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ORIGINAL RESEARCH

Observational Retrospective Study in Patients Treated with Galcanezumab as Preventive Treatment for Migraine: The ORYGAM Study

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ABSTRACT

Introduction: The efficacy of galcanezumab has been demonstrated in randomized controlled trials, but evidence about its use under clinical practice conditions is still limited. This study aimed to describe the characteristics of the patients treated with galcanezumab in routine clinical practice in Spain as well as treatment patterns, persistence, and effectiveness.

Methods: A retrospective chart review study was carried out in six hospitals. Information of adults with migraine, who started treatment with galcanezumab between November 2019 and September 2021, was analyzed until end or loss of follow-up. Continuous variables were described as mean (standard deviation, SD) and

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median (interquartile range, IQR), and categorical variables as frequency and percentages. Persistence to treatment was estimated using Kaplan–Meier analysis.

Results: A total of 314 patients were analyzed over median follow-up period of 17.5 months (13.8–20.7), with a mean age of 46.3 (12.6), 85% women, 80.6% chronic migraine, and reporting a mean of monthly migraine days of 16.7 (7.8). Overall, 72.9% had comorbid conditions, with anxiety and depression disorders being the most frequent. More than 60% had received ≥ 6 previous preventive drugs, the most common being antiepileptics, antidepressants, and botulinum toxin (95.2%, 89.8% and 84.1%, respectively). Overall, 60.3% of the patients with other preventive treatments maintained them after galcanezumab initiation. The median time on galcanezumab was 14.6 months (9.4–22.8); 95.7%, 82.0%, 76.2% and 59.8% of patients were persistent to treatment at 3, 6, 9 and 12 months, respectively. Of the patients who discontinued (151: 48.1%), 57.6% were due to lack of effectiveness and 31.1% were due to improvement in migraine. The average reduction of monthly migraine days at 3, 6, 9 and 12 months was 7.9 (7.2), 9.1 (7.5), 8.8 (6.6) and 9.0 (6.9) days, respectively.

Conclusions: In real clinical practice, galcanezumab is an effective treatment and has a high persistence in patients with migraine, mostly chronic and with multiple use of previous preventive treatments.

Keywords: Antibody; Calcitonin gene-related peptide; Galcanezumab; Migraine; Persistence; Real-life

Key Summary Points

Why carry out this study?

Galcanezumab is a calcitonin gene-related peptide mAb indicated for the prevention of migraine. Clinical trials showed good efficacy and a favorable safety profile. However, there is limited published information on the use of galcanezumab in clinical practice.

This study showed the main characteristics of the patients receiving galcanezumab in clinical practice in Spain, as well as the main treatment patterns, persistence, reasons for discontinuation, and effectiveness.

What were the study outcomes?

Galcanezumab showed a persistence of 95.7%, 82.0%, 76.2%, and 59.8% at 3, 6, 9 and 12 months, respectively. A median time on treatment of 14.6 months (9.4–22.8) was reached. Of those patients who discontinued treatment, 57.6% were due to lack of effectiveness and 31.1% were due to improvement in migraine.

After 3, 6, 9 and 12 months of galcanezumab treatment, patients reported a reduction in monthly migraine days of 7.9 (7.2), 9.1 (7.5), 8.8 (6.6) and 9.0 (6.9) days, respectively.

What has been learned from the study?

Patients with migraine who have previously used multiple preventive treatments are likely to benefit from galcanezumab in real clinical practice as it is an effective treatment with a high persistence rate.

INTRODUCTION

Migraine is a neurologic disease described by the International Classification of Headache Disorders (ICHD-II) as a recurrent headache disorder manifesting in attacks lasting 4–72 h without treatment and with typical characteristics, such as unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia [1]. Migraine is broadly classified into episodic migraine (EM) and chronic migraine (CM). CM is defined by at least 15 headache days per month for more than 3 months, at least 8 days of which meet the criteria for a migraine attack and/or respond to symptomatic migraine-specific treatment. People with fewer than 15 headache days per month are considering having EM [1].

Migraine affects over one billion people worldwide and, in terms of burden, is recognized as the second-highest cause of years lived with disability and the highest cause in patients aged between 15 and 49 years [2]. The current best estimate of global migraine prevalence is 14–15% [3], with prevalence rates among women two to three times higher than among men [4]. The 1-year prevalence of migraine in Spain is approximately 12.6%, with variations between regions ranging from 7.6% in Navarra to 18% in the Canary Islands [5].

Migraine management includes both acute and preventive treatments. Acute migraine treatments are designed to relieve pain and restore a patient's ability to function after an individual migraine attack. In contrast, preventive migraine treatments aim to reduce attacks' frequency, severity, and duration [6].

According to the Spanish Society of Neurology, in line with other international guidelines such as the European Headache Federation, preventive migraine treatments should be considered in patients who suffer three or more migraine attacks per month, those in which the frequency is less but with prolonged duration or intensity (individual attack longer than 24 h), patients with poor response or intolerance to symptomatic migraine treatments, patients who have prolonged auras or auras with basilar symptoms, and those who experience epileptic crisis within migraine attacks. Preventive migraine treatment would also be indicated when there is an established risk of drug overuse (taking symptomatic migraine treatment two or more days per week) [7]. Nevertheless, despite these recommendations constituting a crucial component of migraine management, patients with these characteristics often do not take available preventive migraine treatments. Data have shown that 38% of patients with migraine met the criteria to be offered preventive therapy [8], and fewer than 25% continue on treatment 1 year after its initiation as a result of inconsistent or suboptimal efficacy and side effects, which results in poor adherence [9], and an increase in the healthcare resource use and costs [10].

Drug classes that are effective for preventing migraine include antiepileptics, antidepressants, beta-blockers, calcium antagonists, other antihypertensives, botulinum neurotoxin type A (BoNTA, only indicated for patients with CM), and new therapies, both monoclonal antibodies (mAbs) and oral agents, targeting the calcitonin gene-related peptide (CGRP) pathway, which has demonstrated a role in the pathophysiology of migraine [11]. The leading causes for the lack of effectiveness and poor tolerability of classical therapies are related to the fact that they were not specifically developed for migraine and that most have multiple mechanisms of action [12]. Consequently, CGRP-mAbs have become a key target among researchers for developing new innovative therapies for the preventive treatment of migraine [13, 14].

In a recent update of the European Headache Federation guidelines mAbs targeting the CGRP pathway are recommended for migraine prevention as they are effective and safe, including in the long term. In addition, the guidelines suggest that mAbs targeting the CGRP pathway should be included as a first-line treatment option [15].

Galcanezumab is a humanized CGRP-mAb that inhibits the physiological activity of CGRP, with CGRP playing a vital role in the pathophysiology of migraine and headache disorders.

The European Medicines Agency (EMA) approved galcanezumab (Emgality®) in September 2019 to treat adults with migraine and at least 4 migraine days per month. Galcanezumab has been commercially available in Spain since November 2019, although it is only reimbursed by the Spanish National Health System in patients with at least 8 migraine days per month and at least three previous treatment failures used at sufficient doses for at least 3 months (in the case of CM one of these three treatments includes BoNTA) [16, 17].

Galcanezumab was approved on the basis of three phase 3, randomized, double-blind, placebo-controlled pivotal clinical trials in people with moderate to severe migraine, one in CM (REGAIN study) [18] and two in EM (EVOLVE-1 and EVOLVE-2 studies) [19, 20]. Galcanezumab was associated with a reduction of 2 migraine days per month compared to placebo for both CM and EM. A reduction of at least 50% in the migraine days per month occurred in one out of 4–5 patients with EM and one out of eight patients with CM compared to placebo [21]. Moreover, another randomized, double-blind, placebo-controlled, phase 3 registry study (CONQUER) has shown that galcanezumab confers a significantly greater reduction in the number of migraine days per month versus placebo in patients with previous failure to multiple standard-of-care preventive migraine-specific treatments. In this study, the galcanezumab group showed, on average, 4.1 fewer migraine days per month than the baseline [22]. Therefore, data from clinical trials have shown that galcanezumab may cover an unmet need in patients who require preventive migraine treatment.

Given the recent approval and post-marketing use of galcanezumab, there is limited evidence about the real-world usual practice and treatment patterns for patients initiating this preventive migraine drug [9]. Further research is needed to determine treatment patterns, persistence, and effectiveness of galcanezumab in real-world clinical practice, including a heterogeneous migraine population (e.g., patients with comorbidities) [14].

The present study aimed to identify patient characteristics, treatment patterns, and effectiveness in patients with migraine treated with galcanezumab in usual clinical practice in Spain. Persistence and reasons for discontinuation of galcanezumab treatment were also investigated.

METHODS

Study Design and Study Population

This is a single-cohort, single-country, multicenter, descriptive, and retrospective chart review study conducted at six neurology departments of Spanish hospitals geographically distributed across the country.

The study population comprised all adult patients with confirmed migraine diagnoses in whom galcanezumab was prescribed as a preventive migraine-specific treatment from November 2019 to September 2021 (inclusion period) and with at least one complete follow-up assessment after initiation. Galcanezumab was administered subcutaneously following the summary of product characteristics (SmPC) recommendations, with an initial loading dose of 240 mg followed by 120 mg every month as recommended [15]. All patients in a clinical trial during the treatment with galcanezumab, patients who had not given consent to participate in the study (or who had refused to participate in any research study), and patients in which the medical chart was not available for data extraction were excluded.

The design of the study is shown in Fig. 1. The observation period started on the date of the first preventive migraine-specific treatment prescription and extended to the end of follow-up (date of chart review, depending on the patient) or loss to follow-up (e.g., hospital transfer, death, and all other causes of incomplete follow-up), whichever comes first. The date of the first prescription of galcanezumab was defined as the index date (baseline). The pre-index period was defined as the period from the first preventive treatment prescription to the last assessment before the index date.

The study was designed, conducted, and reported following the ethical principles set out in the Declaration of Helsinki, the Good

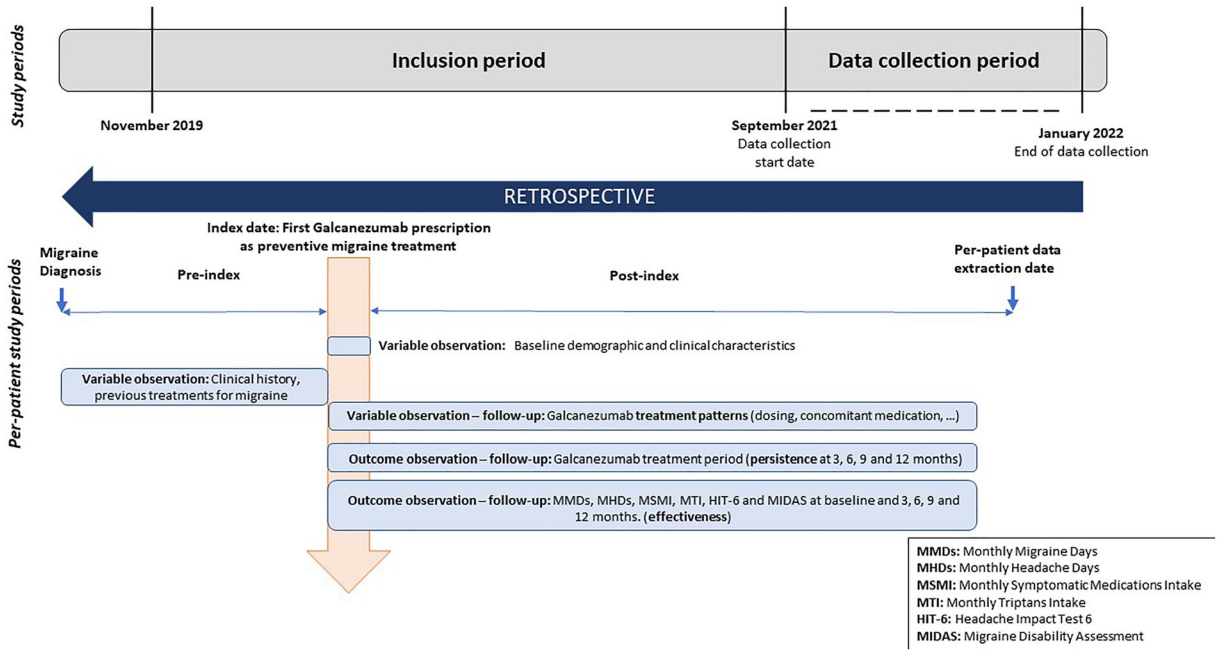

Fig. 1 Study design

Pharmacoepidemiology Practices (GPPs) guidelines of the International Society for Pharmacoepidemiology, and the local rules and regulations. The study protocol was approved by a central ethics committee (Comité de Ética de la Investigación con Medicamentos del Área de Salud Valladolid Este, Spain) and then notified to all the ethics committees of the participant centers which agreed with the conduction of the study.

Data Collection

All data was extracted directly from medical records of people with migraine by site staff within the framework of usual clinical practice. Clinical data management was performed per standards and data cleaning procedures to ensure the integrity of the data.

Outcomes

Patient Characteristics

Considering the date on which galcanezumab was prescribed, we retrospectively collected demographic data (age, sex, height, weight), comorbidities, and the following migraine characteristics: age at diagnosis, family history of migraine, migraine classification, migraine characteristics, and the presence of aura.

Treatment Patterns

Treatment patterns for galcanezumab initiators consisted of a description of all preventive and symptomatic migraine-specific treatments prescribed before, during, and after galcanezumab administration and whether galcanezumab was prescribed as monotherapy, concomitantly with other preventive treatments, added later as an add-on, and the reasons for discontinuation of galcanezumab. The index treatment regimen comprised all the drugs a patient was on ± 30 days of the index date.

Treatment Persistence

Persistence to galcanezumab was defined as the number of days of continuous therapy from the administration date until the end of the follow-up period, allowing for a maximum gap of 30 days. Permanent discontinuation was considered when galcanezumab was discontinued for more than 30 days. The rate of persistence at

specific time periods describes the frequency and percentage of patients who continue on treatment at 3, 6, 9 and 12 months with the Kaplan–Meier model.

The reasons for the discontinuation of galcanezumab based on a predetermined list of options were also collected.

Treatment Effectiveness

Effectiveness was assessed in all patients irrespective of whether they continued on galcanezumab treatment or not ("total study population"). Complementarily, as a part of a sensitivity analysis, effectiveness was also assessed in patients who continued on the treatment of galcanezumab ("population while on treatment"). Treatment effectiveness was assessed as the absolute change, calculated as the difference between the pre-index assessment minus the post-index assessment, monthly migraine days, monthly headache days, monthly symptomatic medications intake, and monthly triptans intake at month 3, 6, 9 and 12 (every 3 months within a timeframe of ± 30 days). A baseline assessment was also performed using the information collected from the 3 months before the prescription of galcanezumab and selecting the measure closest to the prescription.

In addition, other measures of disease severity, such as disability measures according to the Headache Impact Test (HIT-6) scale [23] and Migraine Disability Assessment Scale (MIDAS) questionnaire [24], were considered. Total HIT-6 scores range from 36 to 78, with four impact severity categories: severe impact (60–78), substantial impact (56–59), some impact (50–55), and little or no impact (≤ 49) [23]. Total MIDAS scores indicate the severity of disability: little or no disability (0–5), mild disability (6–10), moderate disability (11–20) and severe disability (≥ 21) [24]. Clinically meaningful changes were defined as at least a 5-point and at least a 6-point decrease for HIT-6 and MIDAS scores, respectively [25].

Sample Size

Using a confidence interval of 95% (95% CI), a sample size of approximately 250 patients allowed precision around observed percentages at 6 months ranging from 10% (± 3.9%) to 50% (± 6.4%) in a categorical variable (e.g., a preventive concomitant migraine-specific treatment prescribed to 30% will have a precision from a lower limit of 24.1% to an upper limit of 35.9%). These estimations assume a 95% confidence level and have been calculated with the Clopper-Pearson method. Similarly, 250 patients produce a two-sided 95% CI with a distance from the mean to the limits equal to 0.13 when the variable considered is a standardized normal variable N (0,1).

Statistical Methods

Statistical analyses were performed using SAS Enterprise Guide version 9.4 higher (SAS Institute, Cary, NC). Continuous variables were described as mean (standard deviation, SD) and median (interquartile range, IQR), and categorical variables as frequency and percentages. Persistence, as the time to discontinuation, and the percentage of patients who remain on treatment at a time point were based on the Kaplan–Meier models. Linear regression models were used to estimate absolute changes in the effectiveness outcomes.

RESULTS

A total of 314 patients with medical records containing sufficient information to be assessed met inclusion and exclusion criteria and were finally included in the study. Overall, 98.7% of patients had a completed follow-up, while 1.3% were lost to follow-up. The mean follow-up duration was 16.3 (5.6) months; median (Q1–Q3) 17.5 (13.8–20.7).

Characteristics of Total Study Population

Demographic and clinical characteristics of patients are described in Table 1. The mean age at the time of prescription of galcanezumab was 46.3 (12.6) years. Most of the patients were women (85%) and had CM (80.6%); 40.1% of the women suffered from menstrual-related

Table 1 Baseline demographic and clinical profile of patients

	Overall
Patients, *n* (%)	314 (100)
Age (years)	
Mean (SD)	46.3 (12.6)
Median (Q1; Q3)	46.0 (39.0; 55.0)
Sex, *n* (%)	
Female	267 (85.0)
BMI (kg/m^2)	
N (missing)	123 (191)
Mean (SD)	25.2 (5.2)
Comorbidities/conditions, *n* (%)	
Yes	229 (72.9)
Type (multi-response), *n* (%)	
Anxiety disorder	91 (39.7)
Depression disorder	76 (33.2)
Obesity	37 (16.2)
Hypothyroidism	33 (14.4)
Fibromyalgia	31 (13.5)
Hypertension	26 (11.4)
Asthma	26 (11.4)
Insomnia	20 (8.7)
Other (freq < 5%)	160 (69.9)
Age at diagnosis of migraine (years)	
Mean (SD)	26.7 (13.7)
Median (Q1; Q3)	25.0 (15.0; 37.0)
Family history of migraine, *n* (%)	
Yes	210 (66.9)
Classification of migraine at baseline, *n* (%)	
Chronic	253 (80.6)
Episodic	61 (19.4)
Presence of aura, *n* (%)	
Yes	38 (12.1)
Characteristics of migraine at baseline (multi-response), *n* (%)	
Photophobia	291 (92.7)
Nausea	276 (87.9)
Phonophobia	271 (86.3)
Aggravation of pain from physical activity	234 (74.5)
Unilateral localization	182 (58.0)
Vomiting	150 (47.8)
Menstrual-related migraine*	107 (40.1)
Osmophobia	87 (27.7)
Other	41 (13.1)
Assessment at baseline (within the previous 3 months)	
Monthly migraine days	
Mean (SD)	16.7 (7.8)
Median (Q1; Q3)	15.0 (10.0; 21.0)
Monthly headache days	
Mean (SD)	19.8 (8.7)
Median (Q1; Q3)	20.0 (12.0; 30.0)
Monthly symptomatic medications intake	
Mean (SD)	17.7 (8.0)
Median (Q1; Q3)	16.0 (11.0; 25.0)
Monthly triptans intake	
Mean (SD)	11.8 (8.3)
Median (Q1; Q3)	11.0 (6.0; 16.0)
HIT-6 scale	
Mean (SD)	68.1 (5.4)
Median (Q1; Q3)	68.0 (65.0; 72.0)
MIDAS	
Mean (SD)	76.2 (54.6)
Median (Q1; Q3)	64.0 (36.0; 107.0)

Table 1 continued

	Overall
Symptomatic medication overuse, *n* (%)	
Yes	228 (74.0)

HIT-6 Headache Impact Test, *MIDAS* Migraine Disability Assessment Scale
*The percentage is calculated on women patients

migraine. Most patients had a family history of migraine (66.9%). Overall, 72.9% presented comorbidities, with anxiety and depression disorders being the most frequent.

At baseline, the mean monthly migraine days was 16.7 (7.8) and monthly headache days 19.8 (8.7). Overall, monthly symptomatic medications intake was needed for 17.7 (8.0) days; monthly triptans intake occurred on an average of 11.8 (8.3) days. Disability measures showed an average of 68.1 (5.4) on the HIT-6 scale and 76.2 (54.6) on the MIDAS questionnaire.

Treatment Patterns

Treatment Patterns Before Prescription of Galcanezumab

Before galcanezumab prescription, all patients had received preventive treatment, and more than 60% of the patients had received at least six previous preventive drugs since the diagnosis of migraine, the most common being antiepileptics, antidepressants, and BoNTA (95.2%, 89.8%, and 84.1%, respectively). Other mAbs were only previously prescribed in 8.3% of the population.

Overall, 97.1% had received any symptomatic treatment, and 31.2% had received at least three symptomatic treatments in the 6 months before the prescription of galcanezumab, mainly triptans (90.8%) and NSAIDs (61.0%) (Table 2).

1. *At the index date*

- **Group 1** (represented in cyan in Fig. 2): A total of 45.2% at the index date received galcanezumab as monotherapy,

Table 2 Frequency and type of all preventive and symptomatic migraine treatments (before administration of galcanezumab)

	Overall
Patients with previous preventive treatments use, *n* (%)	
Yes	314 (100)
Type of treatment (multi-response), *n* (%)	
Antiepileptics	299 (95.2)
Antidepressants	282 (89.8)
BoNTA	264 (84.1)
Beta-blockers	235 (74.8)
Calcium channel blockers	221 (70.4)
ACE inhibitors	101 (32.2)
Other	67 (21.3)
Monoclonal antibody CGRPs	26 (8.3)
No. of previous preventive treatments per patient	
Mean (SD)	7.0 (3.6)
Median (Q1; Q3)	6.0 (5.0; 8.0)
No. of previous preventive treatments per patient by range, *n* (%)	
1–2	3 (1.0)
3–5	120 (38.2)
6–10	145 (46.2)
> 10	46 (14.6)
Symptomatic treatment in the 6 months prior to galcanezumab, *n* (%)	
No	6 (1.9)
Yes	305 (97.1)
Type of treatment (multi-response), *n* (%)	
Triptans	277 (90.8)
NSAIDs	186 (61.0)
Other analgesics*	78 (25.6)
Metamizole sodium	50 (16.4)
Paracetamol	40 (13.1)
Antiemetics	13 (4.3)
Other	13 (4.3)

Table 2 continued

	Overall
No. of previous symptomatic treatments per patient (in the 6 months before)	
Mean (SD)	2.2 (1.1)
Median (Q1; Q3)	2.0 (2.0; 3.0)
No. of previous symptomatic treatments per patient by range (in the 6 months before), *n* (%)	
0	6 (1.9)
1–2	208 (66.9)
3–4	90 (28.9)
> 4	7 (2.3)

Index treatment pattern (Fig. 2)
BoNTA botulinum neurotoxin type A
*Only treatments with a frequency > 10% have been listed

of whom 42.4% (*n* = 133/314) of patients continue on galcanezumab as monotherapy, and 2.9% (*n* = 9/314) had a concomitant preventive added after receiving galcanezumab (represented in orange in Fig. 2).

- **Group 2** (represented in green in Fig. 2): 40.8% (*n* = 128/314) of patients with galcanezumab had a combination with another preventive treatment started before or at the same time as galcanezumab administration.
- **Group 3** (represented in purple in Fig. 2): The remaining 14.0% (*n* = 44/314) followed other treatment patterns (e.g., combination of previous patterns or with lack of information).

2. *During administration of galcanezumab*

Concomitant preventive treatments

During galcanezumab administration, 55.7% of patients received an average of 1.0 (1.1) concomitant preventive drug, the most common being antidepressants, antiepileptics, and

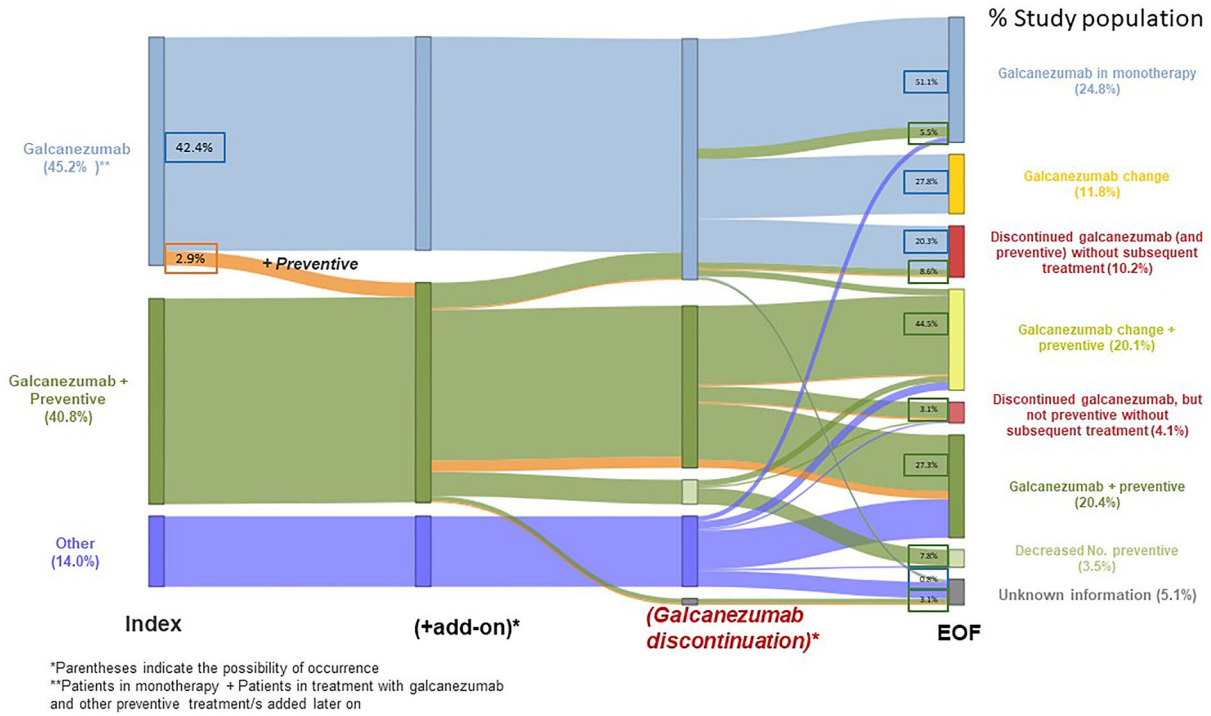

Fig. 2 Migraine treatment patterns: Sankey diagram from the index date up to end of follow-up (EOF)

Table 3 Frequency and type of all preventive and symptomatic migraine-specific treatments (during administration of galcanezumab)

	Overall
Patients, *n* (%)	314 (100%)
Patients with concomitant preventive treatment, *n* (%)	
Unknown	6 (1.9)
No	133 (42.4)
Yes	175 (55.7)
Type of concomitant preventive treatment by patients (multi-response), *n* (%)	
Antidepressants	93 (53.1)
Antiepileptics	75 (42.9)
BoNTA	64 (36.6)
Beta-blockers	32 (18.3)
ACE drugs	20 (11.4)
Other	14 (8.0)
Calcium channel blockers	2 (1.1)
Number of concomitant preventive treatments, *n* (%)	
Total	312 (100)
Concomitant preventive treatment started, *n* (%)	
Before galcanezumab	188 (60.3)
Unknown	87 (27.9)
After galcanezumab	23 (7.4)
At the same time galcanezumab	14 (4.5)
No. of concomitant preventive treatments per patient	
Mean (SD)	1.0 (1.1)
Median (Q1; Q3)	1.0 (0.0; 2.0)
No. of concomitant preventive treatments per patient by range, *n* (%)	
0	133 (43.2)
1–2	145 (47.1)
3–4	27 (8.8)
> 4	3 (1.0)
Patients with concomitant symptomatic treatment, *n* (%)	
No	9 (2.9)
Yes	299 (95.2)
Type of treatment (multi-response), *n* (%)	
Triptans	259 (86.6)
NSAIDs	168 (56.2)
Other analgesics	73 (24.4)
Metamizole sodium	42 (14.0)
Paracetamol	41 (13.7)
Antiemetics	11 (3.7)
Other	6 (2.0)
No. of symptomatic treatments per patient	
Mean (SD)	1.9 (0.9)
Median (Q1; Q3)	2.0 (1.0; 2.0)
No. of concomitant symptomatic treatments per patient by range, *n* (%)	
0	9 (2.9)
1–2	239 (77.6)
3–4	56 (18.2)
> 4	4 (1.3)

BoNTA botulinum neurotoxin type A

BoNTA (53.1%, 42.9%, and 36.6%, respectively). Most of them (60.3%) were started before the prescription of galcanezumab (Table 3, group 2 in Fig. 2).

Concomitant symptomatic treatment during administration of galcanezumab

Overall, 95.2% of patients received concomitant symptomatic drugs during galcanezumab administration, with triptans being the most frequent (86.6%), followed by NSAIDs (56.2%) (Table 3).

3. *Up to the end of follow-up*

Figure 2 shows the percentages of the treatment patterns at the end of follow-up considering the total study population (n = 314).

Group 1:

Patients in which galcanezumab was prescribed as monotherapy (n = 133), monotherapy was maintained in 51.1% (n = 68/133) of them, 27.8% changed to another preventive therapy (n = 37/133), and 20.3% (n = 27/133) discontinued galcanezumab without subsequent treatment.

Group 2:

– *Galcanezumab discontinuation*

- 44.5% (n = 57/128) of patients, already on treatment with galcanezumab and other preventive treatments, changed galcanezumab with a subsequent treatment and stayed on other preventive treatments.
- 8.6% (n = 11/128) discontinued galcanezumab without having a subsequent treatment.
- 3.1% (n = 4/128) discontinued galcanezumab without a subsequent treatment but not the concomitant preventive treatment.

– *Keeping galcanezumab*

- 27.3% (n = 35/128) stayed on galcanezumab and other concomitant preventive treatment.
- 7.8% (n = 10/128) kept galcanezumab and decreased the number of preventive treatments used.
- 5.5% (n = 7/128) left all the preventives and stayed on monotherapy with galcanezumab.

– *Subsequent treatment*

Almost half of the patients (48.1%) permanently discontinued the treatment with galcanezumab, on average after 12 months. The mean time to permanent discontinuation or to the end of the follow-up was 12.1 (6.0) months, and the mean effective time on treatment was 11.7 (6.0) months. Of the patients who discontinued, 57.6% were due to lack of effectiveness and 31.1% were due to improvement in

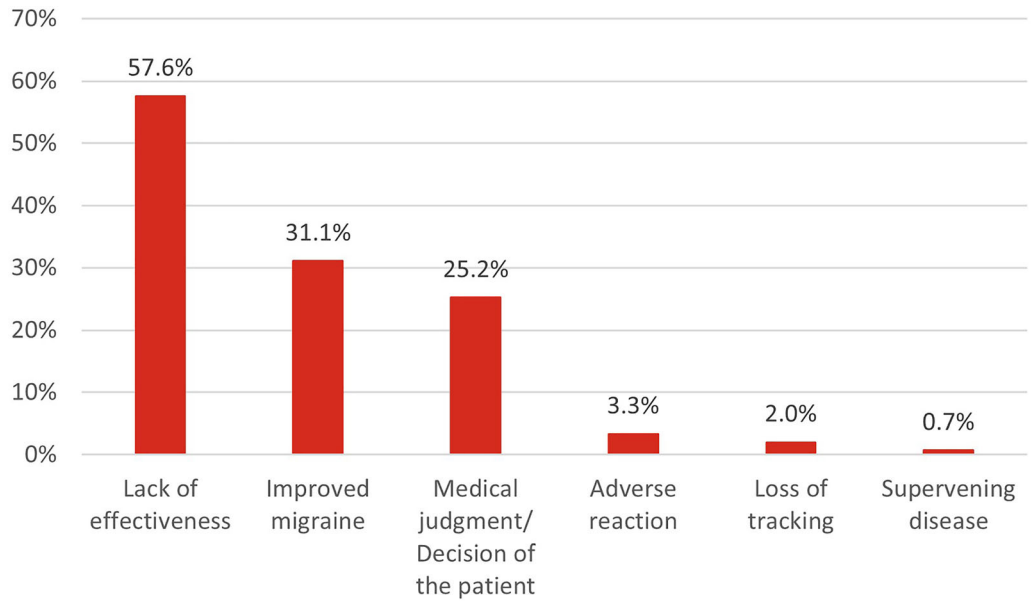

Fig. 3 Reasons for discontinuation from galcanezumab. Possible options of response were lack of effectiveness, adverse reactions, physician judgement/patient decision, special situations (e.g., pregnancy, surgery, supervening disease), improvement in disease progression, referral to other unit/hospital, lost to follow-up, and other reasons

Table 4 Preventive migraine-specific treatments after discontinuation of galcanezumab

	Overall
Patients in the total study population, *n*	314
Patient who permanently discontinued galcanezumab, *n* (%)	151 (100)
Preventive treatments following the permanent discontinuation of galcanezumab until the end of follow-up, *n* (%)	
No	46 (30.5)
Yes	104 (68.9)
Type of treatment (multi-response), *n* (%)	
Monoclonal antibody*	88 (84.6)
Erenumab	58 (55.8)
Fremanezumab	36 (34.6)
Galcanezumab	11 (10.6)
Antiepileptics	17 (16.3)
Antidepressants	9 (8.7)
ACE inhibitors	7 (6.7)
BoNTA	7 (6.7)
Other	3 (2.9)
Calcium channel blockers	2 (1.9)
Beta-blockers	2 (1.9)
No. of preventive treatments per patient	
Mean (SD)	1.0 (1.1)
Median (Q1; Q3)	1.0 (0.0; 1.0)
Number of preventive treatments per patient by range	
0	46 (30.7)
1–2	93 (62.0)
3–5	10 (6.7)
> 5	1 (0.7)

Permanent discontinuation was considered when galcanezumab was discontinued for ≥ 30 days
BoNTA botulinum neurotoxin type A
*Only treatments with a frequency > 10% have been listed

migraine (Fig. 3), and only 3.3% were due to adverse reactions.

Among the patients who discontinued galcanezumab, 68.9% (*n* = 104/151) continued with a preventive treatment after galcanezumab up to the end of follow-up (Table 4).

The mean number of subsequent preventive treatments per patient was 1.0 (1.1). The most used subsequent preventive treatments were mAbs (84.6%), followed by antiepileptics (16.3%) and antidepressants (8.7%). Moreover, among patients using a mAbs as a subsequent preventive treatment, galcanezumab was given in 10.6% of the cases.

Persistence

Almost 60% of patients stayed on the treatment after a year (Fig. 4). Furthermore, the median time on galcanezumab treatment was 14.6 months (9.4–22.8). In particular, 95.7%, 82.0%, 76.2% and 59.8% of the patients were persistent in treatment at 3, 6, 9 and 12 months, respectively (Fig. 4).

Effectiveness

Effectiveness results were analyzed by two different approaches: in the total study population and in the population while on treatment with galcanezumab.

Effectiveness in Total Study Population

Results of effectiveness analyzing the total study population after 3, 6, 9 and 12 months of galcanezumab prescription are summarized in Table 5. Galcanezumab proved to be effective in reducing mean monthly migraine days (from 16.7 to 7.3 days), monthly headache days (from 19.8 to 9.6 days), monthly symptomatic medications intake (from 17.7 to 8.8 days) and monthly triptans intake (from 11.8 to 5.6 days) from baseline to month 12 and at all the intermediate time points analyzed (Table 5). In addition, the mean scores on the HIT-6 scale and the MIDAS questionnaire were also reduced from baseline to month 12 (from 68.1 to 53.2 and from 76.2 to 20.1, respectively) and at all the intermediate time points analyzed.

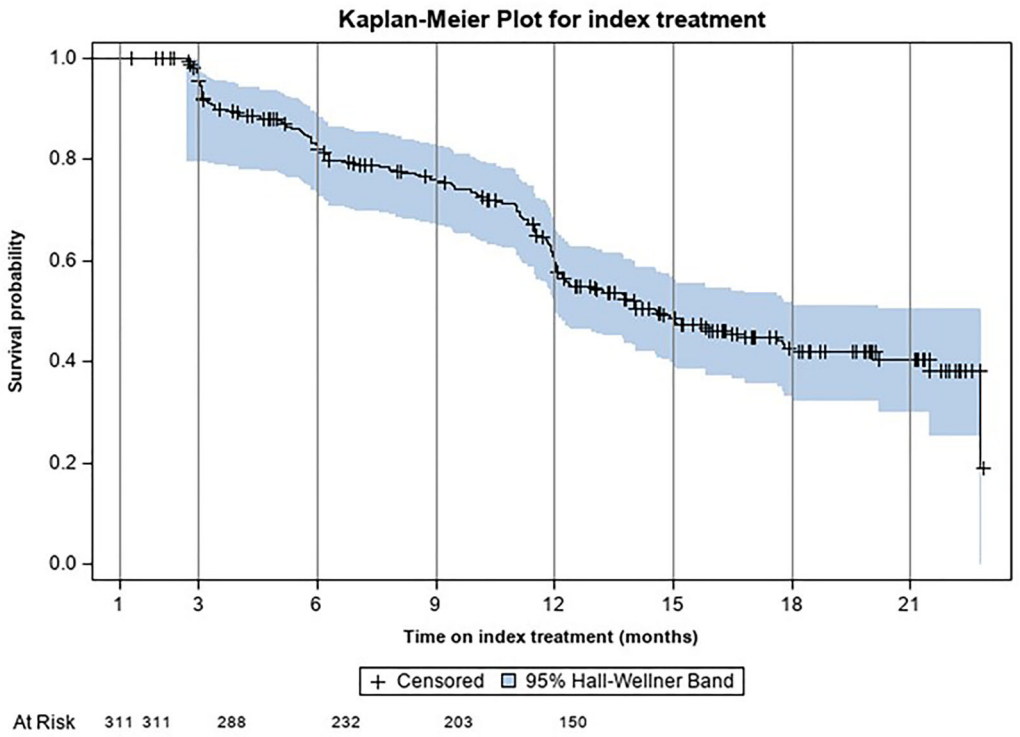

Fig. 4 Time on index treatment: Kaplan–Meier curve

Table 6 shows the absolute mean reductions of all the effectiveness indicators (monthly migraine days, monthly headache days, monthly symptomatic medications intake, monthly triptans intake, HIT-6, MIDAS) at the analyzed time points.

Effectiveness in Population While on Treatment

Results of the effectiveness and absolute change assessment in the population while on treatment after 3, 6, 9 and 12 months of galcanezumab prescription are summarized in Tables 1S and 2S in the Supplementary material. Galcanezumab proved to be effective in reducing mean monthly migraine days (from 16.7 to 7.2 days), monthly headache days (from 19.8 to 9.3 days), monthly symptomatic medications intake (from 17.7 to 8.5 days) and monthly triptans intake (from 11.8 to 5.6 days) from baseline to month 12 and at all the intermediate time points analyzed (Table 1S). In addition, the mean scores on the HIT-6 scale and the MIDAS questionnaire were also reduced from baseline to month 12 (from 68.1 to 53.2 and from 76.2 to 20.3, respectively) and at all the intermediate time points analyzed.

Figure 5 shows the change of the effectiveness at months 3, 6, 9 and 12 for the total study population. A consistent decrease in monthly migraine days, monthly headache days, monthly symptomatic medications intake, monthly triptans intake, HIT-6 scale, and MIDAS questionnaire from baseline to months 3, 6, 9 and 12 is demonstrated, particularly marked from baseline to month 3 and month 6. No differences between the total study population and the population while on treatment were observed (Fig. 1S in Supplementary material).

DISCUSSION

The Observational Retrospective Study in Patients Treated with Galcanezumab as Preventive Treatment for Migraine (ORYGAM) study has provided relevant real-world evidence

Table 5 Effectiveness on total study population at index date and 3, 6, 9 and 12 months after galcanezumab prescription

	Index date (N = 308)		3 months (N = 254)		6 months (N = 194)		9 months (N = 141)		12 months (N = 119)	
	n (missing)	Mean (SD)	*n* (missing)	Mean (SD)	*n* (missing)	Mean (SD)	*n* (missing)	Mean (SD)	*n* (missing)	Mean (SD)
Monthly migraine days	305 (3)	16.7 (7.8)	252 (2)	9.3 (8.2)	193 (1)	7.9 (7.1)	138 (3)	7.5 (6.3)	117 (2)	7.3 (6.7)
Monthly headache days	301 (7)	19.8 (8.7)	250 (4)	11.9 (9.9)	190 (4)	10.2 (8.4)	140 (1)	9.6 (7.5)	116 (3)	9.6 (8.3)
Monthly symptomatic medications intake	284 (24)	17.7 (8.0)	248 (6)	9.7 (8.2)	185 (9)	8.8 (7.3)	134 (7)	8.7 (7.1)	110 (9)	8.8 (7.7)
Monthly triptans intake	270 (38)	11.8 (8.3)	239 (15)	5.4 (6.6)	182 (12)	5.7 (6.2)	132 (9)	5.7 (6.2)	109 (10)	5.6 (6.5)
HIT-6	247 (61)	68.1 (5.4)	198 (56)	58.0 (10.2)	151 (43)	55.9 (11.5)	87 (54)	57.0 (9.6)	73 (46)	53.2 (12.0)
MIDAS	207 (101)	76.2 (54.6)	178 (76)	37.5 (48.2)	141 (53)	26.8 (35.1)	79 (62)	25.2 (30.4)	62 (57)	20.1 (33.4)

N number of patients with available assessment, *HIT-6* Headache Impact Test 6 scale, *MIDAS* Migraine Disability Assessment Scale

on the profile of patients treated with galcanezumab in clinical practice, as well as detailed information about treatment patterns, persistence, and effectiveness of galcanezumab, based on a representative sample of Spanish centers with a mean follow-up of 12 months. It is the first study to analyze the treatment patterns of patients starting galcanezumab treatment at all stages, i.e., before, during, and following treatment discontinuation.

The results have shown that patients treated with galcanezumab were mainly women affected by CM and highly difficult-to-treat migraine. Specifically, 60% of the total study population had previously used at least six preventive medications, and 84% had previously used BoNTA. A high level of comorbid conditions was also observed, mainly anxiety and depression.

These sociodemographic and clinical characteristics are very similar to those of the GalcaOnly Consortio [26] and the GARLIT studies [27], two recently published real-world-evidence studies on galcanezumab. As part of GalcaOnly, efficacy, safety, and long-term retention of galcanezumab were evaluated in 1004 patients at 12 Spanish hospitals, while GARLIT, a multicenter prospective observational cohort study conducted at 13 Italian headache centers, examined the effectiveness, safety, and tolerability of galcanezumab in CM and high-frequency episodic migraine. Similar to our data, these studies primarily included women (approximately 80–85%) with a mean age between 46 and 50 years (50.3 and 47.1 years, in GalcaOnly and GARLIT, respectively) suffering CM (76.4% in the GalcaOnly study, 79.8% in the GARLIT study) and with a high rate of comorbidities. All three studies found similar patterns of comorbidity at baseline with psychiatric comorbidities as the most prevalent condition [26, 27].

The present study shows that galcanezumab is administered as monotherapy in 42.4% of patients and added to previous concomitant preventive treatments in 40.8% of them. Patients receiving monotherapy maintained this pattern in a high percentage of patients (51.1%) throughout the follow-up. When galcanezumab is used concurrently with other

Table 6 Absolute change assessment on the total study population at 3, 6, 9 and 12 months after galcanezumab prescription

	3 months (N = 254)		6 months (N = 194)		9 months (N = 141)		12 months (N = 119)	
	n (missing)	Mean (SD)	n (missing)	Mean (SD)	n (missing)	Mean (SD)	n (missing)	Mean (SD)
Monthly migraine days	249 (5)	7.9 (7.2)	191 (3)	9.1 (7.5)	138 (3)	8.8 (6.6)	117 (2)	9.0 (6.9)
Monthly headache days	248 (6)	7.7 (8.3)	189 (5)	9.4 (9.0)	140 (1)	9.6 (8.1)	116 (3)	9.4 (8.5)
Monthly symptomatic medications intake	242 (12)	8.1 (7.7)	178 (16)	9.5 (7.4)	131 (10)	8.7 (7.5)	108 (11)	8.7 (7.7)
Monthly triptans intake	230 (24)	6.3 (7.2)	173 (21)	6.8 (7.0)	126 (15)	7.1 (6.5)	100 (19)	7.2 (6.8)
HIT-6	189 (65)	10.0 (9.2)	143 (51)	11.7 (11.1)	86 (55)	10.4 (8.8)	70 (49)	13.4 (11.9)
MIDAS	166 (88)	39.3 (46.7)	129 (65)	43.8 (49.5)	72 (69)	42.4 (46.9)	54 (65)	39.3 (52.9)

N number of patients in the study, *HIT-6* Headache Impact Test 6 scale, *MIDAS* Migraine Disability Assessment Scale

drugs (mainly antidepressants, antiepileptics, or BoNTA), there is an important decrease in the percentage of patients using these drugs during follow-up, which has already been described in the literature [28]. After galcanezumab discontinuation, mAbs are the most prescribed option, but it is important to note that galcanezumab was administered as a subsequent preventive treatment in 10.6% of the cases. This finding aligns with one recent study that analyzed discontinuation patterns, in which galcanezumab was restarted in 17% of patients after discontinuation [29].

It is known that the effectiveness of Standard-of-Care (SoC) prophylactic migraine treatments is often undermined by poor treatment persistence [11, 30], which is the reason why it is relevant to examine galcanezumab persistence in clinical practice. In ORYGAM, patients initiating galcanezumab reached a persistence of 82% at 6 months, and a progressive decline in persistence was observed thereafter, reaching 59.8% at 12 months. This persistence rate is slightly lower than that reported in the GalcaOnly study, which indicated that 70.1% of the patients continued treatment for up to 12 months [26]. Differences in the persistence rate between these studies could be explained by possible differences between the characteristics of the populations included in each study or in the management of patients receiving this drug [26].

In patients with migraine, understanding the reasons for discontinuing treatment is essential [2]. The results of our study indicate that the main reason for discontinuation was lack of effectiveness (57.6%) as per the physician's perception. The 31.1% of patients who discontinued galcanezumab treatment were related to migraine improvement in comparison to the 12.5% reported in a subanalysis of the GalcaOnly study, which included patients with migraine and fibromyalgia [31], in which the concomitant pathology could condition the improvement. Furthermore, in the ORYGAM study, the good tolerability described for this group of drugs is corroborated, and only 3.3% discontinued as a result of adverse effects, a

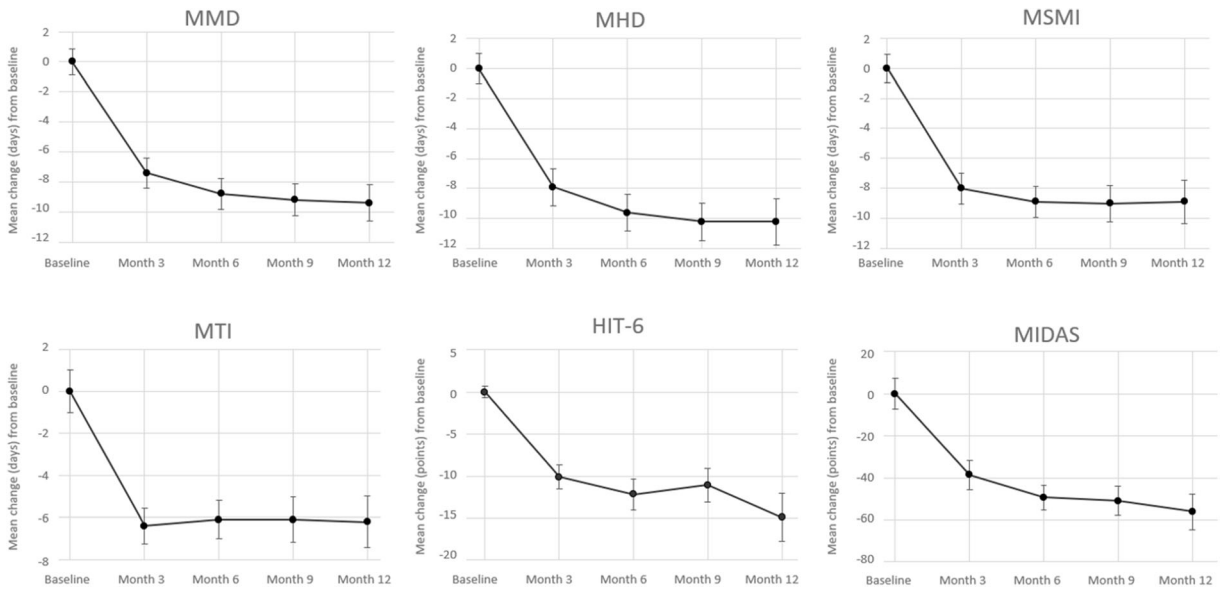

Fig. 5 Change of the effectiveness at months 3, 6, 9 and 12 for the total study population. MMD, monthly migraine days; MHD, monthly headache days; MSMI, monthly symptomatic medication intake; MTI, monthly triptans intake; HIT-6, Headache Impact Test 6 scale; MIDAS, Migraine Disability Assessment Scale

percentage much lower than the 18.5% reported in the GalcaOnly study [26].

Regarding effectiveness, the ORYGAM study provides robust results for various indicators (monthly migraine days, monthly headache days, MIDAS, HIT-6) and shows a decrease in all of them as early as month 3 and which is maintained throughout the follow-up up to month 12. In addition, we also observe this pattern when analyzing the acute and triptan medication reduction measures. This pattern of early and sustained effectiveness has already been shown in other studies [28, 29, 32–35], highlighting in some of them that the effect is observed as early as after a month of treatment [36–38]. Finally, as a novelty, we also analyzed the effectiveness data with two approaches (total study population and population while on treatment) and obtaining similar results, which corroborates the consistency of the results. The results of the "total study population" allow us to put the results of clinical trials into context, and those of the population "while on treatment" help us compare our results with most observational studies.

The benefits observed in ORYGAM appeared to be larger than those observed in randomized controlled trials such as the REGAIN, EVOLVE-1, EVOLVE-2, and CONQUER at 3 and 6 months [18–20, 22, 39], but consistent with results over a similar timeframe of 12 months from the open-label extension of the REGAIN study, which reported a mean change in the monthly migraine days of − 9.0 at month 12 [40]. Regarding our effectiveness results in the population while on treatment compared to the those from the GalcaOnly study [26], we cannot compare directly the monthly migraine days, but instead with the published data about monthly headache days. In this sense, the pattern of response over time is similar in both studies, the reduction in the frequency of monthly headache days from baseline to month 12 being slightly higher in the GalcaOnly study.

The main limitation of the study is inherent to its retrospective design since we can only collect the data recorded in the medical history, with potential missing or inaccurate data. Because of the SARS-CoV-2 pandemic and the disruption of the usual clinical practice, there was flexibility between the prescription and the administration times, leading to some patients taking galcanezumab after 30 days from its

prescription. In addition, time windows of ± 30 days around the planned date for the three-monthly visits had to be defined to allow for a more exhaustive data collection. Finally, only a few visits were recorded after galcanezumab discontinuation, so limited information was available for patients later on.

CONCLUSION

Patients treated with galcanezumab in Spanish routine clinical practice are difficult to treat, mostly have CM with multiple use of previous preventive treatments, and suffer additional comorbidities. Nevertheless, most patients continue galcanezumab for more than a year, showing a rapid and sustained improvement in clinical features and migraine-related disability and reporting a reduction in the need for concomitant preventive and acute treatments.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions.

Declarations

Conflict of Interest. Vicente Medrano, Jesús Porta-Etessam and Ana Roncero declare that they have no competing interests; Javier Viguera, has received speaker honoraria from Lilly, Lundbeck, Novartis and Teva; Samuel Díaz-Insa has received speaker honoraria from Fundació Universitat-Empresa, Abbie-Allergan, Kern Pharma, Lilly, Lundbeck, Novartis, Organon and Teva and participating in advisory boards from Kern Pharma, Lilly, Lunbeck, Novartis and Teva; Ángel Luís Guerrero has received honoraria for lectures or advisory boards from Allergan-Abbvie, Exeltis, Lilly, Novartis, Lundbeck, Pfizer and Teva, and research support from Abbvie-Allergan, Lilly and Teva; Carlos Calle de Miguel has received speaker honoraria from Asociación Madrileña de Neurología and has received payments to support travel to meetings from Lilly; and Antonio Ciudad, Silvia Díaz-Cerezo and Mercedes Núñez are full time employees at Lilly and minor owners of Lilly shares.

Ethical Approval. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Pharmacoepidemiology Practices (GPPs) guidelines of the International Society for Pharmacoepidemiology, and local rules and regulations. The study protocol was sent to the Spanish Health Authorities for classification and was

subsequently evaluated and approved by a central ethics committee (Comité de Ética de la Investigación con Medicamentos del Área de Salud Valladolid Este, Spain). This approval was notified to all the ethics comittees of the participant centers which agreed with the conduction of the study.

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