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ORIGINAL RESEARCH

Long-Term Effectiveness of Galcanezumab in the Prevention of Migraine: An Italian Retrospective Analysis (REALITY)

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ABSTRACT

Background: Galcanezumab is approved in the European Union (EU) as migraine prophylaxis in adults with at least four migraine days per month. The aim of this retrospective observational study was to evaluate the long-term effectiveness of galcanezumab on migraine-related burdens and its impact on the use of healthcare resources for migraine prophylaxis in an Italian setting.

Methods: This retrospective study was conducted in patients with migraine who initiated treatment with galcanezumab for migraine prevention between September 2019 and December 2020. Patient data for monthly

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migraine days (MMDs) and MMDs with acute medication intake were obtained by medical chart reviews. Information on patient-reported outcomes (using the Migraine Disability Assessment [MIDAS] questionnaire and Headache Impact Test 6 [HIT-6] questionnaire) and on the use of healthcare resources were also collected. The time points of interest were 1, 3, 6, 9, 12 months after the initiation of galcanezumab, and the most recent time point available during follow-up.

Results: A total of 207 patients were enrolled in the study. Starting from month 3 after treatment initiation, more than half of the patients presented at least a 50% reduction in MMDs, and approximately one-third of non-responders at month 3 became responders at month 6. From month 3 to month 12, MMDs decreased on average by 10 days. Headache impact and disability, as well as migraine-associated health resource utilization decreased significantly during the treatment period. A positive significant association among the three dimensions of clinical burden (MMDs, MIDAS and days of acute medication intake) was also observed.

Conclusion: The results of this Italian real-world study confirmed that galcanezumab has a rapid onset of effect and provides a long-term response among patients over different migraine-related burdens. The use of healthcare resources was also remarkably reduced.

Keywords: Galcanezumab; Migraine; Migraine prevention; Calcitonin gene-related peptide; Monoclonal antibodies; Long-term treatment

Key Summary Points

Why carry out this study?

Real-world studies assessing the long-term effectiveness of galcanezumab in migraine prevention are limited. The REALITY study thus aimed to provide an understanding of the long-term effectiveness of galcanezumab among patients with migraine in Italy,

The effect of galcanezumab on migraine-related burdens and its impact on the use of healthcare resources for migraine prophylaxis was studied.

What was learned from the study?

The results of the study confirmed that galcanezumab has a rapid onset of effect and provides a long-term response, including reduction in the number of migraines monthly, improvement in migraine-related disability, and reduction in healthcare resource use.

Maintenance of galcanezumab effect was observed with continued use, and previous treatment failures were associated with low response rate.

Patients in the REALITY study were the very first patients to be treated with galcanezumab in the real-world setting in Italy (prior to the Italian Medicines Agency's establishment of criteria for reimbursement)

INTRODUCTION

Migraine is a common neurological disorder with a global prevalence of over 10% [1]. It is an episodic and complex sensory processing disturbance associated with a range of symptoms, with headache being the hallmark [2]. Among migraine patients, approximately one-third experience ≥ 4 headache days per month, and approximately one-tenth experience ≥ 15 headache days per month [3]. Migraine attacks compromise patients' mental and physical health, consequently leading to substantial personal, economic, and societal burdens, including reduced quality of life (QoL), loss of work productivity, and increased healthcare resource utilization [3].

Acute treatments are commonly used for patients who experience migraine attacks, and for those whose QoL is still impaired despite optimized acute therapy, additional preventive treatments are indicated [4]. However, in the

past, migraine prevention has been based on non-specific drugs, and it was only in the last decade that targeting the calcitonin gene-related peptide (CGRP) has emerged as a mechanism for preventing migraine attacks [5]. Galcanezumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to the CGRP ligand and prevents its biological activity, which has been approved in the European Union (EU) since 2018 for the indication of migraine in adults who have at least four migraine days per month [6]. Its efficacy has been published previously in multiple phase 3 studies (EVOLVE-1, EVOLVE-2, and REGAIN trials) [7], and it has also demonstrated efficacy in migraine patients who had previously failed multiple preventive medications [8, 9].

The effectiveness of galcanezumab in real-world practice has been investigated. In one study, 76.5% of patients experiencing episodic migraine (EM) and 63.5% of patients with chronic migraine (CM) from 16 Italian centers demonstrated a $\geq$ 50% in reduction in the number of monthly migraine days (MMDs) after 12 months of therapy [10]. Nonetheless, studies conducted in the real-world setting assessing the long-term effectiveness of galcanezumab in migraine prevention are still scarce. REALITY is an Italian observation study assessing the long-term effectiveness of galcanezumab and its impact on the use of healthcare resources for the prevention of migraine.

METHODS

Study Design

A retrospective observational cohort study was conducted in patients with a diagnosis of migraine who started on galcanezumab as part of routine clinical care between September 2019 and December 2020 in Italy. Patients aged $\geq$ 18 years with the diagnosis of migraine (CM or EM), with or without aura and with or without medication overuse (according to the International Classification of Headache Disorders-3rd edition [ICHD-3] guidelines [11]) were included in the study. Patients were followed-up for 12 months from the start of treatment with galcanezumab, and the 1, 3, 6, 9, and 12-month time points (after starting galcanezumab) were the time points of interest. Data from month 1 to 3 after treatment interruption following the 12 months of galcanezumab therapy were also collected when available, being reported as the "most recent time point." Data were collected between 17 January 2022 and 31 May 2022.

Data Collection

Patients attending the involved sites recorded the information about their headache history via paper diary, which was transferred to their clinical records during standard visits. Patient data was retrieved by medical chart review method.

Endpoints

Primary endpoints included the proportion of patients achieving at least a 50% reduction from baseline in the average number of MMDs, the change from baseline in the average number of MMDs, and the change from baseline in MMDs with acute medication intake (the average number of days in a month with symptomatic drugs taken for migraine-specific acute headache) after 1, 3, 6, 9, and 12 months of galcanezumab treatment.

Secondary endpoints included the mean number of MMDs after 3 months of galcanezumab interruption, the mean difference from baseline in the average Headache Impact Test-6 (HIT-6) score after 1 month of treatment, and the mean difference from baseline in the average Migraine Disability Assessment (MIDAS) score and HIT-6 score after 3, 6, 9, and 12 months of galcanezumab treatment. Usage of concomitant treatments and healthcare resource utilization (HCRU) related to drug treatments, diagnostic/imaging tests, specialist and non-specialist visits, hospitalizations, and emergency room (ER) access was also evaluated. In addition, the potential predictors of clinical response to galcanezumab treatment and the association among the dimensions of clinical burden were assessed.

Statistical Analysis

Demographic and baseline characteristics are descriptively summarized. Continuous variables are summarized by the mean ± standard deviation (SD), median, first and third quartiles, and minimum and maximum. Categorical data are presented as absolute and relative frequencies (*n* and %) or contingency tables. Descriptive statistics are used to provide summary measures of cohort outcomes at baseline and at 1 (± 1 week), 3 (± 4 weeks), 6 (± 4 weeks), 9 (± 4 weeks), and 12 (± 4 weeks) months. Response is defined as a ≥ 50% reduction from baseline in the number of MMDs. Odds ratio (OR) and 95% confidence intervals (CIs) are computed. Potential predictors of response to galcanezumab treatment are investigated by means of a univariate logistic model, and the predictors found in the model to be statistically significant at the 10% level were entered in a multivariable logistic regression model. Clinical burden at each time point is evaluated through Spearman's correlation index. Subgroup analysis by age, frequency of migraine, and medication overuse are presented. Results are presented as a complete case analysis, and an additional sensitivity analysis was performed by applying multiple imputation (MI) and last observation carried forward (LOCF) methods to evaluate the impact of incompleteness of the data for the primary endpoint.

All statistical tables, listings, and analyses were produced using SAS® release 9.4 or later software (SAS Institute, Inc, Cary, NC, USA).

Standard Protocol Approvals, Registrations, and Patient Consent

The study was conducted based on the guidelines outlined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), in accordance with the Declaration of Helsinki of 1964 and its later amendments, Good Pharmacoepidemiology Practices (GPPs), and the regulatory guidelines of the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]). The study protocol was approved by the Ethical Review Board of the local committee of each participating sites (including Comitato Etico dell'Universita Campus Bio-Medico Di Roma, Comitato Etico Fondazione IRCCS Policlinico San Matteo Pavia, Comitato Etico di Area Vasta Emilia Centro CE-AVEC, Comitato Etico dell'Area Vasta Emilia Nord, Comitato Etico Regione Toscana-Area Vasta Centro c/o Azienda Ospedaliero-Universitaria Careggi, Comitato Etico della Provincia di Brescia, Comitato Etico IRCSS San Raffaele Roma, Comitato Etico Universita' Vanvitelli Di Napoli, Comitato Etico I.N.M. Neuromed, and Comitato Etico Milano Area 1 c/o ASST FBF Sacco-P.O.L. Sacco). Written informed consent was obtained from each participant before inclusion in the study. Consent was also obtained for the use of the participant's personal data for scientific publications in a strictly anonymous and/or aggregated format.

RESULTS

Respondents' Disposition and Sociodemographic and Clinical Characteristics

A total of 207 patients were included in the study. Of these, 202 (97.6%) completed the 12-month observation period, while the remaining five (2.4%) patients discontinued the study due to various reasons, including loss to follow-up. The mean (± SD) age of the patients included in the analysis was 47.6 ± 10.8 years, and the majority of patients were female (169 patients; 81.6%). The estimated body mass index (BMI) was 23.9 ± 4 kg/m^2, and more than half of the patients (119 patients, 57.5%) reported at least one comorbid condition. The most common psychiatric comorbidities (51 patients, 24.6%) were anxiety, reported in 28 patients (13.5%), and depression, reported in 27 patients (13.0%). Other comorbidities included gastrointestinal disorders (28 patients, 13.5%), vascular disorders (26 patients, 12.6%), and nervous system disorders (20 patients, 9.7%). Of the vascular comorbidities reported, hypertension (26 patients, 12.6%) was the most frequent complaint.

The patients in the study had a mean migraine onset age of 16.2 ± 8.3 years. CM and EM were diagnosed in 151 and 52 patients, respectively; 105 patients presented with medication overuse headache (MOH). One-third of the patients (32.9%) required HCRU associated with migraine in the 6 months immediately preceding treatment initiation with galcanezumab, with 49 ER visits, 50 hospitalizations, 45 visits with a general practitioner, 64 visits with a neurologist, and 47 visits with other specialists.

Out of the 207 patients, 155 (74.9%) had at least one prior acute migraine treatment, and approximately half of the patients had taken "triptans" (122 patients, 58.9%) or "non-steroidal anti-inflammatory drugs (NSAIDs)" (102 patients, 49.3%). At least one oral preventive was previously administered to 204 patients (98.6%), with the most common ones being topiramate (153 patients, 73.9%), amitriptyline (142 patients, 68.2%), flunarizine (106 patients, 51.2%), propranolol (98 patients, 47.3%), and botulinum toxin type A (98 patients, 47.3%); a small number of patients had been previously treated with erenumab (16 patients, 7.7%). The majority of patients (202 patients, 97.5%) encountered previous treatment failures with acute or preventive treatments for migraine, with 45.4% (94 patients) and 37.7% (78 patients) of them reporting three to four and more than four previous treatment failures, respectively. Table 1 provides an overview of the demographic and baseline headache characteristics in the overall population.

Proportion of Patients Achieving the Primary Outcome

In the overall population, the proportion of patients achieving the primary outcome (≥ 50% reduction from baseline in the average number of MMDs) increased over time from month 1 (93/188 patients, 49.5%) to month 3 (133/205 patients, 64.9%) and remained stable from month 6 (135/199 patients, 67.8%) to month 12 (131/185 patients, 70.8%), with the greatest improvement observed at month 12 (Fig. 1a). Approximately two-thirds of patients experienced a ≥ 50% reduction from baseline in MMDs starting from month 3. These proportions remained similar after imputing missing values using the MI procedure; among 207 evaluable patients, the combined proportion of 20 imputed datasets was equal to 48.2%, 64.6%, 67.0%, and 66.2% at months 1, 3, 6, and 12, respectively. Alternatively, with the LOCF approach, 206 evaluable patients showed response rates of 45.2%, 65.1%, 67.0% and 66.0% at months 1, 3, 6, and 12, respectively. The baseline average (± SD) number of MMDs was 19.5 ± 7.1 days and the average number of MMDs with acute medication intake was 18.4 ± 7.5 days; both values emphasize high medication overuse at baseline (Table 1). As shown in Fig. 2a–d, galcanezumab had a rapid onset of therapeutic effect, with a marked reduction from baseline values as early as month 1. From the index date to month 12, patients reported a relevant decrease in MMDs (from 19.5 ± 7.1 days to 8.2 ± 7.8 days, mean ± SD) and in MMDs with acute medication intake (from 18.4 ± 7.5 days to 7.4 ± 7.7 days). The therapeutic effect was maintained with continued therapy over the 12-month treatment period.

Non-Responders Becoming Late Responders

In the overall population, 72 patients (35.1%) failed to achieve a ≥ 50% reduction from baseline in MMDs at month 3, and these patients were categorized as "non-responders." A greater proportion of non-responders (61.1%) presented with medication overuse headache compared to responders (44.4%), and a greater proportion of non-responders (54.2%) also had experienced > 4 treatment failures compared to responders (29.3%), suggesting that the non-responders were associated with medication overuse and had a higher chance of treatment failure (Table 2). Nevertheless, among the 72 "non-responders" at month 3, almost one-third (20/72 patients, 29.4%) achieved a ≥ 50% reduction in MMDs from baseline at month 6 and were thus considered as late responders. Similar percentages were also observed at

Table 1 Baseline demographic and clinical characteristics of patients included in the study

Patient baseline demographic and clinical characteristics	Overall patient population (*N* = 207)
Demographics	
Age, years (mean ± SD)	47.6 ± 10.8
Sex, *n* (%)	
- Male	38 (18.4)
- Female	169 (81.6)
BMI, kg/m^2 (mean ± SD)	23.9 ± 4
Disease history (mean ± SD)	
Migraine onset age, years	16.2 ± 8.3
Time from diagnosis, years	14.5 ± 12.1
Comorbidities, n (%)	
Psychiatric	51 (24.6)
Surgical and medical procedures	37 (17.9)
Gastrointestinal	28 (13.5)
Vascular	26 (12.6)
Neurological	20 (9.7)
Endocrine	18 (8.7)
Metabolism and nutrition	18 (8.7)
Musculoskeletal and connective tissue	17 (8.2)
Reproductive disorders	14 (6.8)
Type of migraine diagnosis, n (%)	
Chronic migraine	151 (74.4)
Episodic migraine	52 (25.3)
Unknown	4 (1.9)
Medication overuse headache, n (%)	105 (50.7)
Previous treatment failures, n (%)	202 (97.5)
1–2	30 (14.5)
3–4	94 (45.4)
> 4	78 (37.7)
Clinical characteristics of migraine	
MMDs	
- *n* (%)	206 (99.5)
- Mean ± SD, days	19.5 ± 7.1
- Range	4; 30
MMDs with acute medications intake	
- *n* (%)	206 (99.5)
- Mean ± SD, days	18.4 ± 7.5
- Range	3; 31
MIDAS	
- *n* (%)	176 (85.1)
- Mean ± SD, days	76.5 ± 54.6
- Range	7; 270
HIT-6	
- *n* (%)	194 (93.7)
- Mean ± SD, days	67.2 ± 5.8
- Range	46; 78
Previous treatments	
Patients with at least one prior acute migraine treatment, *n* ,(%)	155 (74.9)
- Triptans, *n* (%)	122 (58.9)
- Average number of monthly triptans intake days, (mean ± SD)	14.3 ± 8.7
- NSAIDs, *n* (%)	102 (49.3)
- Average number of monthly NSAIDs intake days, (mean ± SD)	10.7 ± 9.4
Patients with at least one prior preventive migraine treatment, *n* (%)	204 (98.6)
- Topiramate	153 (73.9)
- Amitriptyline	142 (68.2)
- Flunarizine	106 (51.2)
- Propranolol	98 (47.3)
- Botulinum toxin type A	98 (47.3)

BMI Body mass index, *CM* chronic migraine, *EM* episodic migraine, *HIT-6* Headache Impact Test 6, *MIDAS* Migraine Disability Assessment score, *MMDs* monthly migraine days, *MO* medication overuse, *n* number of patients who were assessed, *N* total patient study population, *NSAIDs* nonsteroidal anti-inflammatory drugs

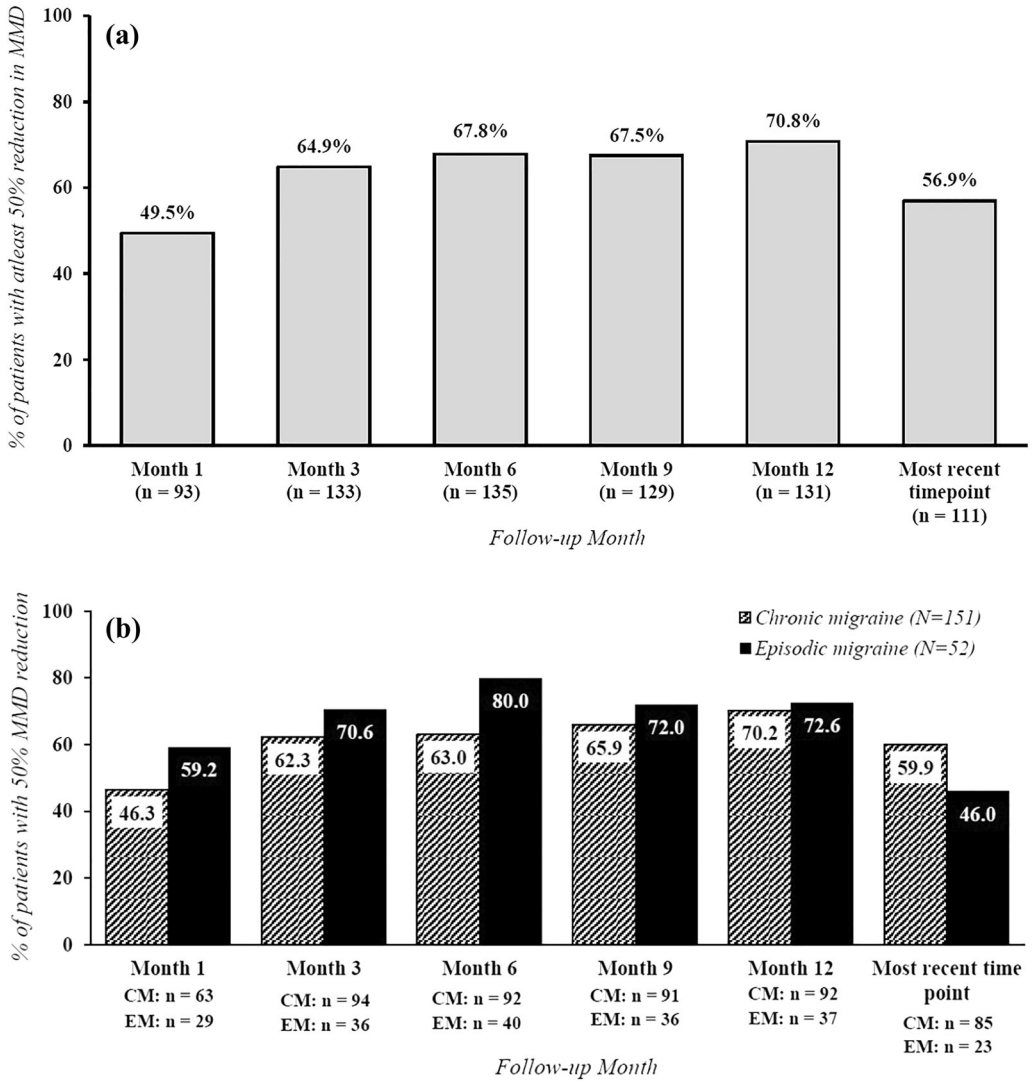


Fig. 1 Frequency of patients with at least a 50% reduction in MMDs from baseline in: **a** the overall population, defined as all included patients that had at least 1 post-baseline assessment related to the primary endpoints, and **b** patient stratified into groups according to experiencing chronic and episodic migraine at baseline. *CM* Chronic migraine, *EM* episodic migraine, *MMDs* monthly migraine days, *n* number of patients who achieved at least a 50% reduction in MMDs from baseline

subsequent time points, with 29.5% and 33.9% of patients achieving a ≥ 50% MMD reduction from baseline at month 9 and month 12, respectively (Fig. 3).

Healthcare Resource Utilization

Patient HCRU decreased markedly throughout the 1-year treatment period. Compared to baseline, at which approximately 30% of the patients needed migraine-associated HCRU, the percentage of patients needing migraine-associated HCRU, assessed based on migraine-specific ER access, hospitalization, visits with a general practitioner, visits with a neurologist, and visits with other specialists, decreased rapidly to < 2% of the patients as early as month 1 and remained fairly constant at all subsequent time points. Fifty patients were hospitalized and 49 accessed the ER during the

6 months before starting treatment; in comparison, during the 12 months of galcanezumab treatment, only seven patients were hospitalized and no patients had required ER access. These data reveal that only a small percentage of patients required HCRU throughout the study, with the highest percentage, 2.9% patients, recorded at month 1. Likewise, the number of patients undergoing imaging and laboratory tests remained low, ranging from one to two patients at each time point (Table 3).

Migraine Evolution After Treatment Interruption

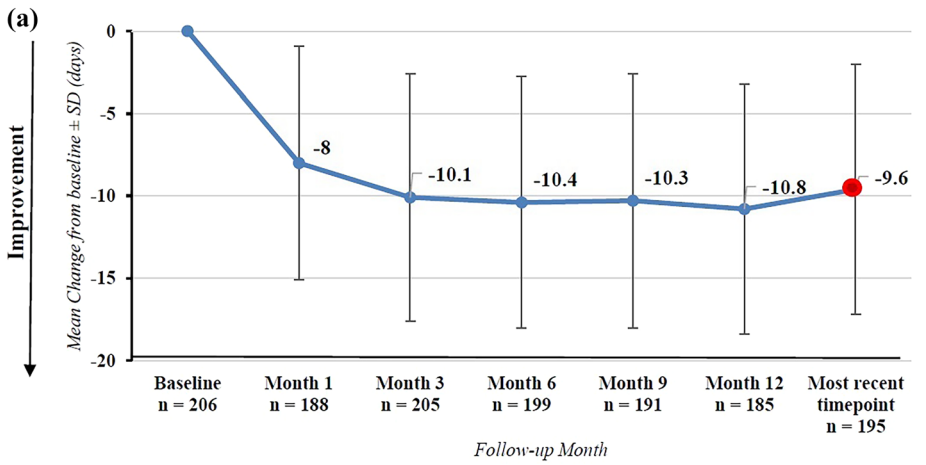
Interruption of treatment after 12 months of galcanezumab treatment was common among the patients due to reimbursement policies in Italy, with 174 (84.1%) patients interrupting their galcanezumab treatment for at least 3 months after the 12-month treatment period. With a treatment interruption of 1 to 3 months, the average number of MMDs increased from 9.7 days to 11.9 days and the average number of MMDs with acute medication intake increased slightly from 8.8 days to 11.4 days, but both values were still lower than the respective baseline value, indicating that the effect of galcanezumab persisted even after treatment interruption. Regarding healthcare resources, although the observation period was only 3 months, HCRU did not increase substantially upon galcanezumab treatment interruption: at baseline, 68 patients required migraine-associated HCRU; during the treatment period, the number of patients requiring HCRU ranged from two to six; and at the most recent time point, five patients required migraine-associated HCRU (Table 3).

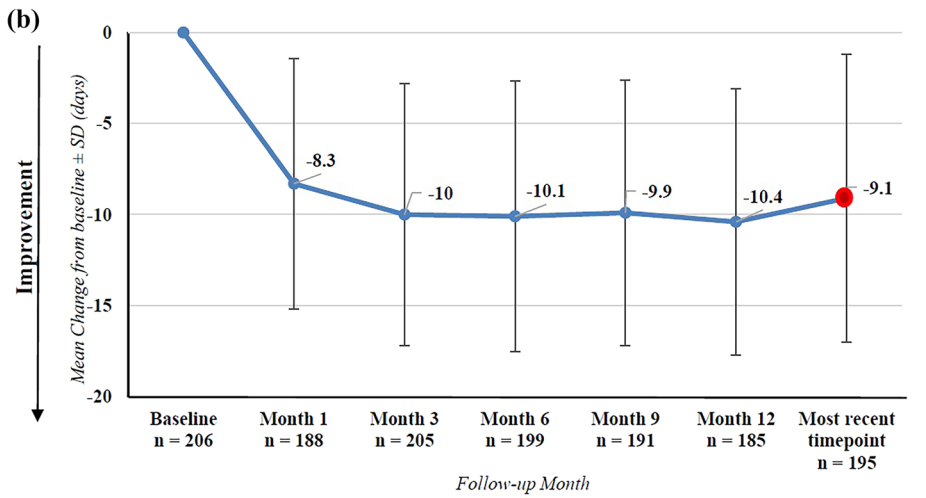
During the follow-up period after treatment interruption, the majority of patients reported administering at least one acute concomitant migraine medication (202 patients, 97.6%). Less than half of the population (90 patients, 43.5%) reported taking preventive concomitant migraine medications, such as amitriptyline (23 patients, 11.1%), topiramate (22 patients, 10.6%), and propranolol (20 patients, 9.7), which are common migraine preventives. In total, 101 patients (47.8%) reported taking at least one concomitant medication, of which the most predominant were psycholeptics, psychoanaleptics, and beta blockers, reported by 37 (17.9%), 27 patients (13.1%), and 19 patients (9.2%), respectively.

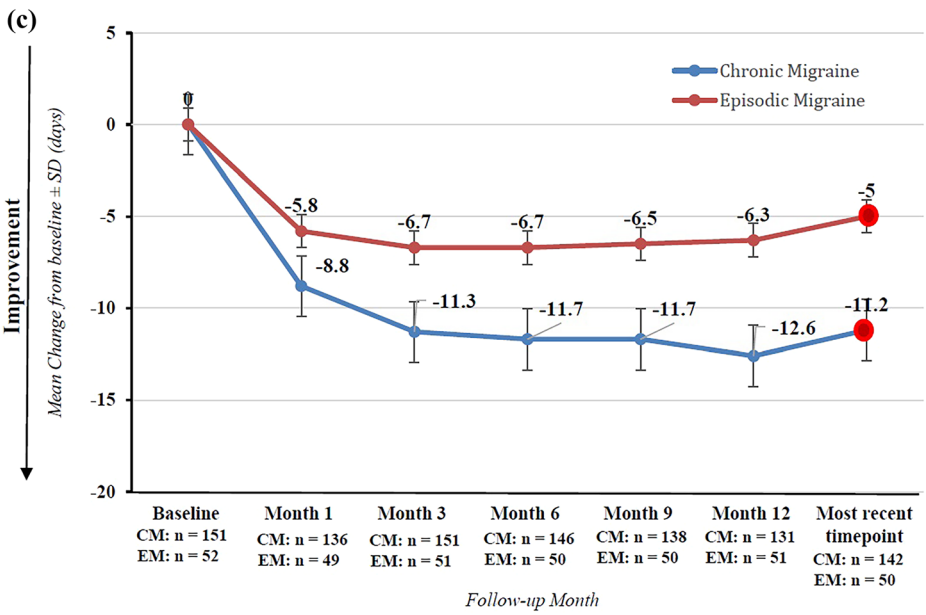
Fig. 2 Variations from baseline in MMDs (**a**), MMDs with acute medications (**b**), and by migraine frequency (**c**, **d**), respectively. Change from baseline was calculated as: post-baseline value − baseline value, and the "most recent time point" refers to either the time frame "month 13 to month 15 during follow-up" or to "1 to 3 months after galcanezumab treatment interruption." Based on the frequency of migraine, the population was stratified into chronic and episodic migraine subgroups at baseline. *CM* Chronic migraine, *EM* episodic migraine, *MMDs* monthly migraine days, *n* number of patients with mean change from baseline, *SD* standard deviation

Absolute Reduction in Migraine-related Disability: HIT-6 and MIDAS

The study participants reported a high level of migraine-related disability at baseline, as evidenced by the high average (± SD) MIDAS score (76.5 ± 54.6 points) and HIT-6 score (67.2 ± 5.8 points), with 58.0% of patients reporting very severe disability as measured by MIDAS (score ≥ 41) and 87.0% reporting severe migraine impact according to the HIT-6 score. The MIDAS score rapidly decreased after the initiation of galcanezumab use, with a mean reduction from baseline to month 3 of − 53.9. By month 12, the average MIDAS score had fallen to 19.6 ± 26.8 points, corresponding to "moderate disability" according to MIDAS score ranges, with only 7.3% of patients reporting very severe disability in terms of MIDAS (score ≥ 41). However, the MIDAS score increased slightly to 27.1 ± 34.9 during the follow-up period after treatment interruption. Similarly, by month 12, the mean HIT-6 score had dropped to 54.1 ± 9.6 points, corresponding to "moderate impact," but increased slightly to 54.9 ± 10.0 after treatment interruption. These results suggest that continued use of galcanezumab is crucial in terms of improvements


(a)
Improvement
Mean Change from baseline ± SD (days)
0
-5
-10
-15
-20
-8
-10.1
-10.4
-10.3
-10.8
-9.6
Baseline n = 206
Month 1 n = 188
Month 3 n = 205
Month 6 n = 199
Month 9 n = 191
Month 12 n = 185
Most recent timepoint n = 195
Follow-up Month


(b)
Improvement
Mean Change from baseline ± SD (days)
0
-5
-10
-15
-20
-8.3
-10
-10.1
-9.9
-10.4
-9.1
Baseline n = 206
Month 1 n = 188
Month 3 n = 205
Month 6 n = 199
Month 9 n = 191
Month 12 n = 185
Most recent timepoint n = 195
Follow-up Month


(c)
Improvement
Mean Change from baseline ± SD (days)
Chronic Migraine
Episodic Migraine
5
0
-5
-10
-15
-20
0
-5.8
-6.7
-6.7
-6.5
-6.3
-5
-8.8
-11.3
-11.7
-11.7
-12.6
-11.2
Baseline CM: n = 151 EM: n = 52
Month 1 CM: n = 136 EM: n = 49
Month 3 CM: n = 151 EM: n = 51
Month 6 CM: n = 146 EM: n = 50
Month 9 CM: n = 138 EM: n = 50
Month 12 CM: n = 131 EM: n = 51
Most recent timepoint CM: n = 142 EM: n = 50
Follow-up Month

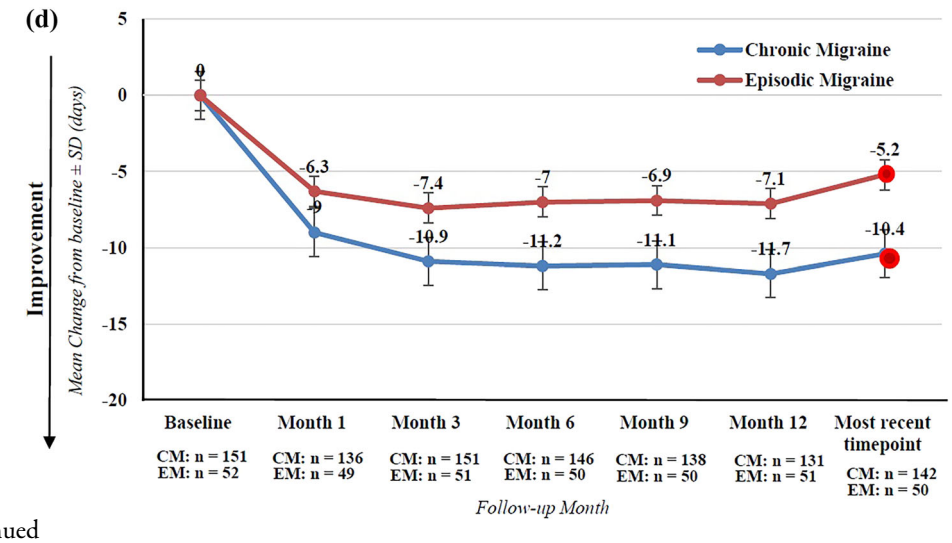


Fig. 2 continued

in disability and maintenance of the effect of this drug (Fig. 4a, b).

Predictive Factors

According to the results from the univariate logistic regression model, the most relevant predictive factor of galcanezumab response was previous treatment failures (OR 0.69, 95% CI 0.49–0.98).

Clinical Burden as a Correlation Between Migraine Frequency, MIDAS, and Use of Drugs for Acute Migraine Attacks

The analysis of clinical burden based on correlation among migraine frequency (MMDs), MIDAS, and use of drugs for acute migraine attacks showed a strong and expected association ($p < 0.0001$) between MMDs and use of drugs for acute migraine attacks at all time points (Spearman correlation coefficient ranged from 0.87 to 0.91 at different time points). A weaker but still significant correlation ($p < 0.0001$) was detected between MMDs and MIDAS (Spearman correlation coefficient varied from 0.34 to 0.57 at different time points) and between MIDAS and use of drugs for acute migraine attacks (Spearman correlation coefficient varied from 0.23 to 0.58 at different time points).

Subgroup Analysis

A subgroup analysis according to frequency of migraine was performed in which patients were stratified to the CM subgroup, defined as patients with headache occurring on ≥ 15 days per month for > 3 months, with the headache having the features of a migraine headache on at least 8 days per month, and the EM subgroup [11]. For the primary endpoint of proportion of patients with a ≥ 50% reduction in MMDs, a similar pattern of increase in the proportion was observed in both CM and EM patients, with a slightly higher response among EM patients, as illustrated in Fig. 1b. In addition, throughout the study, patients in the CM group showed a slightly greater mean reduction from baseline in MMDs and MMDs with acute medication intake compared to patients in the EM group. Regarding the migraine-related disability evaluated by MIDAS, CM patients also demonstrated a greater improvement, with a mean reduction from baseline of − 57.8 points, compared to EM patients who showed a mean reduction from baseline of − 40.1 points.

At baseline, 105 patients presented with MOH. Our results showed that a slightly higher

Table 2 Baseline demographic and clinical characteristics among overall population, responders and non-responders

Baseline demographic and clinical characteristics	Overall population (N = 207)	Responders (N = 133)[a]	Non-responders[b] (N = 72)
Demographics			
Age, years (mean ± SD)	47.6 ± 10.8	46.5 ± 10.7	49.5 ± 11
Sex, *n* (%)			
- Male	38 (18.4)	24 (18.1)	14 (19.4)
- Female	169 (81.6)	109 (82)	58 (80.6)
BMI, kg/m^2 (mean ± SD)	23.9 ± 4	23.5 ± 4.1	24.5 ± 3.6
Disease history			
Migraine onset age, years (mean ± SD)	16.2 ± 8.3	16.3 ± 8.6	15.7 ± 7.3
Time from diagnosis, years (mean ± SD)	14.5 ± 12.1	14.4 ± 11.7	15.0 ± 12.9
Comorbidities, n (%)			
Psychiatric	51 (24.6)	28 (21.05)	22 (30.6)
Surgical and medical procedures	37 (17.9)	21 (15.8)	16 (22.2)
Gastrointestinal	28 (13.5)	15 (11.3)	13 (18.1)
Vascular	26 (12.6)	13 (9.8)	13 (18.1)
Neurological	20 (9.7)	14 (10.5)	5 (6.9)
Endocrine	18 (8.7)	11 (8.3)	6 (8.3)
Metabolism and nutrition	18 (8.7)	9 (6.8)	9 (12.5)
Musculoskeletal and connective tissue	17 (8.2)	10 (7.5)	7 (9.7)
Reproductive disorders	14 (6.8)	4 (3)	10 (13.9)
Type of migraine diagnosis, n (%)			
Chronic migraine	151 (74.4)	94 (70.7)	57 (79.2)
Episodic migraine	52 (25.3)	36 (27.1)	15 (20.8)
Unknown	4 (1.9)	3 (2.3)	0
Medication Overuse headache, n (%)	105 (50.7)	59 (44.4)	44 (61.1)
Previous treatment failures, n (%)	202 (97.5)	131 (98.5)	71 (98.6)
1–2	30 (14.5)	24 (18.1)	6 (8.3)
3–4	94 (45.4)	68 (51.1)	26 (36.1)
> 4	78 (37.7)	39 (29.3)	39 (54.2)
Clinical characteristics of migraine			
MMDs			
- *n* (%)	206 (99.5)	133 (100)	72 (100)
- Mean ± SD, days	19.5 ± 7.1	18.6 ± 6.6	21.2 ± 7.8

Table 2 continued

Baseline demographic and clinical characteristics	Overall population (N = 207)	Responders (N = 133)[a]	Non-responders[b] (N = 72)
Range	4; 30	4; 30	8; 30
MMDs with acute medications			
- *n* (%)*	206 (99.5)	133 (100.)	72 (100)
- Mean ± SD, days	18.4 ± 7.5	17.6 ± 6.7	20.0 ± 8.7
- Range	3; 31	4; 31	3; 30
MIDAS			
- *n* (%)	176 (85.1)	116 (87.2)	58 (80.6)
- Mean ± SD, days	76.5 ± 54.6	69.7 ± 47.9	90.1 ± 64.5
- Range	7; 270	7; 240	12; 270
HIT-6			
- *n* (%)	194 (93.7)	126 (94.74)	67 (93.1)
- Mean ± SD, days	67.2 ± 5.8	67.2 ± 5.7	67.4 ± 6.1
- Range	46; 78	48; 78	46; 78
Previous concomitant treatments			
Patients with at least one prior acute migraine treatment, *n* (%)	155 (74.9)	106 (79.7)	48 (66.7)
- Triptans, *n* (%)	122 (58.9)	90 (67.7)	32 (44.4)
- Average number of monthly triptans intake days, (mean ± SD)	14.3 ± 8.7	14.8 ± 8.7	13.2 ± 8.7
- NSAIDs, *n* (%)	102 (49.3)	66	35
- Average number of monthly NSAIDs intake days, (mean ± SD)	10.7 ± 9.4	10 ± 9.1	12.2 ± 10
Patients with at least one prior preventive migraine treatment, *n* (%)	204 (98.6)	131 (98.5)	71 (98.6)
- Topiramate	153 (73.9)	89 (66.9)	62 (86.1)
- Amitriptyline	142 (68.2)	86 (64.6)	55 (76.4)
- Flunarizine	106 (51.2)	65 (48.8)	40 (55.6)
- Propranolol	98 (47.3)	63 (47.4)	33 (45.8)

Table 2 continued

Baseline demographic and clinical characteristics	Overall population (N = 207)	Responders (N = 133)[a]	Non-responders[b] (N = 72)
- Botulinum toxin type A	98 (47.3)	52 (39.1)	45 (62.5)

BMI Body mass index, *CM* chronic migraine, *EM* episodic migraine, *HIT-6* Headache Impact Test 6, *MIDAS* Migraine Disability Assessment score, *MMDs* monthly migraine days, *MO* medication overuse, *n* number of patients who were assessed, *N* total patient study population, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a]Responders comprise all patients with at least 50% of reduction in MMDs at month 3 respect to baseline

[b]Non-responders comprise all patients who failed to achieve at least 50% of reduction in MMDs at month 3 respect to baseline

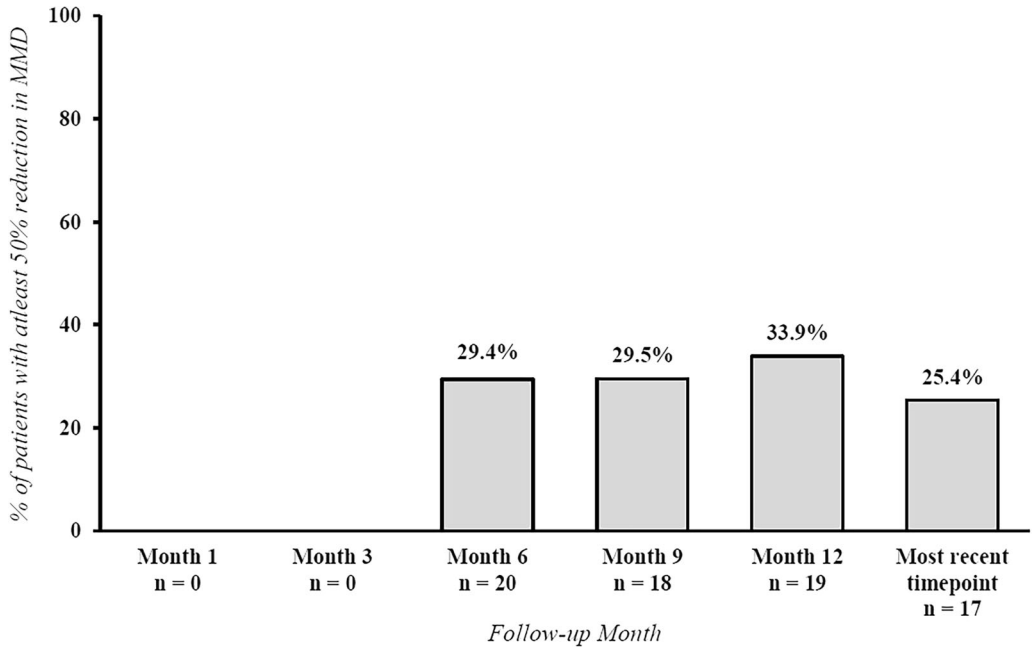


Fig. 3 Frequency of non-responders (n = 72) achieving at least a 50% reduction in MMDs from baseline during follow-up. "Most recent time point" refers to the time frame "month 13 to month 15 during follow-up" or to "1 to 3 months after galcanezumab treatment interruption". Non-responders are patients who did not achieve a 50% reduction in MMD from baseline at month 3 (72/205 patients). *MMDs* Monthly migraine days, *n* number of patients who achieved at least a 50% MMD reduction from baseline

proportion of non-MOH patients had a greater response, with > 55% and > 60% of patients in the MOH and non-MOH groups, respectively, showing a ≥ 50% MMD reduction over approximately three-quarters of the study period, as indicated in Fig. 5.

Subgroup analysis by age was also performed, and the results demonstrated that the proportion of patients achieving a ≥ 50% reduction in MMDs was slightly higher among patients aged < 40 years (n = 44) and 40–59 years (n = 141), respect to patients aged > 60 years (n = 22) at all time-points. Throughout the study, the reduction in MMDs was slightly greater in patients aged < 40 years and in patients aged 40–59 years, compared to patients

Table 3 Summary of healthcare resource utilization (HCRU) at each time point

Healthcare resource utilization	Baseline	Follow-up period					
	Index date, *n* (%)	Month 1, *n* (%)	Month 3, *n* (%)	Month 6, *n* (%)	Month 9, *n* (%)	Month 12, *n* (%)	Most recent time point, *n* (%)
Patients who required migraine-associated HCRU	68 (32.9)	6 (2.9)	4 (1.93)	3 (1.5)	5 (2.4)	2 (1)	5 (2.4)
Type of HCRU							
Visit with general practitioner	45 (21.7)	3 (1.45)	1 (0.48)	1 (0.5)	1 (0.5)	1 (0.5)	–
Visit with neurologist (in addition to the standard scheduled visits)	64 (30.9)	–	1 (0.48)	–	–	–	3 (1.5)
Visits with other specialist	47 (22.7)	3 (1.45)	2 (0.97)	–	2 (1)	–	–
ER access	49 (23.7)	–	–	–	–	–	–
Hospitalization	50 (24.2)	–	–	2 (1)	2 (1)	1 (0.5)	2 (1)
Patients who performed laboratory tests	36 (17.4)	2 (1)	–	2 (1)	2 (1)	1 (0.5)	2 (1)
Patients who performed imaging tests	27 (13.1)	1 (0.5)	–	1 (0.5)	1 (0.5)	2 (1)	1 (0.5)
Type of imaging tests							
MRI scan (including angio-MRI scan)	24 (11.6)	1 (0.5)	–	1 (0.5)	–	1 (0.5)	1 (0.5)
CT scan	2 (1)	–	–	–	1 (0.5)	–	–
Color Doppler ultrasound	3 (1.5)	–	–	–		1 (0.5)	–
Other	2 (1)	–	–	–	–	–	–

"Most recent time point" either refers to the time frame "Month 13 to Month 15 during follow-up" or "1 to 3 Months after galcanezumab treatment interruption"

CT Computed tomography, *ER* emergency room, *HCRU* healthcare resource utilization, *MRI* magnetic resonance imaging,

who were > 60 years. Nevertheless, homogeneous patterns of improvement across all age groups were observed for MIDAS. No marked variations in HCRU among age groups emerged at baseline or during follow-up.

DISCUSSION

The aim of the REALITY study described here was to examine the long-term effectiveness of galcanezumab in migraine patients in Italy, and the results confirm that galcanezumab treatment for 12 months can lead to a consistent reduction in the frequency of migraines and headache-related disability. The patients included in the study are the first patients in Italy to be treated with galcanezumab at tertiary centers; the locations of the participating centers in various regions in Italy means that the results should be geographically representative of Italian migraine patients being referred to this level of headache centers. Galcanezumab has been available in Italy from March 2019, but it was not reimbursed at that time. In fact, these first patients did not necessarily have to fulfil the reimbursement criteria (most of them received the drug directly through hospital dispensation programs before the Italian Medicines Agency established the reimbursement criteria). The

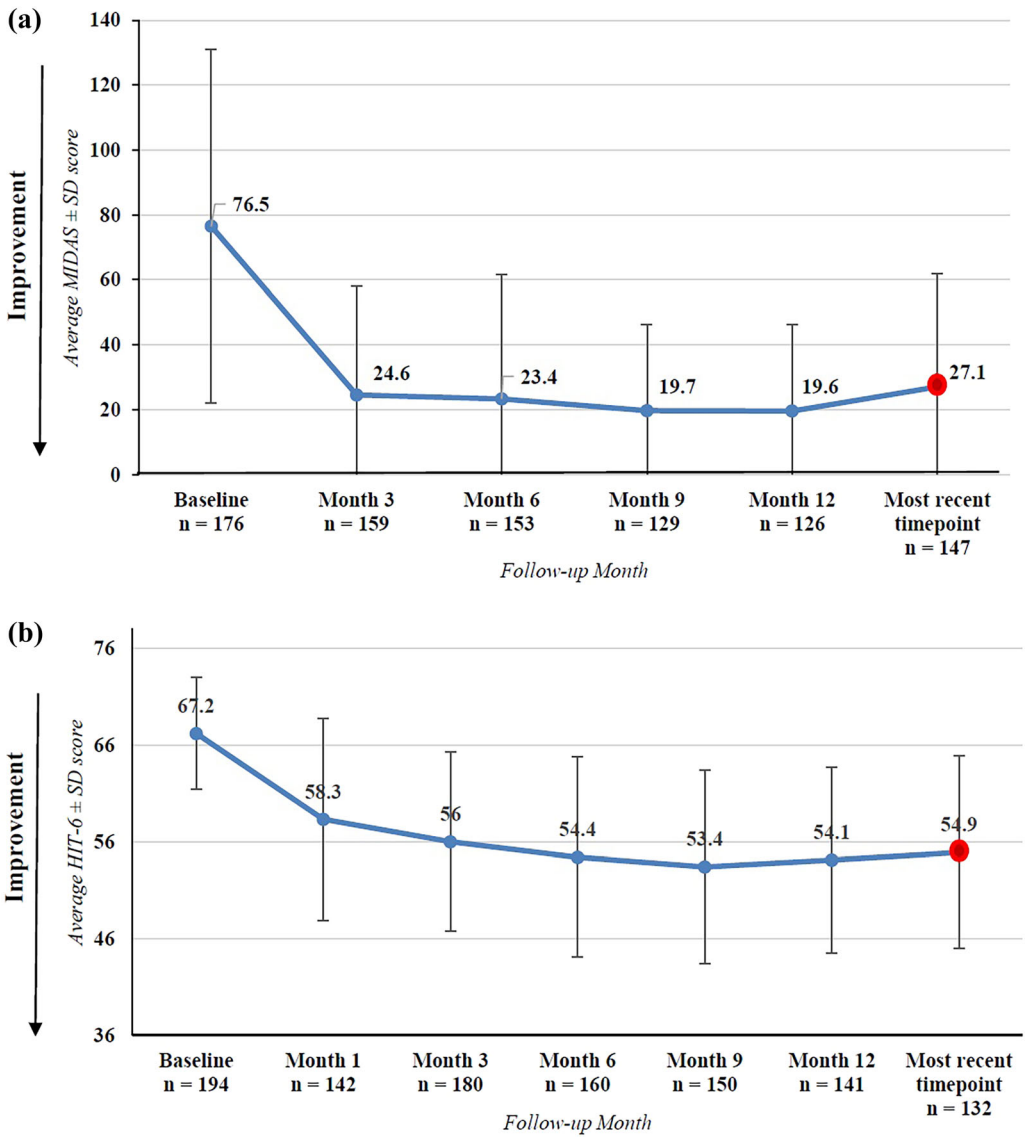


Fig. 4 Impact of galcanezumab treatment on migraine-related disability as measured by MIDAS (**a**) and HIT-6 (**b**). Change from baseline was calculated as: post-baseline value − baseline value, and the "Most recent time point" either refers to the time frame "month 13 to month 15 during follow-up" or to "1 to 3 months after galcanezumab treatment interruption." *HIT-6* Six-Item Headache Impact Test, *MIDAS* Migraine Disability Assessment, *n* number of patients with mean change from baseline, *SD* standard deviation

patient population in our study appeared to have more severe conditions, based on a higher MIDAS score at baseline (mean ± SD, 76.5 ± 54.6), than patients enrolled in the CONQUER trial (MIDAS score: 50.9–51.0), which was a double-blind, placebo-controlled phase 3b study that enrolled 462 migraine patients treated with galcanezumab [9], and based on a higher mean MMD at baseline (19.5 ± 7.1 [present study] compared with 9.1–9.2 in patients in the EVOLVE-1 and EVOLVE-2 trials [7]. In addition, in our study cohort, 202 patients (97.5%) reported previous treatment failures and 94 patients (45.4%) encountered three to four treatment failures (Table 1).

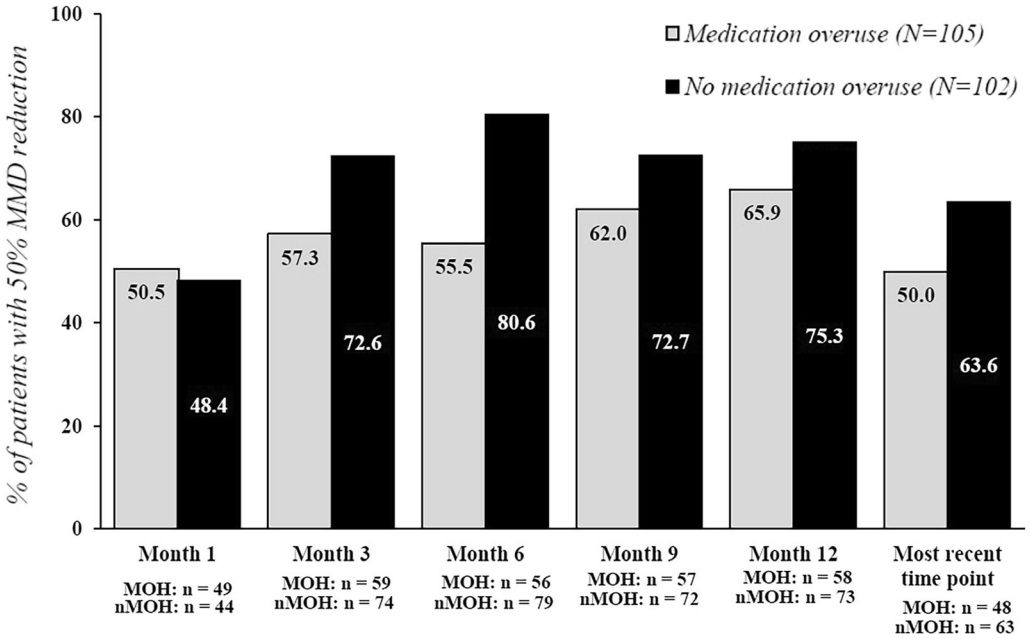


Fig. 5 Proportion of patients with at least a 50% MMD reduction by medication overuse. "Most recent time point" either refers to the time frame "month 13 to month 15 during follow-up" or "1 to 3 months after galcanezumab treatment interruption." *MMDs* Monthly migraine days, *MOH* medication overuse headache, *n* number of patients who achieved at least a 50% MMDs reduction from baseline, *nMOH* no medication overuse headache, *SD* standard deviation

The proportion of patients achieving a ≥ 50% reduction in MMDs (i.e., 50% response rate) compared to baseline is considered worldwide to be the threshold cutoff for prophylactic treatments for migraine. In the present study, more than half of the patients achieved this response within the first 3 months of treatment, and two patients out of three (66%) reached the 50% MMD response rate at every following time point considered. In two clinical trials, namely, EVOLVE-1 and EVOLVE-2, the proportions of patients treated with galcanezumab 120 mg who achieved a ≥ 50% response after 6 months were 62.3% and 59.3%, respectively [12, 13], and in the REGAIN study, 27.6% of the patients administered galcanezumab 120 mg achieved a ≥ 50% response after 3 months [14]. The response in the present real-life studies appears to be higher, at the corresponding time point, than that observed in clinical trials. Moreover, in the GARLIT study [10, 15], which was a multicenter prospective observational cohort study that evaluated the use of galcanezumab in migraine patients, a ≥ 50% reduction in MMDs at month 3 of treatment was observed in > 40% of CM patients [16] and, at month 6, in 64% and 77% of CM and EM patients, respectively [17].

A significant decrease in MMDs and MMDs with acute medication intake was observed in migraine patients treated with galcanezumab for 1 year in the REALITY study, which is similar to results reported in other studies that have investigated the effectiveness of galcanezumab for the treatment of migraine in real-world settings [10, 16–18]. The results of our study also confirmed that galcanezumab has a rapid onset, as a large reduction in MMDs occurred after the first month of treatment, followed by a further slight decrease throughout the treatment period. This result is congruent with those of the post hoc analysis of the CONQUER trial [19], which showed that galcanezumab-treated patients had a significantly greater reduction in MMDs as early as month 1, demonstrating the early onset of galcanezumab.

Interestingly, we observed that approximately one-third of patients who were non-responders at month 3 subsequently achieved a durable treatment response at a later time point. This result is in line with the findings of a previously reported real-life study [20] that investigated the late response to anti-CGRP mAbs, with the authors reporting that half of non-responders to anti-CGRP mAbs at 12 weeks became late responders (at $\leq$ 24 weeks): these patients differed from responders in terms of a higher BMI, more frequent treatment failures, psychiatric comorbidities, and less commonly, unilateral pain, alone or in combination with unilateral cranial autonomic symptoms or allodynia. The authors hypothesized that the speed of action of anti-CGRP mAbs could be slowed down in subject with bilateral pain due to a lower peripheral trigeminal sensitization and that high BMI, depression, or therapeutic failures could increase central CGRP activity, thus delaying the onset of anti-CGRP mAb effects. In fact, CGRP levels are significantly elevated in obese individuals (plasma), in patients with depression (cerebrospinal fluid), and probably also in patients with therapeutic failures due to high disability, medication overuse, and psychiatric comorbidity. These data suggest that the efficacy of galcanezumab, and perhaps the efficacy of other anti-CGRP mAbs, should be assessed at later time points, while treatment extension should be considered being that its effect not fully seen in the first 3 months of therapy.

As patients in this study were having regular physician visits as well as with the prescription of galcanezumab, fewer unscheduled visits were expected. Migraine-related HCRU should therefore be focused on such events as hospital admissions, ER access, and neuroimaging, which are less migraine-dependent factors, to distinguish the effect of galcanezumab in reducing HCRU. Indeed, we observed that migraine-related ER access, hospitalizations, and visits to general practitioners and neurologists were considerably decreased during the 12-month treatment period with galcanezumab, which is in line with findings from larger clinical trials that enrolled patients from different countries [21]. In addition, during the follow-up period after treatment interruption, the use of add-on standard preventives greatly decreased to migraine-related HCRU to approximately 40%, which is consistent with the conclusion drawn by Vernieri et al. [10]. With less HCRU and patients needing a reduced rate of migraine preventives, galcanezumab should be considered a more accessible option for migraine patients for the benefit of patients and society.

In our study, there was a slight clinical benefit to galcanezumab even with 3 months of treatment interruption, with a slight increase in MMDs (from 9.7 days to 11.9 days) and MMDs with acute medication intake (8.8 days to 11.4 days) during the 3 months of treatment interruption. However, MMDs remained lower than the baseline value, indicating a short-term persistence of the galcanezumab treatment effect even after interruption. This result is in line with the findings of other studies, which highlighted that galcanezumab treatment cessation was associated with progressive increase in migraine frequency and acute medication intake over time [22, 23], with the authors suggesting that discontinuation of anti-CGRP mAbs should be reconsidered.

Interestingly, a study by Iannone et al. revealed that approximately 25% of the patients in their study who reported a lower disability scales score before anti-CGRP mAbs treatment showed sustained effectiveness throughout a 3-month cessation period, while those with higher disability scores at baseline did not [24]. Disability scores at baseline might be helpful to individualize the anti-CGRP mAbs treatment discontinuation for patients with different characteristics.

The obvious reduction in MIDAS and HIT-6 scores in the patients in our study demonstrated that patients achieved a great improvement in migraine-related disability upon initiation of galcanezumab and that this effect persisted throughout the study (Fig. 4). These results are also congruent with the findings of Silvestro et al. [25] based on the authors' clinical experience with 43 patients using galcanezumab in an Italian real-world setting with migraine experiencing previous unsuccessful preventative treatments. The results showed that disability

scores, as measured with MIDAS scores, and HIT-6 scores were greatly reduced at month 3 and continued to fall up to month 6 [25].

In our study, there were 202 patients (97.5%) who reported previous treatment failures. Approximately 94 patients (45.4%) encountered three to four treatment failures, while 78 patients (37.7%) had experienced > 4 previous treatment failures. Of these patients with multiple treatment failures, 64.9% and 67.8% had a ≥ 50% reduction in MMDs from baseline to month 3 and month 6, respectively. Similarly, in the CONQUER study in which patients also had two to four prior treatment failures, the response rates were 38.4% and 53.6% in month 3 and month 6, respectively [21]. These findings suggest that galcanezumab may be a promising option for patients who have not responded to traditional migraine preventive medications.

It is, however, also important to keep in mind that a high number of non-successful previous prophylactic medications have been associated with poor response to galcanezumab [16, 17]. Our study confirmed that previous treatment failure(s) was associated with a low galcanezumab response rate. In addition to previous treatment failures, there is evidence that overweight and obesity, interictal allodynia, the presence of daily headaches, and psychiatric comorbidities, including depression, are predictive of a poor response to antiCGRP mAbs; conversely, good response to triptans and unilateral pain with or without unilateral autonomic symptoms are predictors of response in treated patients [26–28].

The main limitations of this study are its observational and retrospective nature, as the patients were fully informed about the active treatment. Other potential limitations include patient selection bias, incomplete or missing data, lack of internal validity, difficulty in interpreting or verifying documented information, and variability between patients in term of the quality of documentation.

CONCLUSION

The results of this multicenter retrospective study confirmed the early and persistent effectiveness of galcanezumab for the prevention of migraine in adult patients in a large population evaluated in a real-life setting. The present findings support data from both clinical trials and previous real-life studies, providing the basis for an appropriate and well-tolerated long-term patient management of migraine prevention. This study also documented a reduction in HCRU, especially for hospitalizations and ER accesses, with the use of galcanezumab.

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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

Conflict of Interest. Fabrizio Vernieri received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan/Abbvie, Amgen, Angelini, Lilly, Lundbeck, Novartis, and Teva. Luigi Francesco Iannone received consulting fees form Eli-Lilly and TEVA, payment or honoraria for lectures/presentations/speaker's bureaus/educational events from Eli-Lilly, TEVA, and Pfizer, and support for attending meetings from Lundbeck. Simona Guerzoni received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Eli-Lilly, TEVA, Pfizer, and Lundbeck. Antonio Russo reports honoraria for lectures, educational events or speaker's bureaus and support for meeting attendance and travel from, as well as advisory board membership with Novartis, Teva, Eli Lilly and Company, Allergan/Abbvie and membership of the Board of Trustee of the Italian Headache Society. Piero Barbanti received travel grants, honoraria for advisory boards, speaker panels, research support and/or clinical investigation study support from Abbvie, Alder, Allergan, Amgen, Angelini, Assosalute, Bayer, Biohaven, electroCore, Eli Lilly, Fondazione Ricerca e Salute, GSK, Lundbeck, Lusofarmaco, 1MED, MSD, New Penta, Noema Pharma, Novartis, STX-Med, Teva, Visufarma, and Zambon, and serves as President of the Italian Neurological Association for Headache Research. Grazia Sances received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Novartis, Eli Lilly, TEVA, Lundbeck, and Pfizer. Sabina Cevoli received travel grants, honoraria for advisory boards, speaker panels, and/or clinical investigation studies from Novartis, Eli Lilly, TEVA, Lundbeck, and BHV. Renata Rao received honoraria for travel grants and honoraria for advisory boards and speaker panels from Novartis, Lillly, Teva, Allergan, Lundbeck. Carlo Lovati received travel grants, honoraria for advisory boards and speaker panels, and/or clinical investigation studies from Novartis, Eli Lilly, Abbvie, Laborest, and Cristalpharma srl. Anna Ambrosini received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Novartis, Eli Lilly, TEVA and Pfizer. Carlotta Buzzoni, Federico Battisti, Laura Vatteone, and Federico Torelli are employees and minor shareholders of Eli Lilly Company.

Ethical Approval. The study was conducted based on the guidelines outlined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), in accordance with the Declaration of Helsinki of 1964 and its later amendments, Good Pharmacoepidemiology Practices (GPPs), and the regulatory guidelines of the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]). The study protocol was approved by the Ethical Review Board of the local committee of each participating site (including Comitato Etico dell'Universita Campus Bio-Medico Di Roma, Comitato Etico Fondazione IRCCS Policlinico San Matteo Pavia, Comitato Etico di Area Vasta Emilia Centro CE-AVEC, Comitato Etico dell'Area Vasta Emilia Nord, Comitato Etico Regione Toscana-Area Vasta Centro c/o Azienda Ospedaliero-Universitaria Careggi, Comitato Etico della Provincia di Brescia, Comitato Etico IRCSS San Raffaele Roma, Comitato Etico Universita' Vanvitelli Di Napoli, Comitato Etico I.N.M. Neuromed, and Comitato Etico Milano Area 1 c/o ASST FBF Sacco- P.O.L. Sacco). Written informed consent was obtained from each participant before inclusion in the study. Consent was also obtained for the use of the participant's personal data for scientific publications in a strictly anonymous and/or aggregated format.

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