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REVIEW

Once-monthly galcanezumab for the prevention of migraine in adults: an evidence-based descriptive review and potential place in therapy

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Abstract: In the last 15 years relevant efforts have been made to demonstrate that calcitonin gene-related peptide (CGRP) antagonism is a valuable and druggable mechanism for treatment or prevention of migraine. Galcanezumab is one of the antibodies developed and studied to prevent migraine by targeting CGRP. The scope of this review is to report data currently available on galcanezumab. According to available data, galcanezumab is safe and efficacious in preventing migraine in episodic migraine patients, also reducing disability and functional impairment due to the disorder. In September 2018, galcanezumab was approved in the USA for the prevention of migraine in adults. The placement of galcanezumab into the current therapeutic scenario will be a revolution for migraine patients, and probably in a less near future also for patients affected by other primary headaches.

Keywords: calcitonin gene-related peptide, headache, LY2951742, monoclonal antibody prophylaxis, CGRP

Introduction

Migraine is one of the most common neurological disorders observed in clinical practice, affecting over 14% of adults worldwide.[1] In 2016, the last release of data from the Global Burden of Disease (GBD) established migraine as the second leading cause of years lived with disability (YLDs).[2] Accordingly, migraine has a strong social impact with an economic burden estimated at around €27 billion per year in Europe and presumably similar in the USA.[3]

Migraine pharmacological treatment is based on acute therapy, aimed to abort ongoing pain and reduce migraine-related symptoms, and on preventive therapy that is required when the frequency of attacks is ≥4 per month and aims to both lower attack frequency and severity and to decrease associated disability.[4]

In some patients, especially in those not taking preventive therapies or in the case of treatment failure, the natural course of migraine is toward an increase of headache frequency with a transition into and out of four distinct stages: no migraine, low-frequency episodic migraine (EM) (<10 days/month), high-frequency EM (10–14 days/month), and chronic migraine (CM) (>15 days/month).[5] It has been estimated that every year approximately 2.5% of patients with EM develop new-onset CM[5] and that, as a whole, 1%–4% of the general population develops CM.[1] Nonmodifiable (eg, female sex, old age, Caucasian race, low education level, worse socioeconomic status, and genetic factors) and modifiable (eg, caffeine use/misuse, stressful life events, bad lifestyle, family or personal history of mood disorders, sleep disorders, and substance use)

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risk factors are involved in migraine progression from EM to CM.[6] In particular, the increase in headache frequency translates into an increase of acute treatment utilization and may associate with the development of medication-overuse headache (MOH). All acute treatments, both specific (ie, triptans and ergot alkaloids) and not specific (ie, nonsteroidal anti-inflammatory drugs [NSAIDs], simple and combination analgesics, opioids, barbiturates, antinausea medications, antihistamines and muscle relaxants), when overused, can be associated with MOH, which in turn decreases responsiveness to acute or prophylactic drugs.[7]

Nowadays, migraine is still a treatable rather than a curable disorder. The preventive treatment armamentarium is quite old, nonspecific, and to a large extent built up on drugs borrowed from other medical indications, such as: antihypertensive agents (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, beta blockers), calcium channel blockers (eg, flunarizine), antiepileptic drugs (eg, topiramate, sodium valproate, gabapentin), tricyclic antidepressants (eg, amitriptyline, nortriptyline), serotonin receptor antagonists (eg, pizotifene), and selective norepinephrine reuptake inhibitors (SNRIs).[6] Preventive therapies may be prescribed to both EM and CM patients. With the exceptions of topiramate and onabotulinum toxin A (the latter authorized only for CM prevention), the use of which is supported by several randomized clinical trials, proof of efficacy for the other medications often comes from single trials[8–13] or open-label studies, and their use is in some cases empirical instead of evidence based.[14] Comparative trials are lacking, similar to evidence about predictive factors or biomarkers of responsiveness. Treatment decision-making should always be driven by clinical considerations, taking into account comorbidities, such as psychiatric and cardiovascular disorders, fibromyalgia, myofascial pain syndromes, and various forms of visceral pain.[15] A certain therapy could be contraindicated in the presence of a specific comorbid disease, while another treatment could be effective to treat both migraine and the other condition, at the same time reducing the medication intake and, consequently, the risk of drug–drug interactions.[16]

Despite the progress in migraine management, a significant portion of patients has unmet needs. Many patients needing prevention do not receive it,[17] and even when it is prescribed, adherence rates are quite low (~35%–50%),[18] mainly due to relatively unsatisfactory efficacy and to side effects.[19–21] Another major reason for the scarce adherence is the requirement for daily intake, often twice or three times per day, to reach the therapeutic dosages. Similar to other therapeutic areas, also in headache medicine, the more complicated the treatment is in terms of the number of daily intakes and/or drugs, the higher the chance that a patient will interrupt the treatment.[22]

In order to be successful, when advising about prophylaxis, the point of view of migraine patients should be borne in mind. Patients need to be open to advice and information, and interventions have to be offered timely in the course of migraine.[23] Migraine patients ask for a preventive treatment that is effective, with an easy route of administration combined with a wide time lag between intakes, also being safe and well tolerated.[24–27] Physicians would add to this list the wish for a treatment with few contraindications and interactions, if any.

As already stated, the preventive therapies currently available are not migraine specific and the development of drugs acting on the crucial steps of migraine pathogenesis will radically change migraine prophylaxis.

Migraine pathophysiology is multifactorial, complex, and not yet completely understood. Currently, the most accredited pathogenic hypothesis is based on the trigeminovascular theory that, although considering a central nervous system dysfunction as the *primum movens* of the genesis of the attacks, indicates a peripheral mechanism as fundamental for pain.[28,29] The mechanism of pain has been identified with neurogenic inflammation, a sterile inflammation phenomenon mediated by the activation of trigeminal perivascular fibers that release neuropeptides, such as substance P, and calcitonin gene-related peptide (CGRP),[30] that are directly responsible for increased blood flow, edema, recruitment of inflammatory cells, and release of proinflammatory and inflammatory molecules.[31] Finally, the activation of meningeal nociceptors could further stimulate the sensory trigeminal fibers, thus perpetuating the release of vasoactive peptides, including CGRP.[30] In this cascade of events, CGRP appears to play a fundamental role.[32]

CGRP is a neuropeptide produced from alternative splicing of the calcitonin gene. CGRP is a highly potent vasodilator and has been identified as a relevant player in mammalian biology, acting a crucial role both in physiological and pathological conditions. In particular, it may potentially be involved in the physiological regulation of the vascular tone and blood pressure, and some evidence has also been collected for some cardiovascular diseases, such as heart failure and ischemia.[33] Finally, data are accumulating about involvement of CGRP in extracardiovascular conditions such as diabetes and arthritis, in addition to the well-known involvement in pain and neurogenic inflammation.[33]

There are two forms of CGRP differently expressed in humans: 1) alpha-CGRP is prevalent in primary sensory

neurons of the dorsal root ganglia, in vagal ganglia, and throughout the trigeminal system; and 2) beta-CGRP is prevalent in intrinsic enteric neurons.[34–36] Accordingly, alpha-CGRP is primarily involved in migraine pathogenesis. The CGRP acts by targeting a G protein-coupled receptor of the B-type constituted by the calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein 1 (RAMP1), both necessary for the functional CGRP receptor.[37]

Several findings support the involvement of CGRP in migraine pathophysiology: 1) CGRP levels are increased during a migraine attack[38] and in CM patients also in the pain-free interval,[39] but return to normality after triptan administration and consequent headache resolution;[40–43] 2) intravenous infusion of CGRP can induce migraine-like attacks in migraine patients,[44,45] as well as dilatation of the middle meningeal arteries and the middle cerebral arteries that reverses after sumatriptan administration;[46] and, finally, 3) animal data suggest that CGRP can induce the generation of light intolerance (photophobia), a typical feature of a migraine attack.[47] Accordingly, in the last 15 years relevant efforts have been made to demonstrate that CGRP antagonism, by means of different drug classes (ie, small molecule antagonists of CGRP receptor,[48–53] anti-CGRP receptor antibody[54–56] and anti-CGRP antibodies,[57–61]) is a valuable mechanism to treat or prevent migraine. Galcanezumab,[62–65] together with erenumab,[54–56] eptinezumab,[57] and fremanezumab,[58–61] is one of the antibodies developed and studied to prevent migraine by targeting CGRP.

Pharmacology of galcanezumab

Pharmacodynamics

Galcanezumab, initially named LY2951742, is a fully humanized IgG4 anti-CGRP monoclonal antibody (MAb). It binds to the human CGRP, thus preventing its binding to receptors. Affinity of the MAb to the ligand is relatively high, with an equilibrium dissociation constant (K_D) of 31 pM.[66] In early clinical development, the evaluation of the target engagement and dose selection of galcanezumab was performed with the capsaicin-induced dermal blood flow (DBF) model.[67] Capsaicin-induced DBF represents a useful pharmacodynamic model to assess "scavenging" of CGRP in vivo.[68] The model concerns the topical application of capsaicin onto the skin, which by the activation of the Transient Receptor Potential Vanilloid 1 (TRPV1) channel expressed by primary sensory neurons provokes the release of CGRP, the key mediator of capsaicin-induced DBF in humans.[69] The Doppler laser scanning technique, utilized to quantify the variations in DBF, demonstrated the reversal of capsaicin-induced DBF by the CGRP blocking agents.[67,70]

To support the clinical development of galcanezumab, a capsaicin-induced DBF model was initially applied in non-human primates. Galcanezumab inhibited capsaicin-induced vasodilation for at least 29 days after a single intravenous injection,[71] a promising attribute for the prophylactic treatment of migraine. In humans, in a Phase I study, a single subcutaneous administration of 5 mg of galcanezumab inhibited the capsaicin-induced DBF from the 28th day after injection, while at higher doses (75, 200, and 600 mg) the effect was already evident from the third day.[72] Inhibition of the capsaicin-induced DBF was observed until the 42nd day, when the last assessment following the single-dose administrations was performed. When galcanezumab was administered in four subcutaneous consecutive doses (150 mg), with a 14-day dosing interval, the inhibition was visible up to 130 days after the last dose.[72] Serum concentrations of galcanezumab closely correlated with the inhibition of capsaicin-induced DBF, corroborating a strong dose–response relationship.

Pharmacokinetics

The pharmacokinetic profile of galcanezumab is different from that of drugs traditionally used in migraine prophylaxis. Like other MAbs, it has considerable dimensions (144.1 kDa) and must be administered parenterally, because of its low permeability through cell membranes and its instability in the gastrointestinal tract. During lactation, the amount of galcanezumab in milk is likely to be very low due to its dimensions, and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract.[73] The plasma half-life (25–30 days) allows the drug to be administered every 2 weeks, or every month.[62,63,74] This attribute is particularly suitable for a variable condition like migraine that does not favor adherence to oral prophylactic therapies on a daily basis.[18] Furthermore, galcanezumab is not apparently metabolized by the hepatic cytochromes, because it follows the antibody elimination routes, via catabolism in smaller peptides and individual amino acids,[75] that can be used for the synthesis of other proteins. Importantly, the metabolism of MAbs does not generate noxious intermediates and, therefore, they are unlikely to induce drug-induced liver injury. Even pharmacological interactions on the liver metabolism or kidney clearance pathways are minimized.

Pharmacokinetic properties of galcanezumab have been characterized by a Phase I study, after a single dose and multiple doses of subcutaneous injection in healthy male volunteers.[72] After subcutaneous administration of a single dose, the mean serum half-life ($t_{1/2}$) of galcanezumab is

between 25 and 30 days.[72] The absorption rate is slow with a median time to peak concentration (T_{max}) between the 7th and 14th day after administration. The peak serum concentration (C_{max}) and the area under the concentration–time curve (AUC) are proportional to the dose. Most of the previous pharmacokinetic parameters do not differ following administration of four consecutive subcutaneous doses of 150 mg, with a 14-day dosing interval.[72] The median T_{max} was equal to 3 days and much shorter than for the single-dose administration, while the $t_{1/2}$ was in accordance with forecasts, corresponding to 31.9 days.[72]

In an open-label, double-arm, randomized, parallel-group study, MAb serum concentrations were similar after subcutaneous administration of galcanezumab 240 mg solution via a prefilled syringe and an autoinjector, in healthy subjects.[76] Similarly, the site of injection (arm, thigh, or abdomen) did not influence the C_{max} or AUC. A statistically significant difference in median T_{max} for the autoinjector (5 days) compared to the prefilled syringe (7 days) was registered; however, this is likely to not be of any clinical relevance, considering that galcanezumab is intended to be administered once monthly as a preventive treatment for migraine. Furthermore, substantial overlap in the range of T_{max} values across the devices was observed.[76]

Mode of action

The site of action of MAbs is still debated.[77,78] Most prophylactic treatments for migraine are supposed to have various effects on the central nervous system, but galcanezumab, similar to other MAbs, seems to not penetrate the blood–brain barrier under physiological conditions. Therefore, the efficacy demonstrated in Phase II and Phase III clinical trials, together with other results obtained with triptans and CGRP receptor antagonists, suggest the presence of peripheral mechanisms.[62,63,74] In addition, there is no evidence that the blood–brain barrier is breeched in patients with migraine, either during or between attacks.[77] Importantly, Schankin et al[79] have demonstrated that the blood–brain barrier remains tight for ^{11}C-dihydroergotamine during acute glyceryl trinitrate-induced migraine attacks, both ictally and interictally. However, considering the ability of some large molecules such as insulin and transferrin to enter the brain because of the expression of transporters,[80] it is too early to declare the debate closed.

There is limited information about any difference in action between MAbs targeting CGRP. In a poster presented at the 2016 Annual Scientific Meeting of the American Headache Society, the first divergences regarding the CGRP intrinsic binding features of eptinezumab, fremanezumab, and galcanezumab were hypothesized.[81] Surface plasmon resonance binding analysis was conducted to characterize the binding of the MAbs to CGRP. Galcanezumab appears to reversibly antagonize its target with rapid CGRP engagement and dissociation. On the contrary, fremanezumab and eptinezumab engage CGRP with an undetectable dissociation, with the latter being able to neutralize CGRP activities twice as rapidly as fremanezumab. Notwithstanding, no significant differences have emerged in anti-CGRP MAbs, in both Phase II and Phase III clinical trials conducted so far.[82]

Efficacy

Galcanezumab induced a strong, dose-dependent, and durable inhibition of capsaicin-induced DBF increase, supporting the clinical development of this drug for prophylaxis in migraine patients.[72]

The efficacy of galcanezumab as a preventive treatment for migraine has been primarily evaluated in subjects affected by EM.

In 2014, Dodick et al[62] published the results of ART-01 (NCT01625988), a randomized, double-blind, placebo-controlled, Phase IIa proof-of-concept study conducted in 35 American centers, the first ever reported efficacy trial with a MAb against CGRP in the prevention of migraine.[83] In ART-01, from 2012 to 2013, 218 adult subjects, with at least a 1-year history of migraine, migraine onset prior to age 50, and 4–14 migraine headache days (MHD), were randomly (1:1) assigned to receive 150 mg galcanezumab or placebo as subcutaneous injections every 2 weeks for 12 weeks. One-hundred and fifty milligrams of galcanezumab was considered the therapeutic dose, according to the assessment of maximum inhibition of the capsaicin-induced DBF effect.[72] During the 28-day baseline period, individuals in the galcanezumab arm reported a mean of 7.0 MHD vs 6.7 MHD in the placebo arm. The primary efficacy endpoint was the mean change from baseline in the number of MHD in a 4-week period (weeks 9–12), as assessed at the 12-week timepoint. Galcanezumab induced a reduction of 4.2 and placebo of 3.0 in MHD from baseline (P=0.0030), with a significant difference of 1.2 MHD in favor of galcanezumab. Moreover, galcanezumab generated statistically significant reduction in headache days (−4.9 vs −3.7, P=0.012) and migraine attacks (−3.1 vs −2.3, P=0.0051). In a *post hoc* efficacy analysis, 49% of subjects in the galcanezumab group had a 75% response compared to 27% in the placebo group, and a complete response was observed in 32% of patients treated with galcanezumab vs 17% of patients on placebo treatment.

As a whole, the results of this study provided the first preliminary report of efficacy of galcanezumab as a preventive therapy for migraine.[62]

In a following dose-ranging, randomized clinical trial (NCT02163993),[63] 410 adult patients affected by EM were randomly assigned in a 2:1:1:1:1 ratio to placebo, 5, 50, 120, or 300 mg galcanezumab subcutaneously injected once monthly for a 3-month period. The study was conducted in the USA in clinics of 37 licensed physicians. The inclusion criteria were identical to those of ART-01. For the primary endpoint, galcanezumab 120 mg significantly reduced the mean number of MHD compared with placebo (−4.8 vs −3.7 days compared to the baseline values of 6.7 and 6.6 days). The overall change from baseline to month 3 in the number of MHD was significant for both the 120 mg and 300 mg dose arms compared with placebo. Galcanezumab 120 mg was also superior to placebo at month 3 for all key secondary efficacy outcomes (ie, number of MHD plus probable MHD, probable MHD, migraine attacks, proportion of patients reporting 50% and 100% reduction in the number of MHD). Despite the relatively short duration of the study, these data provided sufficient efficacy data to justify further development of galcanezumab, 120 and 240 mg, in larger Phase III clinical trials.[63]

Recently, the results of EVOLVE-1 (NCT02614183) and EVOLVE-2 (NCT02614196), two Phase III randomized controlled trials with galcanezumab and placebo in people with EM, have been published.[64,65] These studies were characterized by similar study design. Between January 2016 and March 2017, EVOLVE-1 was conducted at 90 centers in the USA, Puerto Rico, and Canada. At the same time, EVOLVE-2 was performed in 109 study sites in the USA, Europe, Argentina, Korea, Taiwan, and Mexico. In both trials, patients were randomized to receive either placebo or one galcanezumab dose regimen (120 or 240 mg) once a month for 6 months and they were followed for 5 months, after the last injection, in the posttreatment period. At baseline, the mean monthly MHD were 9.1. The primary endpoint was the reduction of MHD per 4 weeks over the entire 6-month double-blind period. With an onset of the effect at month 1, treatment with galcanezumab significantly reduced monthly MHD by 4.7 days (120 mg) and 4.6 days (240 mg) compared with placebo (2.8 days) in EVOLVE-1, and by 4.3 (120 mg) and 4.2 days (240 mg) compared with placebo (2.3 days) in EVOLVE-2. It is noteworthy that no meaningful differences between galcanezumab 120 mg and galcanezumab 240 mg doses were seen on measures of efficacy. Both MAb doses were statistically superior to placebo for monthly MHD with acute medication use and for the mean percentage of patients with at least 50%, at least 75%, and 100% reduction from baseline in monthly MHD during treatment (Table 1).[64,65] A *post hoc* analysis from pooled data of the two trials showed that around 40% of the galcanezumab-treated patients achieved

Table 1 EVOLVE-1 and EVOLVE-2 studies: primary and key secondary efficacy endpoints (least-squares mean change from baseline or estimated percentage) over months 1–6

	EVOLVE-1 study			EVOLVE-2 study		
	Placebo (n=425)	Galcanezumab 120 mg (n=210)	Galcanezumab 240 mg (n=208)	Placebo (n=461)	Galcanezumab 120 mg (n=231)	Galcanezumab 240 mg (n=223)
Primary endpoint						
Monthly MHD	−2.8	−4.7	−4.6	−2.3	−4.3	−4.2
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)		<0.001 (S)	<0.001 (S)
Key secondary endpoints						
≥50% response	38.6	62.3	60.9	36	59.3	56.5
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)		<0.001 (S)	<0.001 (S)
≥75% response	19.3	38.8	38.5	17.8	33.5	34.3
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)		<0.001 (S)	<0.001 (S)
100% response	6.2	15.6	14.6	5.7	11.5	13.8
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)		<0.001 (S)	<0.001 (S)
Monthly MHD with acute medication use	−2.2	−4.0	−3.8	−1.9	−3.7	−3.6
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)		<0.001 (S)	<0.001 (S)

Note: [a]*P*-value indicates nominal significance without multiplicity adjustment.
Abbreviations: MHD, migraine headache days; S, significant after multiplicity adjustment.

100% response in MHD reduction for at least 1 month. More patients had a 100% monthly response in the last 3 months, suggesting that the duration of the treatment plays a role in determining a full clinical answer. Although very few patients (0.7% and 1.4% for galcanezumab 120 mg and 240 mg, respectively) achieved 100% response for all 6 months, it seems encouraging that ~13% of the patients had at least 3 months free from MHD across the 6-month phase.[84] Taken together, the results of EVOLVE-1 and EVOLVE-2 confirmed the data collected in Phase II studies, demonstrating a clinically meaningful level of long-term efficacy of galcanezumab as prophylactic treatment for EM.[64,65]

Galcanezumab also provided effective migraine prevention in patients with CM.

During the 3-month double-blind treatment phase of the Phase III REGAIN study (NCT02614261)[85] in adults with CM, once-monthly galcanezumab 120 and 240 mg were both associated with significantly greater reductions from the baseline mean number of monthly MHD (19.4 for the total sample) compared to placebo (overall mean change −4.8 and −4.6 vs −2.7). Galcanezumab 120 mg had statistical improvement vs placebo on the primary endpoint and the ≥50% response rate, while galcanezumab 240 mg demonstrated statistical improvement compared to placebo on the primary endpoint and all key secondary endpoints, except for the 100% response rate (Table 2). As seen in EVOLVE-1 and EVOLVE-2, there were no statistical differences between doses on any efficacy measures. The results of the 9-month open-label extension of the trial are still not available.[85]

A Phase III, long-term, open-label safety study (NCT02614287)[86] included, as the secondary objective, the evaluation of efficacy measures to assess the long-term effectiveness of galcanezumab 120 or 240 mg, administered subcutaneously once monthly for a year, in adult patients with EM and CM. At baseline, MHD per month were 10.6. In both galcanezumab dose groups (n=135 in each arm), there were statistically significant within-group reductions from baseline in the monthly MHD (−5.6 for 120 mg and −6.5 for 240 mg). Reduction in the mean monthly MHD was apparent as early as the first month and was sustained throughout the 12-month treatment period.[86] There were also significant and meaningful decreases in acute headache medication use from baseline at each monthly visit during the treatment period (overall change from baseline: −5.1 days).[87]

Further relevant efficacy data on galcanezumab in the prophylaxis of migraine come from *post hoc* analysis of integrated EVOLVE-1 and EVOLVE-2 results in EM patients and REGAIN results in CM patients.

The persistence of the effect during the double-blind phase was evaluated in a total of 1,773 adult patients with EM (n=444 for galcanezumab 120 mg; n=435 for galcanezumab 240 mg; n=894 for placebo for two studies pooled) and 1,113 patients with CM (n=278 for galcanezumab 120 mg; n=277 for galcanezumab 240 mg; n=558 for placebo). In

Table 2 REGAIN study: primary and key secondary efficacy endpoints (least-squares mean change from baseline or estimated percentage) over months 1–3

	Placebo (n=538)	Galcanezumab 120 mg (n=273)	Galcanezumab 240 mg (n=274)
Primary endpoint			
Monthly MHD	−2.7	−4.8	−4.6 (0.4)
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)
Key secondary endpoints			
≥50% response	15.4	27.6	27.5
P-value vs placebo[a]		<0.001 (S)	<0.001 (S)
≥75% response	4.5	7.0	8.8
P-value vs placebo[a]		0.031 (NS)	<0.001 (S)
100% response	0.5	0.7	1.3
P-value vs placebo[a]		0.597 (NS)[b]	0.058 (NS)
Monthly MHD with acute medication use	−2.2	−4.7	−4.3
P-value vs placebo[a]		<0.001 (NS)[b]	<0.001 (S)

Notes: [a]*P*-value indicates nominal significance without multiplicity adjustment. [b]Item not tested after all α expended on previous items in multiplicity adjustment testing sequence. It is considered not statistically significant regardless of *P*-value.

Abbreviations: MHD, migraine headache days; NS, not significant after multiplicity adjustment; S, significant after multiplicity adjustment.

EM patients, ≥50% response was maintained in 41.5% and 41.1% of galcanezumab-treated patients (120 mg and 240 mg, respectively) for ≥3 consecutive months and in 19.0% and 20.5%, respectively, for 6 consecutive months; the response was significantly greater than that of the placebo arm (21.4% and 8.0% for ≥3 and 6 consecutive months, respectively). In CM patients, 29% of galcanezumab-treated patients maintained ≥30% response all 3 months compared to 16% of placebo patients, while ≥50% response was maintained in 16.8% and 14.6% of galcanezumab-treated patients (120 mg and 240 mg, respectively) and was greater than placebo (6.3%).[88]

The subgroup of patients treated with both doses of galcanezumab who previously failed two or more preventive therapies (n=172 with EM, n=323 with CM) experienced a statistically significant reduction in the average monthly MHD from baseline vs those treated with placebo (3.45 days for 120 mg and 3.85 days for 240 mg vs 0.81 days for placebo in EM, 5.91 days for 120 mg and 3.30 days for 240 mg vs 1.44 days for placebo in CM), and at least a 50% reduction in monthly MHD compared to the placebo arm (54.6% for 120 mg and 61.2% for 240 mg vs 26.2% for placebo in EM, 30.4% for 120 mg and 18.3% for 240 mg vs 9.7% for placebo in CM).[89]

Interestingly, galcanezumab-treated patients who did not achieve early satisfactory improvement appear to have a reasonable likelihood of continued improvement in the months following the initial treatment. For example, of 155 EM patients whose answer was 30%–50% fewer MHD after 1 month of dosing, 62% achieved "good" (≥50% reduction in baseline MHD) and 20% "better" (≥75% reduction in baseline MHD) responses with continued treatment. Similarly, of 116 CM patients having 10%–30% fewer MHD after 1 month of dosing, 38% achieved "good" and 13% "better" responses with continued treatment.[90] Importantly, available data do not offer any evidence of differential responses from patients affected by migraine with aura vs patients affected by migraine without aura.

Additional clinical trials on galcanezumab for different clinical indications are summarized in Table 3. Interestingly, a trial that aims to investigate galcanezumab in adults with treatment-resistant migraine, the CONQUER study (NCT03559257),[91] began at the end of July 2018. Although the present review is focused on the use of galcanezumab for the prevention of migraine in adults, it is noteworthy that galcanezumab has been also studied in the pediatric population; the Phase III REBUILD study (NCT03432286)[92] has been enrolling participants 6–17 years of age affected by EM, since March 2018. In addition, galcanezumab is being widely studied for the prophylaxis of episodic and chronic cluster headache in Phase III randomized clinical trials (NCT02397473,[93] NCT02438826,[94] NCT02797951).[95]

Safety and tolerability

In a small number of healthy male subjects, galcanezumab was well tolerated when administered as a single subcutaneous dose ranging from 1 to 600 mg and after four consecutive

Table 3 Additional Phase II and III clinical trials of galcanezumab

Main identifier(s)	Condition	Phase	Study status	Location(s)
(NCT02959177) I5Q-JE-CGAN	EM, adults	II	Active, not recruiting	Japan
(NCT02959190) I5Q-JE-CGAP	EM/CM, adults	III	Active, not recruiting	Japan
(NCT03559257) I5Q-MC-CGAW CONQUER	EM/CM, therapy-resistant adults	III	Recruiting	Multinational
(NCT03432286) I5Q-MC-CGAS REBUILD	EM, participants 6–17 years of age	III	Recruiting	USA, Puerto Rico
(NCT02397473) I5Q-MC-CGAL	ECH, adults	III	Completed	Multinational
(NCT02438826) I5Q-MC-CGAM	CCH, adults	III	Active, not recruiting	Multinational
(NCT02797951) I5Q-MC-CGAR	ECH or CCH, adults who completed I5Q-MC-CGAL/I5Q-MC-CGAM	IIIb	Enrolling by invitation	Multinational

Abbreviations: CCH, chronic cluster headache; CM, chronic migraine; ECH, episodic cluster headache; EM, episodic migraine.

doses of 150 mg administered over 6 weeks. The most common treatment-emergent adverse events (TEAEs) were headache, nasopharyngitis, hematuria, and contact dermatitis; they were transient, with no apparent relationship with the prolonged systemic drug exposure, due to the long half-life of the MAb. There were no apparent differences between galcanezumab dose groups or between galcanezumab dose groups and placebo in terms of frequency and type of any TEAEs (with the exception of hematuria that was absent in the placebo arm) or changes from baseline in vital signs (ie, pulse rate, systolic and diastolic blood pressure, and body temperature), laboratory values, or electrocardiogram (ECG) parameters. The administration of galcanezumab was not associated with time or dose-related cardiovascular or hepatotoxic effects.[72]

The safety and the tolerability of monthly galcanezumab in migraine patients have been further demonstrated in both randomized double-blind Phase II studies[62,74] and Phase III studies.[64,65,85] A similar profile of TEAEs was reported in both the placebo group and active arm/s, except for EVOLVE-2 where the proportion of patients who referred at least one TEAE was significantly greater in the galcanezumab 240 mg group than in the placebo group (71.5% vs 62.3%) (Table 4). Across all trials, most TEAEs were of mild to moderate intensity and transient. The profile of TEAEs was consistent with a peripheral site of action for galcanezumab. TEAEs related to the injection site, such as injection-site pain, injection-site erythema, and injection-site pruritus, urinary tract infections, upper respiratory tract infections, and nasopharyngitis were frequently reported. In particular, in Phase III trials, injection-site pain was the most common TEAE in all three treatment groups without statistically significant differences (Table 5). Furthermore, no clinically significant differences were found in mean change from baseline for vital signs, body weight,[64,65,85] laboratory values, and ECGs[85] between the active groups and the placebo arm.

In REGAIN, treatment-emergent suicidal ideation, assessed by the Columbia-Suicide Severity Scale (C-SSRS), was reported by the 1% of patients in the three arms of the study (four patients on placebo, three patients in the galcanezumab 120-mg group, and two patients in the galcanezumab 240-mg group), with no suicidal behavior.[85]

Similar to placebo, galcanezumab was associated with low discontinuation rates owing to TEAEs (<1% in Phase IIb study for all galcanezumab doses, 3.8% and 3.1% for the two galcanezumab doses in EVOLVE-1 and EVOLVE-2, respectively, and 0.9% for the two galcanezumab doses in REGAIN). In the same way, the percentage of serious adverse events (SAEs), none of which was considered to be related to galcanezumab, was low and no deaths were reported (Table 3).

In Phase II studies,[62,74] the development of treatment-emergent antidrug antibodies (ADAs) following galcanezumab administration did not appear to have any clinically meaningful effect on safety profile, pharmacokinetics,

Table 4 Overview of adverse events in EVOLVE-1, EVOLVE-2, and REGAIN trials

AEs			
EVOLVE-1	**Placebo (n=432)**	**Galcanezumab 120 mg (n=206)**	**Galcanezumab 240 mg (n=220)**
TAEs	261 (60.4%)	135 (65.5%)	149 (67.7%)
SAEs	5 (1.2%)	7 (3.4%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to AEs	10 (2.3%)	9 (4.4%)	7 (3.2%)
EVOLVE-2	**Placebo (n=461)**	**Galcanezumab 120 mg (n=226)**	**Galcanezumab 240 mg (n=228)**
TAEs	287 (62.3%)	147 (65%)	163 (71.5%)[a]
SAEs	5 (1.1%)	5 (2.2%)	7 (3.1)
Deaths	0 (0.0%)	0 (0%)	0 (0%)
Discontinuation due to AEs	8 (1.7%)	5 (2.2%)	9 (4%)
REGAIN	**Placebo (n=558)**	**Galcanezumab 120 mg (n=273)**	**Galcanezumab 240 mg (n=282)**
TAEs	279 (50%)	158 (58%)[a]	160 (57%)
SAEs	4 (0.7%)	1 (0.4%)	5 (1.8%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to AEs	6 (1.1%)	1 (0.4%)	4 (1.4%)

Note: [a]$P<0.05$ vs placebo.
Abbreviations: AE, adverse event; SAE, serious adverse event; TAE, treatment-emergent adverse event.

Table 5 Main treatment-emergent adverse events reported by at least 2% of galcanezumab-treated patients in EVOLVE-1, EVOLVE-2, and REGAIN trials

TAEs			
EVOLVE-1	**Placebo (n=432)**	**Galcanezumab 120 mg (n=206)**	**Galcanezumab 240 mg (n=220)**
Patients with ≥1 TAE	261 (60.4%)	135 (65.5%)	149 (67.7%)
Injection-site pain	75 (17.4%)	33 (16%)	45 (20.5%)
Nasopharyngitis	27 (6.3%)	16 (7.8)	6 (2.7%)
Urinary tract infections	15 (3.5%)	8 (3.9)	13 (5.9%)
Injection-site reaction	4 (0.9%)	7 (3.4)[a]	12 (5.5%)[a]
Injection-site erythema	11 (2.6%)	10 (4.9)	9 (4.1%)
Injection-site pruritus	1 (0.2%)	9 (4.4)[a]	10 (4.6%)[a]
EVOLVE-2	**Placebo (n=461)**	**Galcanezumab 120 mg (n=226)**	**Galcanezumab 240 mg (n=228)**
Patients with ≥1 TAE	287 (62.3%)	147 (65%)	163 (71.5%)[a]
Injection-site pain	39 (8.5%)	21 (9.3%)	20 (8.8%)
Nasopharyngitis	41 (8.9%)	19 (8.4%)	16 (7%)
Upper respiratory tract infections	16 (3.5%)	13 (5.8%)	12 (5.3%)
Injection-site reaction	0 (0%)	7 (3.1%)[a]	18 (7.9%)[a]
Injection-site erythema	4 (0.9)	6 (2.7%)	7 (3.1%)[a]
Injection-site pruritus	0 (0%)	6 (2.7%)[a]	7 (3.1%)[a]
REGAIN	**Placebo (n=558)**	**Galcanezumab 120 mg (n=273)**	**Galcanezumab 240 mg (n=282)**
Patients with ≥1 TAE	279 (50%)	159 (58%)[a]	160 (57%)
Injection-site pain	24 (4%)	17 (6%)	20 (7%)
Nasopharyngitis	26 (5%)	17 (6%)	9 (3%)
Upper respiratory tract infections	13 (2%)	9 (3%)	9 (3%)
Injection-site reaction	10 (2%)	8 (3%)	15 (5%)[b]
Injection-site erythema	5 (1%)	4 (1%)	13 (5%)[c,d]
Injection-site pruritus	1 (0%)	0 (0%)	7 (2%)[b,d]

Notes: [a]$P<0.05$ vs placebo. [b]$P<0.01$ vs placebo. [c]$P<0.001$ vs placebo. [d]$P<0.05$ vs galcanezumab.
Abbreviation: TAE, treatment-emergent adverse event.

or mechanism of action. These results were confirmed in larger populations where treatment-emergent ADAs and neutralizing ADAs, antibodies that recognize the target-binding sites on galcanezumab and compete with its binding to CGRP in vitro, showed no impact on either safety or efficacy.[64,65,85]

The safety and tolerability profile of galcanezumab has been furtherly characterized in a Phase III, long-term, open-label safety study, in which galcanezumab 120 or 240 mg was administered subcutaneously once monthly for a year, in adult patients with EM and CM.[86] The completion rate was high, with 77.8% of patients completing all 12 months of treatment, 3.7% of patients experienced an SAE, and 4.8% discontinued due to AEs. TEAEs with a frequency ≥10% of patients in either dose group were injection-site pain, nasopharyngitis, upper respiratory tract infection, injection-site reaction, back pain, and sinusitis. As shown in previous studies, laboratory values, vital signs, ECGs, and treatment-emergent ADAs did not show any clinically meaningful differences between galcanezumab doses. Although nearly 17% of the patients had comorbid depression and four patients reported suicidal ideation on the C-SSRS, no treatment-emergent suicidal behavior was registered.[86]

Patient-focused perspectives

The relevance given to patient-reported outcome measures (PROMs) has been growing in recent years and is especially important in pain conditions, such as migraine. Accordingly, some PROMs have been assessed in trials aimed at establishing galcanezumab efficacy.

In ART-01, patients treated with galcanezumab showed a greater improvement in quality of life than did those who were administered placebo, as highlighted by the Migraine Specific Quality of Life (MSQL) and the Headache Impact Text (HIT-6) scores at week 12; however, no formal statistical analyses were performed on these data.[62] In the dose-ranging trial, a *post hoc* secondary analysis showed

that, in comparison with placebo, galcanezumab 120 mg was associated with significant functional improvements as reflected by changes in MSQL scores, at 12 weeks post treatment. Reduction in MHD was associated with improvements in MSQL and reductions in HIT-6 scores, suggesting that galcanezumab may have a benefit on headache frequency, as well as on disease-specific health-related quality of life and disease burden.[96] In the EVOLVE-1 and EVOLVE-2 trials, treatment with both 120 mg and 240 mg dosages of galcanezumab was associated with statistically significant reduced functional impairment due to migraine as measured in the MSQ role-function restrictive domain at month 6 vs placebo. Similarly, significant improvement in patients' global impression of severity of their disease estimated by the Patient Global Impression of Severity (PGI-S) rating and in total Migraine Disability Assessment (MIDAS) scores was detected in comparison with placebo at the end of the 6-month treatment period.[64,65] In the REGAIN study, a statistically significant improvement in the MS role-function restrictive domain and in PGI-S rating was identified at month 3 in the group treated with galcanezumab 240 mg compared to the placebo arm.[85] In the Phase III, long-term, open-label safety study, at least 69% of patients treated with galcanezumab responded with high levels of overall satisfaction, preference, and less impact from side effects over previous treatments at months 1, 6, and 12. In this trial, there were within-group reductions from baseline in migraine-specific healthcare resource utilization (per 100 patient-years) with galcanezumab for healthcare professional visits (from 173.4 to 59.6, statistically significant for both arms), emergency room visits (from 20.2 to 4.7, statistically significant for the galcanezumab 240 mg arm), and hospital admissions (from 3.7 to 0.4) during the treatment period.[87] Of the 270 patients who participated in the study, 179 used both the prefilled syringe and the autoinjector at least once. Patient-rated ease of usability was assessed with the Subcutaneous Administration Assessment Questionnaire (SQAAQ) and compared between devices. Over 90% of the patients (combined dose groups) reported positive experiences with the first use of the autoinjector, and these ratings remained very positive with subsequent use. A higher proportion of "agree/strongly agree" responses on the SQAAQ items were reported with the autoinjector than the prefilled syringe.[76]

Conclusion and place in therapy

According to available data, galcanezumab is safe and efficacious in preventing migraine in EM patients, also reducing disability and functional impairment due to the disorder. The high tolerability of this drug, as shown by the low percentages of discontinuations during the clinical trials, creates a significant premise for good adherence to treatment in real-life patients. Hopefully, and similar to results obtained with other MAbs,[32] efficacy and safety will be proved also for CM. The placement of galcanezumab in the current therapeutic scenario will be a revolution for migraine patients, and probably in a less near future for patients affected by other primary headaches (eg, cluster headache). After years from the launch of triptans and for the first time after methysergide has been withdrawn from the market, migraine patients may have access to a mechanism-driven therapy. Importantly, the treatment schedule will save patients from daily intake of drugs, favoring their adherence[97] and, consequently, the effectiveness of the treatment. The real value of galcanezumab, together with that of other MAbs, should be calculated considering not only direct costs due to the treatment (ie, drug costs), but also indirect costs prevented, such as visits to the emergency room and absenteeism. To this aim, the precise definition of the cardiovascular safety of galcanezumab and similar drugs will be fundamental. In addition to the abovementioned results emerging from clinical trials, available data collected for erenumab, which did not impair exercise time in patients with high cardiovascular risk,[98] support that inhibition of the CGRP receptor does not favor myocardial ischemia occurrence. Finally, according to the distribution of the clinical response observed in the trials, with some patients showing excellent responses and others not responding at all, it is likely that in the future a differential place in therapy may be considered for diverse migraine endophenotypes, hopefully identifiable through a reliable biomarker – that, however, still has to be found. Additional data are needed to draw a complete profile, in terms of both efficacy and safety, of this new drug class, including galcanezumab, and to optimally place it in therapy. The recent release of marketing authorization from both the US Food and Drug Administration (erenumab, galcanezumab) and the European Medicines Agency (erenumab) for different antibodies blocking the CGRP pathway, allowing their use in real practice, will be fundamental to this aim.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Guerzoni participated as coinvestigator in the I5Q-MC-CGAI trial (NCT02614261) and in the I5Q-MC-CGAW trial (NCT03559257). Dr Lupi participated as coinvestigator in

the I5Q-MC-CGAI trial (NCT02614261), in the I5Q-MC-CGAL trial (NCT02397473), and in the I5Q-MC-CGAM trial (NCT02438826). Dr Benemei and Dr Negro report no conflicts of interest in this work.

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