fewer than 8 MMD—due to AIFA reimbursement constraints—limits applicability to lower-frequency migraine populations. Second, the study sample included more CM than HFEM patients, limiting the extrapolation to the latter group. Third, the small sample size and the short 12-week follow-up preclude firm conclusions on long-term safety and effectiveness. Finally, the lack of electronic headache diaries represents a potential source of recall bias.

In conclusion, the GIANT study documents the effectiveness, safety, and tolerability of atogepant for the prevention of HFEM and CM in a real-world population with multiple therapeutic failures and comorbidities. These findings extend RCT evidence by demonstrating early onset of effect, reductions in pain intensity and interictal disability, benefits in prior mAb non-responders, and high patient-reported satisfaction. Further large-scale studies are warranted to confirm these results and to better define the place of atogepant within individualized migraine treatment strategies.

Abbreviations

CGRP	Calcitonin gene-related peptide
mAbs	Monoclonal antibodies
CM	Chronic migraine
RCTs	Randomized controlled trials
GIANT	AtoGepant IN reAl life in iTaly
HFEM	High-frequency episodic migraine
I-GRAINE	Italian miGRAINe rEgistry
AIFA	Italian Medicines Agency
NRS	Numerical Rating Scale
MAI	Monthly analgesic intake
HIT-6	Headache Impact Test
MIDAS	Migraine Disability Assessment Scale
MIBS-4	Migraine Interictal Burden Scale
PGIC	Patient Global Impression of Change
MMD	Monthly migraine days
MHD	Monthly headache days
SD	Standard deviation
RR	Response rates
BMI	body mass index
UAS	unilateral cranial autonomic symptoms
CAPS	Cranial Autonomic Parasympathetic Symptom Scale
ASC-12	Allodynia Symptom Checklist

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-02068-2.

Additional file 1.

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Authors' contributions
PB, GE, PT and AM designed the study, PB and GE drafted the manuscript, AM and SB carried out data analysis, GE, CA, PT, FP, SS, PS, SR, AS, FF, AG, MA, SM, AD, LDC, MZ, AR, LB, MA, CC, FB, PB, RV, VD, GF, CT AND Italian Migraine Registry (I-GRAINE) study group performed data collection, PB, GE and SB revised the manuscript. The author(s) read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All patients provided written informed consent prior to participation.
The study was conducted in accordance with the Declaration of Helsinki, approved by the Lazio 5 Institutional Review Board (approval number 0003898), and mutually recognized by the ethics committees of all participating centers.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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