BioDrugs (2022) 36:341–358
https://doi.org/10.1007/s40259-022-00530-0

REVIEW ARTICLE

Calcitonin Gene-Related Peptide (CGRP)-Targeted Monoclonal Antibodies and Antagonists in Migraine: Current Evidence and Rationale

Fred Cohen[1] · Hsiangkuo Yuan[1] · Stephen D. Silberstein[1]

Accepted: 21 March 2022 / Published online: 27 April 2022
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Abstract
Calcitonin gene-related peptide (CGRP), a 37 amino-acid neuropeptide found mostly in peptidergic sensory C-fibers, has been suggested to be implicated in the pathogenesis of migraine, which is one of the most common neurological disorders seen in medical practice, affecting almost 16% of the US population. While previously thought to be a vascular condition, migraine attacks are the result of neurogenic inflammation and peripheral/central sensitization through dysfunctional activation of the trigeminovascular system. To date, two classes of therapeutic agents have been developed to interrupt the function of CGRP: CGRP-targeted monoclonal antibodies (mAbs) and small-molecule antagonists (gepants). There are currently four CGRP-targeted mAbs and three gepants that are US Food and Drug Administration (FDA) approved for the treatment of migraine. Multiple phase II and III studies have established the efficacies and tolerability of these treatments. Previously, we reviewed the fundamental role of CGRP in migraine pathogenesis. Here, we discuss in depth the clinical evidence (randomized controlled trials and real-world studies), safety, and tolerability of CGRP-targeted mAbs and gepants for treating migraine.

Key Points

Phase II and III randomized clinical trials have demonstrated the efficacy of CGRP-targeted mAbs and gepants for the treatment of migraine.

Open-label extension and real-world data studies have demonstrated a favorable safety and tolerability profile of both drug classes.

Additional randomized controlled trials and open-label extension studies are currently underway, including the investigation of a new third-generation gepant.

1 Introduction

Migraine is one of the most common neurological disorders seen in medical practice, affecting almost 16% of the US population [1]. Migraine headache is typically pulsating or throbbing, with associated neurologic, gastric, and autonomic symptoms, and a duration of 4–72 h. It can be a severely debilitating condition, reported by the Global Burden of Disease Survey 2019 as the second highest cause of years lived with disability, first among women under 50 years of age [2]. A recent epidemiology study reported over 43% of migraineurs suffer from moderate to severe disability [3]. In addition to personal burden, migraine has a significant economic impact on society. In the USA, the annual direct healthcare cost for patients with migraine is estimated at US$22,364 per person, with a total indirect cost estimate of over US$19 billion [4]. This extensive socioeconomical impact warrants increased efforts to expand the understanding of migraine pathophysiology and facilitate the development of new treatments.

Migraine was believed to be a vascular condition, with headache pain secondary to vasodilation [5]. Now we believe that vasodilation is not the cause of pain but rather the result of neurogenic activation and inflammation [6].

✉ Stephen D. Silberstein
Stephen.silberstein@jefferson.edu

[1] Jefferson Headache Center, Department of Neurology, Thomas Jefferson University, 900 Walnut Street, Suite 200, Philadelphia, PA 19107, USA

Calcitonin gene-related peptide (CGRP), a 37 amino-acid neuropeptide, has been suggested to be implicated in the pathogenesis of migraine through dysfunctional activation of the trigeminovascular nociceptive system [7–9]. CGRP was discovered in 1982, and first postulated to be associated with migraine (and other head and facial pain) in 1985 [10, 11]. The pathophysiology of migraine, structure and nature of CGRP, and its relationship to migraine have been discussed in further detail in our previous article [12].

There are two treatment classes of drugs that inhibit the function of CGRP: monoclonal antibodies (mAbs) and small-molecule antagonists (gepants). To date, there are four CGRP-targeted mAbs (Table 1) and three gepants (Table 2) that are US Food and Drug Administration (FDA) approved for the treatment of migraine. The mechanism of action of CGRP-targeted mAbs was discussed in our previous article [12]. In this article, we discuss the current clinical evidence and rationale for CGRP-targeted therapies for migraine and other headache disorders.

2 Calcitonin Gene-Related Peptide (CGRP)-Targeted mAbs

2.1 Erenumab

Formerly known as AMG 334, erenumab (Aimovig®, Amgen, Thousand Oaks, CA, USA) is an IgG_2 mAb that targets the CGRP receptor [13]. Erenumab was the first CGRP-targeted mAb to receive FDA approval (17 May 2018) [14]. Erenumab is administered as a monthly subcutaneous injection with dosages of 70 mg and 140 mg. Erenumab has a mean T_{max} (time to peak drug concentration) of ~ 6 days and a plasma half-life of 28 days [15].

The efficacy and safety of several phase II and III studies (i.e., STRIVE, ARISE) have been detailed in our previous article (Table 3) [12]. In the open-label extension (OLE) of the early phase II studies, the benefit of erenumab continued beyond the double-blind phase. Ashina et al. reported a monthly migraine day (MMD) reduction (70 mg and 140 mg combined) of − 5.3 from baseline after 5 years in patients with episodic migraine (EM) [17]. Tepper et al. [19] also showed a MMD reduction (70 mg and 140 mg combined) of − 9.3 days from baseline after 52 weeks in patients with

Table 1 Calcitonin gene-related peptide (CGRP) monoclonal antibodies

Name	IgG	Target	Route	$T_{1/2}$	T_{max}	Dose	Frequency
Erenumab (AMG334)	IgG_2	CGRP receptor	SC	28 days	6 days	70 mg 140 mg	QM QM
Fremanezumab (TEV48125)	IgG_2	α-,β- CGRP ligand	SC	32 days	5 days	225 mg 675 mg	QM QLT
Galcanezumab (LY2951742)	IgG_4	α-,β- CGRP ligand	SC	27 days	5 days	120 mg[a]	QM
Eptinezumab (ALD403)	IgG_1	α-,β- CGRP ligand	IV	27 days	1–3 h	100 mg 300 mg	QLT QLT

$T_{1/2}$ half-life, T_{max} time to peak drug concentration, *IV* intravenous, *SC* subcutaneous, *QLT* quarterly, *QM* monthly

[a]Start with 240 mg loading

Table 2 Calcitonin gene-related peptide (CGRP) small molecule antagonists (gepants)

Name	Target	Route	$T_{1/2}$	T_{max}	Dose	Frequency
Ubrogepant (MK-1602)	CGRP receptor	PO	5–7 h	1.5 h	50 mg 100 mg	PRN[a]
Rimegepant (BMS-927711)	CGRP receptor	PO	11 h	1.5 h	75 mg	PRN[a] QoD[b]
Atogepant (MK-8031)	CGRP receptor	PO	11 h	2 h	10 mg 30 mg 60 mg	QD[b]

PO oral, *QoD* every other day, $T_{1/2}$ half-life, T_{max} time to peak drug concentration, *QD* daily, *PRN* as needed

[a]As an abortive agent

[b]As a preventive agent

Table 3 Summary of erenumab randomized controlled trials and related open-label extension studies

Study	Phase	Inclusion criteria	Study period/*n*	Primary endpoint[a]
NCT01952574 Sun et al. [16]	II	EM and ≤ 2 prior classes of failed preventive treatments	3 months *n* = 483	MMD reduction: Placebo: − 2.3 70 mg: − 3.4 ($p = 0.021$) 7 mg and 21 mg not significant
Ashina et al. [17][b]			5 years *n* = 383	MMD reduction: − 5.3
NCT02066415 Tepper et al. [18]	II	CM and ≤ 3 prior classes of failed preventive treatments	3 months *n* = 667	MMD reduction: Placebo: − 4.2 70 mg: − 6.6 ($p < 0.0001$) 140 mg: − 6.6 ($p < 0.0001$)
NCT02174861 Tepper et al. [19][b]			12 months *n* = 451	MMD reduction: 70 mg: − 8.5 140 mg: − 10.5
NCT02456740 Goadsby et al. (STRIVE) [20]	III	EM and ≤ 2 prior classes of failed preventive treatments	4-6 months *n* = 955	MMD reduction: Placebo: − 1.8 70 mg: − 3.2 ($p < 0.001$) 140 mg: − 3.7 ($p < 0.001$)
Godasby et al. [21][b]			12 months *n* = 845	MMD reduction: 70 mg: − 4.2 140 mg: − 4.6
NCT02483585 Dodick et al. (ARISE) [22]	III	EM and ≤ 2 prior classes of failed preventive treatments	3 months *n* = 577	MMD reduction: Placebo: − 1.8 70 mg: − 2.9 ($p < 0.001$)
NCT03096834 Reuter et al. (LIBERTY) [23]	III	EM and 2-4 prior classes of failed preventive treatments	3 months *n* = 246	50% or greater reduction rate of MMD: Placebo: 14% 140 mg: 30% ($p = 0.002$)
Goadsby et al. [24][b]			64 weeks *n* = 204	50% or greater reduction rate of MMD: 44.3%
NCT02630459 Sakai et al. [25]	II	EM and ≤ 2 prior classes of failed preventive treatments	4–6 months *n* = 475	MMD reduction: Placebo: 0.06 28 mg: − 1.25 ($p = 0.004$) 70 mg: − 2.31 ($p < 0.001$) 140 mg: − 1.89 ($p < 0.001$)
NCT03812224 Takeshima et al. [26]	III	EM and CM, and ≤ 3 classes of failed preventive treatments	4–6 months *n* = 261	MMD reduction: Placebo: − 1.98 70 mg: − 3.60 ($p < 0.001$)
NCT03828539 Uwe et al. [27]	IV	EM and ≤ 2 prior classes of failed preventive treatments	6 months *n* = 777	Rate of discontinuation: 70 mg/140 mg: 10.6% Topiramate 100 mg: 38.9% ($p < 0.001$)
NCT03333109 Wang et al. EMPOwER [28]	III	EM and ≤ 2 prior classes of failed preventive treatments	3 months *n* = 900	MMD reduction: Placebo: − 3.1 70 mg: − 4.2 ($p = 0.002$) 140 mg: − 4.8 ($p < 0.001$)

All erenumab treatments were given as monthly subcutaneous injections

EM episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day

[a] *p* Values are results compared against placebo

[b] Open-label extension study

chronic migraine (CM). OLE data from STRIVE after 52 weeks showed a MMD reduction of − 4.2 and − 4.6 for erenumab 70 mg and 140 mg, respectively [21].

A phase II randomized controlled trial (RCT) conducted in Japan evaluated erenumab 28 mg, 70 mg, and 140 mg. After 4–6 months, patients receiving erenumab 28 mg, 70 mg, and 140 mg reported a MMD decrease of − 1.25 (95% confidence interval (CI) − 2.10 to − 0.41; $p = 0.004$), − 2.31 (95% CI − 3.00 to − 1.62; $p < 0.001$), and − 1.89 (95% CI − 2.58 to − 1.20; $p < 0.001$) compared to placebo, respectively [25]. OLE data after 72 weeks reported a MMD reduction of − 2.9 from baseline [29]. A phase III RCT conducted

in Japan assessed erenumab 70 mg in patients with EM and CM for 4–6 months. Patients receiving erenumab 70 mg reported a MMD reduction of 3.6 days compared to 1.98 days in those receiving placebo (95% CI − 2.52 to − 0.73, $p < 0.001$) [26]. When stratified by diagnosis, participants with EM receiving erenumab 70 mg reported a statistically significant MMD reduction difference of − 1.62 compared to placebo (95% CI − 2.56 to − 0.78, $p < 0.001$), while patients with CM receiving erenumab 70 mg reported a statistically insignificant MMD reduction difference of − 1.57 compared to placebo (95% CI − 3.39 to 0.24, $p = 0.089$). When stratified by treatment history, erenumab was found to be effective in patients who had previously failed preventive treatments and in patients receiving erenumab as monotherapy or concurrently with another preventive treatment [30]. Additionally, patients receiving erenumab reported using less acute medications for migraine days monthly, − 2.57 days in the erenumab group compared to − 1.10 for the placebo group (95% CI − 2.24 to − 0.71, $p < 0.001$) [26].

Unlike STRIVE and ARISE, LIBERTY enrolled patients with EM that failed between two to four preventive treatments. In total, 246 participants were randomly assigned between erenumab 140 mg and placebo. After 12 weeks, 30% of patients receiving erenumab 140 mg reported a 50% or greater reduction of MMD compared to 14% from the placebo group (95% CI 1.4–5.2; $p = 0.002$) [23]. A 64-week OLE reported an increase to 44.3% of patients reporting a 50% or greater reduction of MMD [24]. The 3-year OLE of the LIBERTY study is currently ongoing. A subgroup analysis examining patients who met the criteria for medication overuse headache (MOH) reported erenumab 70 mg and 140 mg to reduce MMD by − 6.6 days [31]. Additionally, patients taking erenumab reported greater functional improvement than patients taking placebo [32].

A phase IV RCT aimed to compare the tolerability and efficacy of erenumab to topiramate as migraine preventive treatment. The primary outcome was rate of discontinuation, which was 10.6% for patients taking erenumab compared to 38.9% of patients taking topiramate ($p < 0.001$) [27]. Additionally, adverse events (AEs) were more common in patients taking topiramate than in patients taking erenumab (81.2% vs. 55.4%, respectively),

A meta-analysis of phase II and III RCTs reported MMD reductions with erenumab 70 mg of − 1.3 after 12 weeks (95% CI − 1.7 to − 1.0, $p < 0.001$) and − 1.6 after 24 weeks (95% CI − 2.2 to − 1.0, $p < 0.001$) compared to placebo [33]. Similarly, erenumab 140 mg displayed a MMD reduction of − 1.9 after 12 weeks (95% CI − 2.3 to − 1.4, $p < 0.001$) and − 2.1 at 24 weeks (95% CI − 2.7 to − 1.5, $p < 0.001$) compared to placebo. Ashina et al. conducted a post hoc analysis and stratified MMD reductions in patients with and without aura. In patients with EM receiving erenumab 70 mg and 140 mg, patients without aura reported MMD reductions of − 1.2 and − 2.5, compared to patients with aura reporting MMD reductions of − 1.1 and − 0.9 [34]. In patients with CM receiving erenumab 70 mg and 140 mg, patients without aura reported MMD reductions − 2.7 and − 2.1, compared to patients with aura reporting MMD reductions of − 2.1 and − 3.1.

Pooled data reported AEs occurring in 51.7% of patients receiving erenumab, of which 1.8% were reported to be serious [33]. Common AEs were injection site reaction, nasopharyngitis, upper respiratory tract infection, fatigue, and constipation. Another pooled analysis investigated specifically for vascular AEs, reporting no difference between erenumab and placebo [35]. Lastly, an ongoing 5-year OLE study reported an AE rate similar to the placebo-controlled studies [36]. Constipation with serious complications has been observed in the post-marking setting, with reported cases requiring hospitalization and surgery. Development and worsening of hypertension were also reported in the post-marketing setting. Current safety data suggest while patients with constipation or hypertension should not be excluded from taking erenumab, screening and monitoring is warranted [37].

In addition to RCTs, several prospective studies evaluating erenumab have been conducted. EARLY was a prospective real-life study assessing patients with high-frequency EM (HFEM) or CM. After 12 weeks, patients reported a decrease of MMDs by 4.5 and 9.3 days with HFEM and CM, respectively [38]. EARLY 2 was a 48-week longitudinal real-life study assessing erenumab 70 mg and 140 mg in patients with HFEM and CM who failed ≥ three prior preventive treatments. After 48 weeks, erenumab achieved a MMD reduction of 4.3 in patients with HFEM, and a MHD reduction of 12.8 patients with CM [39]. Studies reporting real-world data (RWD) reported a range of 35–55% of patients achieving at least 50% reduction of MMD, and a range of 5.6–8.4 mean decrease of MMD [40–42]. AEs rates from OLE of RCTs, prospective studies, and RWD have varied greatly, ranging from 18.6 to 91.9% [24, 29, 39–44]. Constipation was one of the most common adverse effects reported, with rates as high as 43% [43].

Furthermore, erenumab has been used as a possible treatment for cluster headache (CH). A case series of five patients reported an improvement in intensity and frequency of cluster attacks after receiving erenumab 40 mg for 3–5 months [45].

2.2 Galcanezumab

Initially named LY2951742, galcanezumab (Emgality®, Eli Lilly, Indianapolis, IN, USA) is a humanized IgG_4 mAb with high affinity to α- and β-CGRP [46]. Galcanezumab has a T_{max} of ~ 5 days, and a half-life of 27 days [15]. Galcanezumab obtained FDA approval on 27 September 2018, and

became the first (and at the time of writing, only) CGRP-targeted mAb FDA approved for the treatment of episodic CH on 4 June 2019 [47].

EVOLVE-1, EVOLVE-2, and REGAIN have been reported in our previous article (Table 4) [12]. A post hoc study pooling patients who failed ≥ two preventives from EVOLVE-1 and 2 showed a MMD reduction of 2.60 days (95% CI − 3.95 to − 1.25) and − 3.37 days (95% CI − 4.78 to − 1.96) for galcanezumab120 mg and 240 mg, respectively. OLE of the REGAIN trial reported a MHD reduction of −6.5 to −7.3 at 6 months and −8.0 to −9.0 at 12 months [52]. A meta-analysis of these RCTs reported the most common AEs were injection site pain (10.9%), nasopharyngitis 5.8%, injection site reaction (4.7%), and upper respiratory

Table 4 Summary of galcanezumab clinical trials and related open-label extension studies

Study	Phase	Inclusion criteria	Study period/*n*	Primary endpoint[a]
NCT01625988 Dodick et al. [47]	II	EM and ≤ 2 prior classes of failed preventive treatments	3 months *n* = 218	MHD reduction: placebo: − 3.0 150 mg: − 4.2 ($p = 0.003$)
NCT02959177 Sakai et al. [48]	II	EM and ≤ 2 prior classes of failed preventive treatments	6 months *n* = 915	MMD reduction: placebo: − 0.59 120 mg: − 3.60 240 mg: − 3.36 (both $p < 0.001$)
NCT02614183 Stauffer et al. (EVOLVE-1) [49]	III	EM and ≤ 2 prior classes of failed preventive treatments	6 months *n* = 858	MMD reduction: placebo: − 2.8 120 mg: − 4.7 240 mg: − 4.6 ($p < 0.001$ for both)
NCT02614196 Skljarevski et al. (EVOLVE-2) [50]	III	EM and ≤ 2 prior classes of failed preventive treatments	6 months *n* = 915	MMD reduction: placebo: − 2.3 120 mg: − 4.3 240 mg: − 4.2 ($p < 0.001$ for both)
NCT02614261 Detke et al. (REGAIN) [51]	III	CM and ≤ 3 prior classes of failed preventive treatments	3 months *n* = 1113	MHD reduction: placebo: − 2.7 120 mg: − 4.8 240 mg: − 4.6 ($p < 0.001$ for both)
Detke el al. [52][b]			12 months *n* = 1022	MHD reduction: 120 mg/240 mg: − 8.0 to − 9.0
NCT02397473 Goadsby et al. [53]	III	Episodic cluster headache	8 weeks *n* = 106	Mean reduction of weekly frequency of cluster headache attacks: placebo: − 5.2 300 mg: − 8.7 ($p = 0.04$)
NCT02438826 Dodick et al. [54]	III	Chronic cluster headache	3 months *n* = 237	Mean reduction of weekly frequency of cluster headache attacks: placebo: − 4.6 300 mg: − 5.4 ($p = 0.334$)
NCT03559257 Mulleners et al. (CONQUER) [55]	III	EM and CM, and 2–4 prior classes of failed preventive treatments	3 months *n* = 462	MMD reduction: placebo: − 1.0 120 mg: − 4.1 ($p < 0.0001$)
Reuter et al. [56][b]			6 months *n* = 449	MMD reduction[c] − 5.2 vs. − 5.6 EM: − 3.8 vs. − 4.5 CM: − 6.5 vs. − 8.2

All galcanezumab treatments were given as monthly subcutaneous injections

EM episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day, *MHD* monthly headache day

[a] *p* Values are results compared against placebo

[b] Open-label extension study

[c] Mean change (baseline to end of open-label extension) from placebo vs. active treatment group (original allocation)

tract infections (3.7%) [57]. A post hoc analysis of these three RCTs showed galcanezumab is also effective in treating patients with MOH [58].

Similar to the LIBERTY trial for erenumab, CONQUER was a phase III RCT assessing galcanezumab in patients who failed two to four preventive therapies. However, unlike LIBERTY, CONQUER included patients with CM. Participants received placebo or a loading dose of galcanezumab 240 mg followed by galcanezumab 120 mg monthly. After 12 weeks, participants who received galcanezumab reported a MMD reduction of − 4.1 compared to − 1.0 with placebo (95% CI − 3.9 to − 2.3; $p < 0.0001$) [55]. When stratifying by EM and CM, galcanezumab achieved a MMD reduction of − 2.88 and − 5.90, respectively. OLE data of CONQUER reported galcanezumab achieved a MMD reduction of − 5.6 in the galcanezumab continuous group, and − 5.2 in those who switched from placebo to galcanezumab [56].

Several prospective and open-label studies assessing galcanezumab have been conducted. A phase III open-label study assessed galcanezumab 120 mg and 240 mg over 12 months, reporting a MMD reduction of − 5.6 and − 6.5, respectively [59]. AEs rates were similar between the two groups, except for a greater rate of upper respiratory tract infections seen in galcanezumab 240 mg (14.9% compared to 7.0% in the 120 mg group). GARLIT, an open-label prospective study in Italy, assessed galcanezumab 120 mg with HFEM and CM. After 6 months, MMD reductions were reported as − 8 days and − 13 days in patients with HFEM and CM, respectively (both $p < 0.001$) [60]. A phase II RCT from Japan reported galcanezumab 120 mg and 240 mg to be effective for EM [48]. A 12-month OLE further confirmed safety and tolerability of galcanezumab in patients with EM and CM. Of all patients, nasopharyngitis was the most common AE (45.7%), followed by injection site erythema (19.0%) and injection site pruritis (16.7%) [61].

In addition to being used for the prevention of migraine, galcanezumab has been established as an effective treatment for episodic cluster headache. A phase III RCT assessed galcanezumab 300 mg against placebo, reporting a mean reduction in the weekly frequency of cluster headache attacks of − 8.7 and − 5.2, respectively (95% CI 0.2–6.7; $p = 0.04$) [53]. A similar RCT was constructed to assess galcanezumab for the treatment of chronic cluster headache. No statistically significant difference was seen between galcanezumab and placebo after 12 weeks, with a reported mean change in weekly cluster attacks of − 5.4 for galcanezumab and − 4.6 for placebo ($p = 0.334$) [54].

2.3 Fremanezumab

Formerly known as TEV-48125 (as well as LBR-101, PF-04427429, and RN307), fremanezumab (Ajovy®, Teva, Petah Tikva, Israel) is a IgG_2, humanized CGRP mAb. The fremanezumab mechanism of action involves targeting both α and β isoforms of CGRP ligands. Fremanezumab is given as a subcutaneous injection in doses of 225 mg monthly and 675 mg quarterly, with a mean T_{max} of 7 days and 5 days, respectively [62]. Fremanezumab has a half-life of 32 days [15].

Several phase II studies and the phase III HALO studies were discussed in our previous article (Table 5) [12]. Subgroup analyses have since been published from HALO-CM. Patients treated with fremanezumab who also had concurrent MOH reported a statistically significant reduction of monthly medication use days compared to placebo [70]. A subgroup analysis on patients receiving fremanezumab with moderate to severe depression had improved Patient Global Impression Change (PGIC) assessments and HIT-6 scores [71]. A long-term study extension of 52 weeks was conducted from the HALO trials. Fremanezumab monthly dosing reduced MMD in patients with EM and CM by − 5.1 and − 8.0, respectively. Fremanezumab quarterly dosing reduced MMD in patients with EM and CM by − 5.2 and − 7.2, respectively. The most common AE reported was injection site reactions (induration 33%, pain 31%, and erythema 26%) [67].

FOCUS was a phase III RCT assessing fremanezumab in EM and CM who failed two to four preventive medications. FOCUS reported fremanezumab to be effective in MMD reduction in both patient populations. A post hoc analysis of FOCUS stratified the results by age and sex, and reported fremanezumab to be effective in all age groups in both men and women [72]. A phase III RCT of fremanezumab patients with CM conducted in Japan and Korea reported fremanezumab to be effective (both monthly and quarterly dosing) in reducing MHDs. Additionally, patients receiving fremanezumab reported lower HIT-6 scores than those in the placebo group [69].

Several phase II RCTs are underway assessing fremanezumab for treating patients with migraine and major depressive disorder, post-traumatic headache, and fibromyalgia [73]. RWD of fremanezumab after 6 months have revealed MMD reductions of − 7.7 and − 10.1 in patients with EM and CM, respectively [74]. A 24-month prospective, observational study of fremanezumab in EM and CM is currently ongoing in Europe [75]. Fremanezumab was assessed for the treatment of CH (NCT02964338), and subsequently found to be ineffective for reducing chronic CH frequency after 12 weeks [76].

2.4 Eptinezumab

Originally labeled ALD403, eptinezumab (Vyepti®, Lundbeck, Deerfield, IL, USA) is a IgG_1 humanized kappa mAb targeting both α and β isoforms of CGRP ligands [77]. Eptinezumab is the first and only CGRP-mAb to be available

Table 5 Summary of fremanezumab randomized controlled trials and related open-label extension studies

Study	Phase	Inclusion criteria	Study period/*n*	Primary endpoint[a]
NCT02025556 Bigal et al. [63]	II	HFEM and ≤ 2 prior classes of failed preventive treatments	3 months *n* = 297	MMD reduction: placebo: − 3.46 225 mg: − 6.27 675 mg: − 6.09 (both $p < 0.0001$)
NCT02021773 Bigal et al. [64]	II	CM and ≤ 2 prior classes of failed preventive treatments	3 months *n* = 264	Mean reduction of headache h: placebo: − 37.10 675/225 mg: [c] − 59.84 ($p = 0.0386$) 900 mg: − 67.51 ($p = 0.0057$)
NCT02621931 Silberstein et al. (HALO-CM) [65]	III	CM and < 2 prior classes of failed preventive treatments	3 months *n* = 1130	MHD reduction: placebo: − 2.5 225 mg: − 4.6 675 mg: − 4.3 (both $p < 0.001$)
NCT02638103 Goadsby et al. [65][b]			12 months *n* = 1110	MMD reduction: 225 mg: − 8.0 675 mg: − 7.2
NCT02629861 Dodick et al. (HALO-EM) [66]	III	EM and < 2 prior classes of failed preventive treatments	3 months *n* = 875	MMD reduction: placebo: − 2.2 225 mg: − 3.7 675 mg: − 3.4 (both $p < 0.001$)
NCT02638103 Goadsby et al. [67][b]			12 months *n* = 780	MMD reduction: 225 mg: − 5.1 675 mg − 5.2
NCT03308968 Ferrai et al. (FOCUS) [68]	III	EM or CM and 2–4 prior classes of failed preventive treatments	3 months *n* = 838	MMD reduction: placebo: − 0.6 225 mg: − 4.1 675 mg: − 3.7 (all *p* values < 0.0001)
NCT03303079 Sakai et al. [69]	III	CM and < 2 prior classes of failed preventive treatments	3 months *n* = 571	MHD reduction: placebo: − 2.4 225 mg: − 4.1 675 mg: − 4.1 (both $p < 0.001$)

All fremanezumab treatments were given intravenously. Fremanezumab 225 mg dosages were given monthly, 675 mg dosages were given every 3 months

EM episodic migraine, *HFEM* high-frequency episodic migraine, *CM* chronic migraine, *MMD* mean monthly migraine day, *MHD* monthly headache day

[a] *p* Values are results compared against placebo

[b] Open-label extension study

[c] Patients received 675 mg in the first month, followed by doses of 225 mg in the second and third months

in an intravenous (IV) formulation. Eptinezumab achieves a 100% bioavailability at the end of infusion, and has a half-life of 27 days [78]. The recommended dose is 100 mg every 3 months, although some patients may benefit from a dose of 300 mg [77].

Several phase I and II studies as well as PROMISE-1 were discussed in our previous article (Table 6) [12]. PROMISE-1 was extended for 1 year, with patients receiving 30 mg, 100 mg, and 300 mg reporting MMD reductions of − 5.0, − 4.5, and − 5.3, respectively [82]. PROMISE-2 was a RCT trials assessing eptinezumab for migraine preventive therapy for CM. After 12 weeks, patients receiving eptinezumab 100 mg and 300 mg reported a MMD of − 7.7 and − 8.2, respectively (both $p < 0.0001$) [86]. Nasopharyngitis was the only AE reported, with a rate > 2%. After 24 weeks, patients on eptinezumab 100 mg and 300 mg reported a MMD of − 8.2 and − 8.8, respectively (both $p < 0.001$) [84]. A 6-month OLE further confirmed the efficacy of eptinezumab [84].

Table 6 Summary of eptinezumab randomized controlled trials and related open-label extension studies

Study	Phase	Inclusion criteria	Study period/*n*	Primary endpoint[a]
NCT01772524 Dodick et al. [79]	II	EM	3 months *n* = 174	MMD reduction: placebo: − 4.6 1000 mg: − 5.6 ($p = 0.03$)
NCT02275117 Dodick et al. [80]	II	CM	3 months *n* = 616	≥ 75% migraine responder rate: placebo: 20.7% 10 mg: 33.3% ($p = 0.033$) 30 mg: 31.4% ($p = 0.072$) 100 mg: 28.2% ($p = 0.201$) 1000 mg: 26.8% ($p = 0.294$)
NCT02559895 Ashina et al. (PROMISE-1) [81]	III	EM	3 months *n* = 888	MMD reduction: placebo: − 3.2 30 mg: − 4.0 ($p = 0.0046$) 100 mg: − 3.9 ($p = 0.0182$) 300 mg: − 4.3 ($p = 0.0001$)
Smith et al. [82]			48 weeks *n* = 888	MMD reduction: placebo: − 4.1 30 mg: − 5.0 (95% CI − 1.61 to − 0.11) 100 mg: − 4.5 (95% CI − 1.13 to 0.37) 300 mg: − 5.3 (95% CI − 1.95 to − 0.46)
NCT02974153 Lipton et al. (PROMISE-2) [83]	III	CM	12 weeks *n* = 1072	MMD reduction: placebo: − 5.6 100 mg: − 7.7 ($p < 0.0001$) 300 mg: − 8.2 ($p < 0.0001$)
Silberstein et al. [84][b]			24 weeks *n* = 1072	MMD reduction: placebo: − 6.2 100 mg: − 8.2 ($p < 0.001$) 300 mg: − 8.8 ($p < 0.001$)
NCT04152083 Winner et al. (RELIEF) [85]	III	CM	Acute treatment *n* = 480	Time to headache pain freedom: placebo: 9 h 100 mg: 4 h ($p < 0.001$) Time to absence of MBS: placebo: 3 h 100 mg: 2 h ($p < 0.001$)

All eptinezumab treatments were given intravenously

EM episodic migraine, *CM* chronic migraine, *MBS* most bothersome symptom, *MMD* mean monthly migraine day

[a] *p* Values are results compared against placebo

[b] Open-label extension study

PREVAIL (NCT02985398) was a long-term OLE study assessing the safety of eptinezumab in patients with CM over 2 years. The most common AEs reported were nasopharyngitis (14.1%), upper respiratory tract infection (7.8%), sinusitis (7.8%), influenza (6.3%), and bronchitis (5.5%) [87]. Five patients (3.9%) experienced a serious AE (only one was considered related to eptinezumab), and the rate of study-drug discontinuation due to AEs was 6.3%. Several on-going studies are assessing eptinezumab in pediatric populations (NCT04537429 and NCT04965675), and RWD are still being collected [88].

In addition to being an effective preventive migraine treatment, a phase III RCT assessed eptinezumab as an abortive agent. Eptinezumab was reported to achieve headache pain freedom after 4 h [compared to 9 h with placebo ($p < 0.001$)] and absence of the most bothersome symptom (MBS; photophobia, phonophobia, or nausea) after 2 h [compared to 3 h with placebo ($p < 0.001$)] [85]. After 2 h, 23.5% of patients receiving eptinezumab reported being free of headache pain [compared to 12.0% with placebo (95% CI 1.39–3.72, $p < 0.001$)] and 55.5% reported absence of MBS [compared to 35.8% with placebo (95% CI 1.55–3.25, $p < 0.001$)]. Of the treatment-emergent AEs, 10.9% were from the eptinezumab group and 10.3% from the placebo group, with the most common AE being hypersensitivity reactions.

3 Small-Molecule CGRP Antagonists

With CGRP established to have a critical role in migraine pathophysiology, CGRP-receptor antagonists, known as gepants, were developed. The mechanism of action of gepants consists of inhibition of CGRP receptors and reversal of CGRP-induced vasodilation and neurogenic inflammation [76]. Gepants also inhibit trigeminovascular nociceptive activation and block cAMP production and cAMP response element-binding protein (CREB) phosphorylation [89]. The first generation of gepants were telcagepant (Merck, Kenilworth, NJ, USA), olcegepant (Boehringer Ingelheim GmbH, Germany), and MK-3207 (Merck, Kenilworth, NJ, USA). These early gepants were found to be more effective than placebo and comparable to triptans [90–93]. However, further research of these therapies was discontinued due to their potential hepatoxicity [94]. Development of gepants continued with the release of the second-generation therapies: rimegepant (Biohaven, New Haven, CT, USA), ubrogepant (Allergan, Dublin, Ireland), and atogepant (Allergan, Dublin, Ireland). Zavegepant, a third-generation gepant, is currently in development at the time of writing. It is worth noting that while other existing acute migraine medications (e.g., triptans or ergots) can cause rebound headache or MOH, gepants have not been seen to cause rebound headache or MOH [95].

3.1 Olcegepant

Initially called BIBN-4096, olcegepant (Boehringer Ingelheim GmbH, Germany) was the first selective CGRP receptor antagonist administered IV. A phase I/II RCT assessed escalating doses of olcegepant (up to 10 mg), and determined the gepants to have a half-life of 2.5 h [96]. In an RCT, patients were given either olcegepant 2.5 mg or placebo followed by 1.5 mg/min of human αCGRP. None of the patients receiving olcegepant developed a CGRP-induced headache [97]. Another RCT assessed olcegepant 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, and 10 mg. Olcegepant was more effective than placebo for pain relief after 2 h, with olcegepant 2.5 mg providing a response rate of 66% and 27% for placebo ($p = 0.001$) [90]. Paresthesia was reported in 8% of the study population receiving olcegepant, raising tolerability concerns. Ultimately, development for olcegepant was discontinued due to difficulties in creating an oral formulation [98].

3.2 Telcagepant

Originally labeled as MK-0974, telcagepant (Merck, Kenilworth, NJ, USA) was the first-generation oral CGRP receptor antagonist. Telcagepant has a T_{max} at 1.5 h and a half-life of ~ 6 h [99]. Several phase II and III RCTs demonstrated telcagepant to be superior to placebo and as effective as triptans for the acute treatment of migraine [91, 92, 100, 101].

A phase II RCT was conducted assessing telcagepant as a preventive treatment for migraine [94]. 660 patients were enrolled, and received telcagepant 140 mg, telcagepant 280 mg, or placebo. However, after reviewing data of ~ 100 patients, an independent safety monitoring board terminated the study due to a concern for hepatoxicity. Of the patients receiving telcagepant, 13 developed alanine aminotransferase (ALT) levels ≥ 3 the upper limit of normal (ULN), and seven patients developed aspartate aminotransferase ≥ 3 the ULM. Two patients developed ALTs > 30 times the ULM, both cases resolving after telcagepant was discontinued. While telcagepant demonstrated promising results for the treatment of migraines, the concerns for hepatoxicity led to the discontinuation of further testing.

3.3 Ubrogepant

On 23 December 2019, ubrogepant (previously labeled MK-1602; Ubrelvy®, Allergan, Dublin, Ireland) became the first gepant to receive FDA approval for the acute treatment of migraine. Ubrogepant has a T_{max} at 1.5 h and a half-life of 5–7 h [102]. A phase II RCT assessed ubrogepant 1 mg, 10 mg, 25 mg, 50 mg, and 100 mg against placebo with a primary endpoint of freedom of pain and headache response at 2 h. Only the 100 mg dose was found to be statistically significant in 2-h pain freedom compared to placebo (8.9%; $p < 0.001$) [103].

Two phase III clinical trials, ACHIEVE I and II, assessed ubrogepant 50 and 100 mg doses versus placebo and ubrogepant 25 and 50 mg, respectively (Table 7) [104, 105]. ACHIEVE I and II enrolled 1,672 and 1,686 participants, respectively, and had primary end-points of freedom of pain after 2 h and resolution of MBS. In ACHIEVE I, Ubrogepant 50 mg and 100 mg achieved 19.2% and 21.2% freedom of pain after 2 h, respectively, compared to 11.8% for placebo ($p = 0.002$) [104]. Ubrogepant 50 mg and 100 mg achieved 38.6% and 37.7% resolution of MBS, respectively, compared to 27.8% for placebo ($p = 0.002$). In ACHIEVE II, ubrogepant 25 mg and 50 mg achieved 20.7% (95% CI 1.5–11.5; $p = 0.03$) and 21.8% (95% CI 2.6–12.5; $p = 0.01$) freedom of pain after 2 h, respectively, compared to 14.3% in the placebo group [105]. Ubrogepant 25 mg and 50 mg achieved 34.1% (95% CI 0.6–12.7; $p = .07$) and 38.9% (95% CI 5.4–17.5; $p = .01$) resolution of MBS, respectively, compared to 27.4% in the placebo group. A pooled post hoc analysis of both ACHIEVE I and II reported 20.5% who received ubrogepant 50 mg had freedom from pain after 2 h compared to 13% with placebo (95% CI 1.34–2.22; p

Table 7 Summary of ubrogepant randomized controlled trials

Study	Phase	Inclusion criteria	*n*	Primary endpoint[a]
NCT01613248 Voss et al. [103]	II	2–8 migraine attacks per month	527	2-h headache pain freedom: Placebo: 8.9% 1 mg: 5.6% ($p = 0.344$) 10 mg: 14.8% ($p = 0.211$) 25 mg: 21.4% ($p = 0.013$) 50 mg: 21.0% ($p = 0.020$ 100 mg: 25.5% ($p = 0.003$)
NCT02828020 Dodick et al. (ACHIEVE-1) [104]	III	2–8 migraine attacks per month	1672	2-h headache pain freedom: Placebo: 11.8% 50 mg: 19.2% ($p = 0.002$) 100 mg: 21.2% ($p < 0.001$) 2-h absence of MBS: Placebo: 27.8% 50 mg: 38.6% ($p = 0.002$) 100 mg: 37.7% ($p = 0.002$)
NCT02867709 Lipton el al. (ACHIEVE-2) [105]	III	2–8 migraine attacks per month	1686	2-h headache pain freedom: Placebo: 14.3% 25 mg: 20.7% ($p = 0.03$) 50 mg: 21.8% ($p = 0.01$) 2-h absence of MBS: Placebo: 27.4% 25 mg: 34.1% ($p = 0.07$) 50 mg: 38.9% ($p = 0.01$)

All ubrogepant treatments were given as oral formulations

MBS most bothersome symptom

[a]*p* Values are results compared against placebo

< 0.001) [106]. The pooled analysis also showed 38.7% of patients receiving ubrogepant 50 mg had resolution of MBS, compared to 27.6% with placebo (95% CI 1.37–2.05; $p < 0.001$.) The most common adverse effects were nausea and somnolence. The pooled analysis also showed no clinical signs of hepatoxicity [106]. Pooled results also reported improvement in patient satisfaction and functional disability compared to placebo [107].

3.4 Rimegepant

Previously known as BMS-927711, rimegepant (Nurtec®, Biohaven, New Haven, CT, USA) is a gepant originally designed for acute treatment of migraine. Rimegepant achieves T_{max} after 1.5 h and a half-life of approximately 11 h. A phase 1 studies established rimegepant can be tolerated in single doses up to 1,500 mg [108]. A phase II study assessed several dosages of rimegepant (75 mg, 150 mg, 300 mg, and 600 mg) compared to placebo and sumatriptan (Table 8). Rimegepant was found to provide greater pain freedom at 2 h when compared to placebo, while sumatriptan was found to be more effective (however the study was not designed for such a comparison) [109].

Several phase III RCTs assessed the efficacy of rimegepant (75 mg) as an abortive therapy [109–111]. The primary endpoints for all the trials were headache pain freedom and resolution of MBS at 2 h. Rimegepant was found to be statistically superior to placebo in all the trials for both primary endpoints (Table 8). Secondary endpoints included sustained pain relief at 24 h, use of rescue medication within 24 h, and sustained relief from MBS at 48 h. A meta-analysis of the clinical trials found rimegepant 75 mg to be statistically superior to placebo in providing pain relief after 2 h (58.6% vs. 44.6%, RR = 1.34, 95% CI 1.25–1.44, $p < 0.001$) headache pain freedom after 2 h (20.6% vs. 12.5% for rimegepant vs. placebo RR = 1.70, 95% CI 1.39–2.08, $p < 0.001$), freedom from the MBS (36.0% vs. 25.1% for rimegepant vs. placebo RR = 1.44, 95% CI 1.23–1.68, $p < 0.001$) [112]. Common adverse effects of rimegepant are dizziness, nausea, and urinary tract infections (UTIs). Rimegepant was found to have no statistically significant difference in liver function test abnormalities compared to placebo. The safety of rimegepant in patients < 18 years old, pregnant, or breastfeeding has not been established.

In addition to acute treatment, rimegepant has been explored as a preventive therapy. Croop et al. conducted a phase II/III RCT assessing the efficacy of rimegepant 75 mg every other day against placebo for 3 months. Rimegepant displayed a statistically significant larger reduction in migraine days compared to placebo (4.3 vs. 3.5 days, 95% CI − 1.46 to − 0.20; $p = 0.0099$) [113]. Study participants who received rimegepant and placebo were equally likely

Table 8 Summary of rimegepant randomized controlled trials

Study	Phase	Inclusion criteria	*n*	Primary outcome[a]
NCT01430442 Marcus et al. [109]	II	2–7 migraine attacks per month	885	2-h headache pain freedom: Placebo: 15.3% Sumatriptan 100 mg: 35.0% ($p < 0.001$) 75 mg: 31.4% ($p = 0.002$) 150 mg: 32.9% ($p < 0.001$) 300 mg: 29.7% ($p = 0.002$)
NCT03237845 Lipton et al. [110]	III	2–8 migraine attacks per month	1186	2-h headache pain freedom: Placebo: 12.0% 75 mg: 19.6% ($p < 0.001$) 2-h freedom from MBS: Placebo: 25.2% 75 mg: 37.6% ($p < 0.001$)
NCT03461757 Croop et al. [111]	III	2–8 migraine attacks per month	1811	2-h headache pain freedom: Placebo: 11.0% 75 mg: 21.0% ($p < 0.001$) 2-h freedom from MBS: Placebo: 27.0% 75 mg: 35.0% ($p < 0.001$)

All rimegepant treatments were given as oral formulations

MBS most bothersome symptom

[a]*p* Values are results compared against placebo

to have an AE, and AEs were similar to the previous acute treatment RCTs. One study participant in the rimegepant group had an alanine aminotransferase elevation greater than ten times the ULN. On 27 May 2021, rimegepant became the first gepant to obtain regulatory approval for the preventive treatment of EM. CHALLENGE-MIG (NCT05127486), a phase IV RCT comparing galcanezumab and Rimegepant, is currently underway.

3.5 Atogepant

While the previously mentioned gepants were initially designed as an abortive migraine treatment, atogepant was developed specifically as a preventive therapy. Atogepant (Qulipta®, AbbVie, Chicago, IL, USA) is a potent, selective, competitive, second-generation oral CGRP receptor antagonist with a T_{max} of ~ 2 h and a half-life of ~ 11 h [114]. A phase I study found atogepant was tolerated in single doses up to 300 mg [115].

A phase II/III study assessed atogepant 10 mg once daily, 30 mg once daily, 60 mg once daily, 30 mg twice daily, and 60 mg twice daily against placebo (Table 9). Atogepant was found to decrease monthly headache days by − 4.0 ($p = 0.024$) for 10 mg daily, − 3.8 ($p = 0.039$) for 30 mg once daily, − 3.6 ($p = 0.039$) for 60 mg once daily, − 4.2 ($p = 0.0034$) for 30 mg twice daily, and − 4·1 ($p = 0.0031$) for 60 mg twice daily, compared to − 2.9 in the placebo group [116]. Another phase III study assessed a change in MMDs 12 weeks of atogepant 10 mg daily, 30 mg daily, and 60 mg daily or placebo. Patients reported a mean change from baseline in MMDs of − 4.0 for atogepant 30 mg, − 4.2 for atogepant 60 mg, and − 2.5 for placebo ($p < 0.001$ for all comparisons with placebo) [117].

The most reported AEs in the clinical trials were nausea, constipation, and upper respiratory tract infections [116, 117]. No hepatoxicity was observed in the clinical trials for atogepant, including in a 28-day hepatic safety study [118]. Atogepant was found to have no drug-drug interactions with acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, and oral contraceptives [119–121]. Atogepant received FDA approval for preventive treatment of migraine on 28 September 2021.

3.6 Zavegepant

Previously known as vazegepant and BHV-3500, zavegepant is both the first third-generation and intranasally delivered gepants [122]. Zavegepant has a T_{max} of 15–20 min; however, the half-life is unobtainable at the time of writing [89]. Zavegepant was recently assessed as an acute migraine therapy in a recent phase II/III clinical trial (NCT03872453). Patients received zavegepant 5 mg, 10 mg, 20 mg, and placebo. Pain relief at 2 h was reported as 19.6% ($p = 0.1214$) for 5 mg, 22.5% ($p = 0.0113$) for 10 mg, and 23.1% ($p = 0.0055$) for 20 mg compared to placebo (15.5%). Freedom from MBS was reported as 39.0% ($p = 0.1162$) for 5 mg, 41.9% ($p = 0.0155$) for 10 mg, and 42.5% ($p = 0.0094$) for 20 mg compared to placebo (33.7%) [123].

Table 9 Summary of atogepant randomized controlled trials

Study	Phase	Inclusion criteria	Study period/*n*	Primary endpoint[a]
NCT02848326 Goadsby et al. [116]	II/III	EM and ≤ 2 prior unsuccessful preventive treatments	3 months 834	MMD reduction: placebo: − 2.9 10 mg: − 4.0 ($p = 0.024$) 30 mg: − 3.8 ($p = 0.039$ 60 mg: −3.6 ($p = 0.039$) 30 mg twice daily: − 4.2 ($p = 0.0034$) 60 mg twice daily: − 4.1 ($p = 0.0031$)
NCT03777059 Ailani et al. [117]	III	EM and < 4 prior unsuccessful preventive treatments	3 months 910	MMD reduction: placebo: − 2.5 10 mg: − 3.7 30 mg: − 3.9 60 mg: − 4.2 ($p < 0.001$ for all)

All atogepant treatments were given as oral formulations

EM episodic migraine, *MMD* mean monthly migraine day

[a]*p* Values are results compared against placebo

Commonly reported side effects were dysgeusia (13.5–16.1%) and nasal discomfort (1.3–5.2%) [124]. There was no reported hepatoxicity. Zavegepant is currently being explored as a potential treatment option for COVID-19 infection [125]. CGRP is expressed in healthy lungs and is essential for maintaining lung homeostasis. CGRP is released when lung tissue is injured, suggesting targeting CGRP could modulate the severity of lung diseases [126]. At the time of writing, zavegepant remains investigational.

4 Expert Opinion for Use in Migraine Treatment

As discussed above, CGRP-targeted mAbs and gepants are effective in preventing both EM and CM. While not yet included in the American Academy of Neurology (AAN) guidelines, the American Headache Society (AHS) has released a consensus statement recommending both drug classes. The AHS recommends starting a CGRP-targeted mAb when at least two of the following treatments have failed: beta-blockers, topiramate, divalproex sodium/valproate sodium, tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and any other level A or B treatments [127, 128]. The European Headache Federation (EHF) released a statement recommending CGRP-mAbs be prescribed for migraine prevention after patients have failed at least two standard-of-care preventive treatments [129].

The AHS recommends a gepant trial if there is an inadequate response to two or more triptans [127]. While gepants have been demonstrated to be superior to placebo in the acute treatment of migraine, they appear to be less effective than triptans. A meta-analysis comparing ditans to gepants reported more patients receiving lasmiditan having freedom from pain at 2 h by 9.8% and 9.5% compared to ubrogepant and rimegepant, respectively [130]. Another meta-analysis reported triptans being associated with higher odds ratios (ORs) for pain relief at 2 h compared to rimegepant [OR 1.33 (95% CI 1.01–1.76) to OR 3.01 (95% CI 2.33–3.88)], and ubrogepant [OR 1.38 (95% CI 1.02–1.88) to OR 3.13 (95% CI 2.35–4.15)] [131]. Although gepants have less efficacy than triptans, they carry much less cardiovascular risk. Gepants, along with lasmitidan, are good alternative therapies to triptans for patients with cardiovascular risk factors [132]. Ubrogepant and rimegepant have displayed no vasoconstrictive effects on coronary arteries [133].

4.1 Concurrent Therapy

Concurrent use of CGRP-targeted mAb and gepant is currently debated. Freitag et al. conducted an open-label, longitudinal treatment study that reported no increase in AEs when gepants were combined with CGRP mAbs [134]. In an open-label study (NCT03266588) assessing the acute treatment of rimegepant, a subset of 13 patients used CGRP-targeted mAbs (erenumab $n = 7$, galcanezumab $n = 2$, and fremanezumab $n = 4$). Three patients reported AEs that were considered potentially treatment related. However, no serious AEs or treatment discontinuation were reported [135]. A retrospective chart review assessing concordance of response to gepants in patients taking or who had previously taken CGRP-targeted mAbs reported there was not a predictive response to gepant based on response to CGRP-targeted mAb and vice versa [136]. However, in the analysis of subgroups of gepant responders, CGRP-targeted mAb response

appeared much more likely with concurrent use. Although these initial findings suggest concurrent gepant and CGRP-targeted mAb is safe, prospective data are limited and further studies are needed to confer safety and tolerability.

Concurrent use of CGRP-targeted mAbs with onabotulinumtoxinA (onabot) has been an ongoing discussion. There is a rationale for using dual preventive therapy when monotherapy is inadequate for treating CM [137]. Several retrospective studies have been conducted assessing the efficacy of adding a CGRP-targeted mAb to patients receiving onabot injections. Cohen et al. assessed 153 patients receiving concurrent therapy, reporting 72.5% reported a decrease in either headache pain severity or MHDs [138]. On a smaller subset study population (n = 66) with quantifiable MHD data, patients receiving combined therapy have decreased 5.7 MHDs from onabot alone ($p < 0.001$) and a total decrease of 16.6 MHDs (64.5% reduction from baseline, $p < 0.001$). Blumenfeld et al. assessed 257 patients receiving concurrent onabot and CGRP-mAb therapy, reporting a MHD decrease of 3.5–4.0 [139]. Additionally, patients reported a mean decrease in Migraine Disability Assessment (MIDAS) scores of 6.1–11.1 points. Cohen et al. and Blumenfeld et al. reported an AE rate of 8.5% and 27.8%, respectively, with constipation being the most common AE. No serious AEs were reported in either study. Concurrent therapy has been shown to reduce the wear-off phenomenon seen toward the end of their onabot treatment cycle [138].

While caution should be exercised when prescribing polypharmacological treatment strategies, CGRP-targeted mAbs have not been reported to have any drug-antibody interactions [140]. Traditionally, polypharmacy is correlated with decreased drug adherence. CGRP-targeted mAbs are offered in monthly and quarterly dosages, therefore can potentially improve drug adherence [129]. The AHS has labeled concurrent therapy of CGRP-targeted mAbs and onabot as "probably effective" [127]. The AHS recommends initiation of combination therapy when patients on a single preventive therapy require further migraine treatment [141]. The EHF recommends employing combined used of CGRP-targeted mAbs with other migraine preventives in patients with an inadequate response to monotherapy [137]. Further assessment of concurrent onabot and CGRP-targeted-mAb in controlled trials is warranted.

Prescribing a different CGRP-mAb when a previous one has failed is also a current area of interest. A recent retrospective cohort study assessed 78 patients who switched from erenumab to fremanezumab or galcanezumab. After 3 months, switching from erenumab to fremanezumab or galcanezumab resulted in a ≥ 30% response in 32% and ≥ 50% response in 12% of patients [142]. However, stratified analysis revealed no significant response from switching CGRP-mAbs in patients with daily headache.

4.2 Impact on Migraine Burden

Migraine has been shown to cause a significant burden, both on a personal and societal level. A recent epidemiological study reported 42.4% of migraineurs suffer from a moderate or greater degree of disability, 8% were unemployed, and 6.8% were on disability [143]. In the USA, migraine is estimated to cost the economy US$19 billion a year. Each of the currently available CGRP-targeted mAbs and gepants have demonstrated improvement in functional and quality-of-life assessments (e.g., MIDAS, headache impact test (HIT-6), and health-related quality of life (HRQoL) [84, 107, 117, 144–147].

5 Conclusion

What was once considered a vascular disorder, migraine has been established as a syndrome involving vasodilation, neurogenic inflammation, and pain sensitization. CGRP has been identified as having a central role in migraine pathophysiology through various mechanisms, including trigeminal nociception sensitization, local inflammation, and neuronal activation. Multiple studies have established CGRP-targeted mAbs and gepants as effective therapies. Further studies, OLE, and RWD of concurrent therapies with CGRP-targeted mAbs and gepants are underway.

Declarations

Funding This paper received no funding.

Conflicts of interest F.C. has no conflicts of interest or financial disclosures. H.Y. has previously served as a consultant for Supernus Pharmaceuticals, Inc. and Trillen Medical Inc, and currently receives research grants from NIH (R44NS115460). S.S. receives honoraria from Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; Depomed; Dr. Reddy's Laboratories; eNeura Inc.; electroCore Medical, LLC; Ipsen Biopharmaceuticals; Medscape, LLC; Medtronic, Inc.; Mitsubishi Tanabe Pharma America, Inc.; NINDS; St. Jude Medical; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals and Trigemina, Inc.

Ethics approval Not applicable.

Consent to participate/publish Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions F.C. H.Y., and S.S. were involved in the design, writing, and revision of this article.

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