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REVIEW

The Biology of Monoclonal Antibodies: Focus on Calcitonin Gene-Related Peptide for Prophylactic Migraine Therapy

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Abstract

Calcitonin gene-related peptide (CGRP) is 37-amino-acid neuropeptide, crucially involved in migraine pathophysiology. Four monoclonal antibodies (mAbs) targeting the CGRP pathway are currently under evaluation for the prevention of episodic and chronic migraine: eptinezumab (ALD403), fremanezumab (TEV-48125), galcanezumab (LY2951742), and erenumab (AMG334). As reviewed in this article, all 4 antibodies have been proven effective, tolerable, and safe as migraine prophylactic treatments in phase II clinical trials. The mean decrease in migraine days per month was between 3.4 and 6.3 days/month after 8 to 12 weeks of treatment, and the placebo subtracted benefit ranged from 1 to 2.18 days. Notably, up to 32% of subjects experienced total migraine freedom after drug administration. Substance class-specific adverse events and treatment-related serious adverse event did not occur. Further long-term and large-scale trials are currently under way to verify the safety and efficacy profile of mAbs. In particular, the potential risk of vascular adverse events and the role of anti-drug antibodies deserve special attention. Anti-CGRP peptide and anti-CGRP receptor antibodies are the first effective treatments, which were specifically developed for the prevention of migraine. Their site of action in migraine prevention is most likely peripheral due to large molecule size, which prevents the penetration through the blood–brain barrier and thereby shows that peripheral components play a pivotal role in the pathophysiology of a CNS disease.

Key Words Migraine · Tolerability · Safety · Efficacy

Introduction

Almost all migraine episodes require acute therapy. Patients with high-frequency episodic migraine (EM) and with chronic migraine (CM) should receive preventative treatment [1]. The indications for migraine prevention are manifold. It can be necessary to start prophylaxis in subjects with only 1 attack/month, e.g., if the pain cannot be controlled with acute medication [1]. With limited progress in the last decades, migraine frequency management remains often problematic. Approximately half of the patients with an indication for preventive treatment do not receive therapy for several reasons [2]. Moreover, all preventive therapies on the market have not been developed primarily for migraine and were originally licensed for other purposes. Their efficacy and tolerability are often unsatisfactory [3, 4]. In fact, ~50% of CM patients treated with current available preventive medications discontinue therapy because of poor tolerability or safety issues within half a year, and in a substantial percentage, treatment response is insufficient [2, 5].

Migraine's pathophysiology is complex and multifactorial. However, migraine is a CNS disorder, in which activation and sensitization of the trigeminovascular system plays a pivotal role [6]. Stimulation of the trigeminal nerve system leads to the release of neuropeptides, notably calcitonin gene-related peptide (CGRP) [7]. CGRP binds to the CGRP receptor on vascular smooth muscle cells and thereby causes vasodilatation. Neurons also express the receptor, which mediates the neurotransmitter function of the peptide [6, 8].

CGRP and Its Role in Migraine Pathophysiology

CGRP was discovered 35 years ago in rats as a potent endogenous vasodilator [8, 9]. In the peripheral nervous system, it is located in unmyelinated C fibers and small

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myelinated Aδ fibers, both responsible for pain transmission [10]. Centrally, it is widely distributed throughout several structures, including the hypothalamus, thalamus, and cerebellum [10]. CGRP exists in 2 isoforms, α and β. αCGRP results from alternative splicing of mRNA and proteolytic processing of the calcitonin gene [9]. It consists of 37 amino acids and is particularly present in the trigeminal system, where half of the neurons synthesize it [9]. βCGRP is transcribed from a different gene and is expressed primarily in the enteric nervous system [9]. Based on several lines of evidence which suggest CGRP as an important molecule in the pathogenesis of migraine [10–20], this neuropeptide and its receptor have become attractive targets for the development of migraine treatment strategies [10, 21, 22].

The first successful attempt to antagonize the CGRP mechanism in acute migraine therapy was performed with intravenously administered BIBN 4096 BS [12]. Several trials with small molecule CGRP receptor antagonists in oral formulations also demonstrated that targeting this pathway is an effective way for treating acute migraine; however, their development was complicated by signs of hepatotoxicity and pharmacokinetic issues [23–25]. New small molecules such as ubrogepant, atogepant, and remegepant are currently investigated in clinical trials for acute and preventive migraine therapy. However, attention has recently shifted to the development of monoclonal antibodies (mAbs) targeting the CGRP pathway for the prophylactic treatment of migraine [25].

Monoclonal Antibodies

In 1982, the first report from a patient with B cell lymphoma demonstrated that monoclonal antibodies have therapeutic activity. The patient received murine antibodies against his tumor cells and showed a complete response [26]. In the past 35 years, the clinical utility of mAbs has expanded dramatically [27]. In migraine prevention therapy, mAbs have several benefits compared with small molecule receptor antagonists. First, they have a longer duration of action that allows for less-frequent dosing [28]. Second, antibodies are highly specific and can provide a more effective blockade [27]. Third, antibodies are mostly eliminated by proteolytic degradation, not involving the liver, and are not substrates for P450 cytochrome isoenzymes [29]. Therefore, the potential for hepatotoxicitiy and drug–drug interactions is massively reduced [27]. Because of their large dimensions, low permeability through cell membranes, and instability in the gastrointestinal tract, as they are proteins, mAbs must be administered parenterally [30]. They do not penetrate into the brain unless the blood–brain barrier is wide open or respectively destroyed, as is in stroke or meningitis [30].

Four monoclonal antibodies are currently in development for migraine prevention. Three of them bind to CGRP: eptinezumab (ALD403), galcanezumab (LY291742), and fremanezumab (TEV-48215). Erenumab (AMG334) binds to and blocks the CGRP receptor specifically. In both ways, the CGRP-induced activation of central trigeminal pathways is largely blocked [28].

In the following, we will review the clinical trials conducted so far in humans for each of these 4 antibodies.

Eptinezumab

Eptinezumab is a genetically engineered humanized anti-CGRP IgG1 antibody. In contrast with the other anti-CGRP antibodies, it is produced using yeast (*Pichia pastoris*), which should guarantee faster production and thus economic advantages [28]. Eptinezumab binds potently and selectively to both α- and β-isoforms of human CGRP [31].

Phase I Trials

Results of a phase I trial (NCT01579383) were presented as a poster in 2015 [32]. The study determined the safety, tolerability and pharmacokinetics of eptinezumab between 2012 and 2013. About 100 healthy subjects received an intravenous or subcutaneous formulation in ascending dose, without a negative safety signal. Gender had no influence on pharmacokinetic or pharmacodynamic parameters. Half-life of intravenous (i.v.) eptinezumab was ~32 days for the 1000-mg infusion and pharmacokinetics was linear for doses ranging from 1 to 1000 mg. A single eptinezumab infusion led to a dose-dependent reduction of dermal vasodilatation induced by capsaicin, which persisted through week 12. Sumatriptan in combination with eptinezumab did not show pharmacokinetic interactions. The subcutaneous formulation had 70% bioequivalence with the intravenous formulation.

For all further studies, the intravenous formulation was chosen because of the rapidly efficacious dosing with immediate physiological effect [28].

Phase II Trials

In 2014, Dodick et al. published the results of a randomized, double-blind, placebo-controlled, proof-of-concept, phase II trial of eptinezumab for the prevention of frequent EM (NCT01772524), which used a single dosing paradigm in 163 subjects in 26 US centers [31]. Subjects with 5 to 14 migraine days per month in the 3 months before screening could participate. Regular use of any headache-preventive drug within 3 months before screening or botulinum A toxin within 6 months before screening was not permitted. At

baseline, subjects had a mean of 6.7 migraine days per month in the verum group and 7.0 in the placebo group.

The primary aim of this trial was the safety of eptinezumab 12 weeks after infusion; 57% of subjects with 1000 mg eptinezumab ($n = 81$) and 52% with placebo ($n = 82$) experienced adverse events (AEs), most frequently respiratory tract infection, urinary tract infection, fatigue, back pain, nausea, and arthralgia. Most AEs were mild to moderate in severity, and there was no significant difference in the type or frequency of AEs between both groups. Three subjects reported serious adverse events (SAEs), all considered unrelated to the study drug (fibular fracture, pyelonephritis, and repetitive non-cardiac chest pain episodes). There were no clinically significant differences in vital signs, 12-lead ECGs, or laboratory parameters between both groups.

The primary efficacy endpoint, defined as change in migraine days' frequency from baseline to weeks 5 to 8 was met with − 5.6 for eptinezumab compared with − 4.6 for placebo ($p = 0.0306$). Efficacy was not superior to placebo in weeks 8 to 12. Eptinezumab reduced migraine episodes, migraine hours, migraine severity, acute migraine drug use, and headache frequency superior to placebo. However, the study was not powered to detect statistical differences between treatment groups in these parameters. In weeks 8 to 12 after infusion, 61% of subjects on eptinezumab experienced a 50% reduction in migraine days, 33% and 75% reduction, and 16% and 100% reduction, meaning no migraine attacks at all. The placebo group had about 20% lower response rates, and no patient reached migraine freedom. Similarly to the phase 1 trial, the mean elimination half-time was 27.9 days.

Eleven subjects with eptinezumab developed anti-drug antibodies (ADA) during the study. However, they appeared to have no effect on pharmacokinetics or efficacy.

A phase IIb parallel group, double-blind, randomized, placebo-controlled, dose-ranging trial in the prevention of chronic migraine was completed in March 2016 (NCT02275117) [33]. First results were presented in a poster in 2016. Six hundred and sixteen ($n = 616$) subjects with CM received a single infusion of either eptinezumab 300 mg, 100 mg, 30 mg, 10 mg, or placebo. The study met the primary efficacy endpoint, which was the percentage difference of subjects achieving a 75% reduction in migraine days from baseline to week 12. A 75% response was achieved by 33% of subjects in the 300-mg group, 31% in the 100-mg group, and 21% in the placebo group. This 75% endpoint is difficult to achieve based on historic experience. There was a rapid onset on action with a significant separation between eptinezumab and placebo within the first 4 weeks after dosing. Eptinezumab reduced severe migraine headache days for all doses *versus* placebo (− 21% for 300 mg, − 16% for 100 mg, − 18% for 30 mg, − 16% for 10 mg, and − 10% for placebo).

The severity of AEs was mostly mild to moderate; the most frequent AEs were upper respiratory tract infections, dizziness, and nausea. The trial team recorded 10 SAEs, 2 in the placebo group (bronchitis and suicidal ideation), and 8 with eptinezumab (affective disorder, atrial fibrillation, cholelithiasis, viral gastroenteritis, pelvic pain, respiratory disease, seizure, and vaginal abscess). None of them was considered related to the investigational product.

Phase III Trials

Results of 2 phase III trials are not published in full paper yet: PROMISE 1 (PRevention Of Migraine via Intravenous ALD403 Safety and Efficacy 1; NCT02559895) is a double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of eptinezumab administered intravenously in 900 subjects with frequent EM [34]. Primary outcome measure is the change in frequency of migraine days during weeks 1 to 12. The primary endpoint was reportedly achieved. Secondary outcome measures are the responder rates, changes in laboratory variables and ECG parameters, and AEs during a period of 56 weeks. PROMISE 2 (NCT02974153) aims to evaluate the efficacy and safety of eptinezumab in subjects with CM [35]. The study started in November 2016, is expected to enroll 1050 subjects, and to be completed by June 2018. The primary and secondary outcomes are the same as for PROMISE 1.

Table 1 summarizes phases II and III trials with eptinezumab trials.

Galcanezumab

Galcanezumab is a fully humanized IgG4 monoclonal anti-CGRP antibody.

Phase I Trials

Results of phase I studies (NCT02576951, NCT02104765, and NCT01337596) look promising, although peer-reviewed primary publications do not exist [30]. Galcanezumab showed a good tolerability profile, both as single subcutaneous administration (1–600 mg), and in repeated dosing (150 mg every second week for 6 weeks) [36–38]. Elimination half-time was about 28 days and maximum serum concentration was reached after 7 to 13 days [39].

Phase II Trials

From 2012 to 2013, 35 American centers conducted a phase II, randomized, double-blind, placebo-controlled study in order to assess the safety and efficacy of galcanezumab for the prevention of EM (NCT01625988) [39]. The trial consisted in a screening period, a baseline period, followed by a treatment period of 12 weeks and a safety follow-up of 12 weeks. Failure to respond to more than 2 approved preventive treatments was 1 of the exclusion criteria.

Table 1 Completed and ongoing phases II and III clinical trials with ALD403

NCT number	Phase	Start date	Primary completion date[a]	Condition	Population size	Arm and modality of administration	Primary endpoint—decrease from baseline (active *vs.* placebo)	Patients (%) with any AE (active *vs.* placebo)	Common AEs	Reference
NCT01772524	II	January 2013	December 2013	Episodic migraine	163	ALD403 1000 mg or placebo, i.v., once	MHD/28 days at weeks 5–8 (5.6 *vs.* 4.6)	57 *vs.* 52	Upper respiratory tract infections, urinary tract infections, and fatigue	[31]
NCT02275117	II	October 2014	March 2016	Chronic migraine	616	ALD403 300 mg, 100 mg, 30 mg, 10 mg, or placebo, i.v. once	Patients with 75% reduction in MHD (38 for 300 mg *vs.* 24)	NA	Upper respiratory tract infections, dizziness, and nausea	[33]
NCT02559895	III	September 2015	February 2017	Episodic migraine	900	ALD403 in 3 dose levels or placebo, i.v., once	MHD/28 days at weeks 9–12 (NA)	NA	NA	[34]
NCT02974153	III	November 2016	(estimated) June 2018	Chronic migraine	1050	ALD403 in 2 dose levels or placebo, i.v., once	MHD/28 days at weeks 9–12 (NA)	NA	NA	[35]

AE = adverse event; MHD = migraine headache days

[a] Final data collection date for primary outcome measure

A total of 218 subjects received placebo or 150 mg galcanezumab in a 1:1 randomization ratio as subcutaneous injections every 2 weeks for 12 weeks. The trial assessed a dose of 150 mg because of its safety on repeat exposure in phase I trials, and good efficacy, measured by inhibition of capsaicin effect on dermal blood flow [39].

At baseline, subjects in the placebo group had a mean of 6.7 migraine headache days per month *versus* 7.0 days in the galcanezumab arm. The primary efficacy endpoint was the mean change in migraine days per 4 weeks in the last month (weeks 8–12) within the double-blind treatment phase compared with baseline. Galcanezumab led to a reduction of − 4.2 days and placebo to − 3.0, respectively ($p = 0.0030$). The mAb generated a significant reduction in headache days (− 4.9 *vs.* − 3.7, $p = 0.012$), and migraine attacks (− 3.1 *vs.* − 2.3, $p = 0.0051$). Forty-nine percent of subjects in the active group had a 75% response (*vs.* 27% in the placebo group), and 32% had a 100% response (*vs.* 17% in the placebo group). Quality-of-life questionnaires were better in the galcanezumab group; however, the study was not powered to detect statistical differences in the latter outcome measures.

There were no differences in frequency or type of AEs between both groups: 72% (galcanezumab) and 67% (placebo) of subjects reported at least 1 AE, most frequently upper respiratory tract infections and injection site pain.

Six subjects experienced SAEs, all judged to be unrelated to the investigational product. Two SAEs occurred in the active group: pregnancy and peripheral vascular disease; 4 SAEs in the placebo group: menorrhagia, cholelithiasis, diverticulitis, and common bile duct stone. Five subjects in the active study arm, but none in the placebo group had hypertension.

Twenty subjects developed ADAs by the end of the study. The presence of ADAs had no significant impact on results.

A phase IIb study is still ongoing in the open-label extension (OLE) phase (NCT02163993) [40]. Four hundred ten subjects with EM were randomly assigned in a 2:1:1:1 ratio to placebo, 5, 50, 120, and 300 mg galcanezumab, given once monthly for 3 months. The 120-mg dose met the primary objective of significant reduction in the number of migraine days compared with placebo ($p = 0.004$). Galcanezumab proved a good tolerability and safety profile at all doses. Subsequently, phase III trials used the 120- and 240-mg doses galcanezumab.

Phase III Trials

EVOLVE-1 (NCT02614183) and EVOLVE-2 (NCT02614196) are randomized, double-blind, placebo-controlled studies in subjects with EM [41, 42]. Galcanezumab or placebo were administered subcutaneously in 2 different doses once a month for 6 months. Each study enrolled 825 subjects. Primary endpoint was the reduction of migraine days per 4 weeks over the entire 6-month double-blind period.

REGAIN (NCT02614261) is a randomized, double-blind, placebo-controlled study in subjects with CM [43]. The study started in November 2015 and enrolled 825 subjects; the primary completion date was March 2017. Primary outcome measure was the mean change from baseline in the number of monthly migraine headache days in weeks 8 to 12. REGAIN, EVOLVE-1 and EVOLVE-2 have met their endpoints as recently reported.

The long-term, open-label safety study of galcanezumab started in November 2015 (NCT02614287) [44]. Two doses of galcanezumab were administered once a month for up to 12 months. The primary outcome measure was the number of subjects who discontinued from the study.

Table 2 offers a summary of phases II and III galcanezumab trials.

Fremanezumab

Fremanezumab (previously known as LBR-101, RN-307 or PF-04427429) is a fully humanized monoclonal IgG2 antibody, which selectively binds to both α- and β-CGRP [45].

Phase I Trials

Bigal et al. and Walter and Bigal published the pooled results of 6 separate phase I studies in 2014/15 [29, 45]. In 4 studies (NCT01011296, NCT01117233, NCT01117233, and NCT01147432), fremanezumab was administered as a single intravenous infusion in healthy subjects with doses ranging from 0.2 to 2000 mg. In a fifth study (NCT01511497), subjects received 2 infusions of fremanezumab at 30 or 300 mg 2 weeks apart, to examine the safety of repeat doses. One final trial (NCT01991509) confronted intravenous and subcutaneous administration.

Overall, fremanezumab showed a good safety and tolerability profile. There was no clinical relevant change in vital signs, ECG parameters, or laboratory data. Particularly, parameters of hepatic function were within normal ranges at all times. Patients on fremanezumab reported on average 1.3 AEs/subject and 1.4 AEs with placebo, respectively. A specific AE pattern was not identified. Two SAEs occurred: glaucoma and aggravated thoracic aneurysm (in a subject with unknown Ehlers-Danlos syndrome). A causal relation to treatment was not detected.

The subcutaneous route was as safe and tolerable as the intravenous one, with a similar terminal half-life. For doses ranging from 30 to 2000 mg, mean terminal half-life was between 40 and 48 days, and thus the longest among the anti-CGRP antibodies. A second dose of fremanezumab led to a terminal half-life of 41 to 50 days.

Phase II Trials

In 2014, 2 multicenter, randomized, double-blind, placebo-controlled phase IIb studies (NCT02025556 and NCT02021773) started in parallel at 62 sites in the USA, recruiting subjects for high-frequency EM and CM [46, 47].

The EM study included 297 subjects with more than 8 and less than 15 headache-days per month. Subjects could use 1 standard preventive treatment in a stable regimen and acute migraine drugs up to 14 days per month. Fremanezumab 225 or 675 mg or placebo were administered as 4 subcutaneous injections monthly for 3 months. The choice of doses was based on the assumption to sufficiently block CGRP activity (225 mg) and to guarantee safety margins (675 mg) with enhanced efficacy. The subjects reported a mean of 11.4 migraine days/month and thereby more than any other mAb phase II trial for EM. The primary efficacy endpoint was defined as the decrease in migraine days from baseline to weeks 9 to 12. Both doses of fremanezumab significantly reduced the number of migraine days *versus* placebo (− 6.09 for 675 mg, − 6.27 for 225 mg, *vs.* − 3.46 for placebo; $p < 0.0001$ for both groups). Fremanezumab also led to a significant reduction of headache days of any severity during all treatment cycles. The mean change in migraine days from baseline to weeks 9 to 12 was − 6.41 in the 225-mg group, − 6.10 in the 675-mg group, and − 3.52 in the placebo group.

Several other secondary endpoints were met: both doses significantly decreased the number of days of acute drug use, the days of moderate or severe headache intensity, the number of headache hours, the number of hours with moderate or severe headache, the days with photophobia and phonophobia, and the mean Migraine Disability Assessment Score (MIDAS).

Fifty-six percent (placebo), 46% (225 mg), and 59% (675 mg) of subjects experienced AEs. The most common ones were injection site pain or erythema, with similar rates in all groups. Only 4 SAEs were reported: 1 patient had a fibula fracture and 1 other migraine associated with hypertensive crisis (225 mg fremanezumab), 1 anti-phospholipid antibody syndrome, and 1 other tremor (675 mg fremanezumab). ADAs were detected in 2 subjects at baseline, but no patient developed ADAs during treatment with fremanezumab.

In the CM study, 264 subjects were enrolled. Fremanezumab (675/225 and 900 mg) was subcutaneously injected monthly for 3 months and compared with placebo. The use of a maximum of 2 different preventative therapies in stable doses for at least 3 months before screening was allowed in the study. At baseline, subjects had a mean of 16.8 migraine days per month. The primary efficacy endpoint was defined as mean change in the number of headache hours during weeks 9 to 12, which is a rather unusual primary endpoint. Both doses reached significant differences compared with placebo, with − 59.84 h in the 675/225-mg arm, −

Table 2 Completed and ongoing phases II and III clinical trials with LY2951742

NCT number	Phase	Start date	Primary completion date[a]	Condition	Population size	Arm and modality of administration	Primary endpoint—decrease from baseline (active *vs.* placebo)	Patients (%) with any AE (active *vs.* placebo)	Common AEs	Reference
NCT01625988	II	June 2012	September 2013	Episodic migraine	218	LY2951742 150 mg or placebo, s.c. every 2 weeks for 12 weeks	MHD/28 days at weeks 9–12 (4.3 *vs.* 3.0)	72 *vs.* 67	Upper respiratory tract infections; injection site pain	[39]
NCT02163993	II	July 2014	August 2015	Episodic migraine	410	LY2951742 300, 120, 50, or 5 mg *vs.* placebo, s.c., monthly for 12 weeks	MHD/28 days at weeks 9–12 (NA)	NA	Injection site pain; upper respiratory tract infection; nasopharyngitis	[40]
NCT02614183	III	November 2015	March 2017	Episodic migraine	825	LY2951742 in 2 dose levels *vs.* placebo, s.c., monthly for 6 months	MHD/28 days at week 24	NA	NA	[41]
NCT02614196	III	December 2015	March 2017	Episodic migraine	825	LY2951742 in 2 dose levels *vs.* placebo, s.c., monthly for 6 months	MHD/28 days at week 24	NA	NA	[42]
NCT02614261	III	November 2015	March 2017	Chronic migraine	825	LY2951742 in 2 dose levels *vs.* placebo, s.c., monthly for 3 months	MHD/28 days at week 12	NA	NA	[43]
NCT02614287	III	November 2015	May 2017	Episodic and chronic migraine	250	LY2951742 in 2 dose levels *vs.* placebo, s.c., 1 monthly for 12 months	Percentage of participants who discontinued	NA	NA	[44]

AE = adverse event; MHD = migraine headache days

[a] Final data collection date for primary outcome measure

67.51 h in the 900-mg arm, and − 37.10 h in the placebo arm ($p = 0.039$ and $p = 0.005$, respectively).

Headache days of at least moderate severity during weeks 9 to 12 were significantly more reduced with fremanezumab than in the placebo group (− 6.04 days in the 675/225-mg group, − 6.16 days in the 900 mg-group, − 4.2 days in the placebo group; $p = 0.034$ and $p = 0.024$). Additionally, the days using acute specific anti-migraine medications were significantly reduced in both doses.

Forty percent, 53% and 48% (placebo *vs.* 675/225 mg *vs.* 900 mg) reported AEs, e.g., injection site pain and pruritus. One SAE occurred in the placebo group (nephrolithiasis), 1 in the 675/225 mg group (pneumonia), and 2 in the 900-mg group (irritable bowel syndrome, depression with suicide attempt). SAEs were not related to study treatment. In 2 subjects, ADAs were detected at screening, but no new antibody-response emerged during treatment.

In a post hoc analysis, the authors examined the onset of efficacy of fremanezumab in their CM study [48]. The 900-mg dose reached a difference from placebo in the mean number of headache hours after 3 days (− 3.08 h *vs.* + 0.36 h for placebo, $p = 0.031$) and the 675/225-mg group after 7 days (− 7.28 h *vs.* − 1.59 h for placebo, $p = 0.049$). At week 2, both doses were superior to placebo in reducing headache days of at least moderate intensity, with means of − 0.79 for placebo, − 1.34 for 675/225 mg ($p = 0.031$), and − 1.51 for 900 mg ($p = 0.005$). This shows early onset activity of fremanezumab.

Phase III Trials

Two registration trials in EM and CM have recently also reportedly reached the primary endpoint (NCT02629861 and NCT02621931). These are multicenter, randomized, double-blind, placebo-controlled, parallel-group study, comparing the efficacy and safety of 2 doses of subcutaneous fremanezumab *versus* placebo for the preventive treatment of EM and CM [49, 50]. The primary endpoints were the mean change in the monthly average number of migraine days in weeks 9 to 12 and the percentage of participants with AEs. The study for EM included 878 subjects, and for CM 1134 subjects. Recently, the results from a large phase III trial in CM have been published. Fremanezumab reduced the number of moderate- to severe-headache days significantly within the 12-week double-blind, placebo-controlled treatment phase after the first injection using a monthly (− 4.6 days) and a quarterly (− 4.3 days) dosing scheme compared with placebo (− 2.5 days; $p < 0.001$ both doses) [50]. Fremanezumab was also superior to placebo in all secondary endpoint measures in this trial. Notably, 41% of subjects in the monthly dosing group, 38% in the quarterly dose regimen, and 18% (placebo) had a 50% reduction of moderate- to severe-headache days/month within the 12-week observation period ($p < 0.001$). Safety and tolerability findings were also beneficial in this trial in line with prior observations [50].

Long-term safety, tolerability, and efficacy of subcutaneous administration of fremanezumab for the preventive treatment of EM and CM are under study (NCT02638103) [51].

Table 3 summarizes phases II and III trials with fremanezumab.

Erenumab

Erenumab is a fully human monoclonal IgG2 antibody. It is the only antibody in development that targets the CGRP receptor [52].

Phase I Trials

The results from 2 phase I studies (NCT01688739 and NCT01723514) have recently been published by De Hoon et al. [53]. In a sequential-dose escalation, single-dose study and a multidose study (81 healthy subjects/28 migraine patients) erenumab showed a dose-dependent pharmacokinetic profile between 1 and 70 mg and a linear profile from 70 to 210 mg. The elimination half-life time for the 70-mg dose was 21 days. Erenumab led to a significant suppression of capsaicin-induced increased dermal blood flow, with results ranging between 75% and 95%.

Six healthy subjects with erenumab tested positive for ADAs, and 1 subject developed neutralizing antibodies. However, these appeared to have no impact on efficacy or safety.

In the single-dose study, 83.3% of healthy subjects and 91.7% of migraine patients reported mild AEs, most frequently headache, nasopharyngitis, arthralgia, and influenza-like illness. In the multiple-dose study, AEs of any kind happened in 84.4% of healthy subjects and 100% of migraine patients among these 3 SAEs: mild polyarthritis ($n = 1$; 70 mg), depression ($n = 1$; 140 mg), and neutropenia ($n = 1$; 21 mg). There were no significant changes in vital signs or laboratory parameters.

NCT02741310 evaluated the effect on blood pressure of erenumab given concomitantly with subcutaneous sumatriptan to 30 healthy subjects [54]. Results of the study are not published yet.

Phase II Trials

Erenumab was tested for safety and efficacy in the prevention of EM in a randomized, double-blind, placebo-controlled, phase II trial, in 59 centers in North America and Europe (NCT01952574) [55]. The study included a screening and baseline phase, 12 weeks of double-blind treatment, up to256 weeks of OLE and a safety follow-up. The open-label phase is still ongoing. Results after 1 year have just been published [56].

Table 3 Completed and ongoing phases II and III clinical trials with TEV-48125

NCT number	Phase	Start date	Primary completion date[a]	Condition	Population size	Arm and modality of administration	Primary endpoint—decrease from baseline (active *vs.* placebo)	Patients (%) with any AE (active *vs.* placebo)	Common AEs	Reference
NCT02025556	II	January 2014	January 2015	Episodic migraine	297	TEV-48125 675 or 225 mg *vs.* placebo, s.c., monthly for 3 months	MHD/28 days at weeks 9–12 (6.27 in the 225-mg group *vs.* 3.46)	46 in the 225-mg group *vs.* 56	Injection site pain and erythema	[47]
NCT02021773	II	January 2014	February 2015	Chronic migraine	264	TEV-48125 900 mg and 675/225 mg, *vs.* placebo, s.c. monthly for 3 months	Headache hours at weeks 9–12 (− 63.51 in the 900-mg group *vs.* − 37.10)	48 in the 900-mg group *vs.* 40	Injection site pain and pruritus	[48]
NCT02638103	III	March 2016	(estimated) September 2018	Episodic or chronic migraine	1842	TEV-48125 at 2 dose levels, s.c., monthly for 18 months	% of participants with AEs (NA)	NA	NA	[51]
NCT02629861	III	January 2016	April 2017	Episodic migraine	878	TEV-48125 at 2 dose levels, *vs.* placebo, s.c. monthly for at weeks 9–12 (NA)	MHD/28 days at weeks 9-12 (NA)	NA	NA	[49]
NCT02621931	III	January 2016	April 2017	Chronic migraine	1134	TEV-48125 at 2 dose levels, *vs.* placebo, s.c. monthly for 3 months	Mean MHD/28 days within the 12-week double-blind phase (-4.6 in the monthly dosing group vs. -2.5)	71 in the monthly dosing group *vs.* 64	Injection site pain, induration and erythema	[50]

AE = adverse event; MHD = migraine headache days

[a] Final data collection date for primary outcome measure

In this trial, failure to more than 2 preventive treatment categories and medication overuse were exclusion criteria. Four hundred eighty-three subjects were assigned in a 3:2:2:2 ratio to placebo, 7 mg, 21 mg, or 70 mg erenumab, each given monthly subcutaneously. Only the 70-mg dose reached a significant reduction in monthly migraine days from baseline to weeks 9 to 12 (− 3.4 days *vs.* placebo − 2.3 days; $p = 0.021$). Additionally, subjects in the 70-mg arm reported higher 50% responder rates at week 12 (46% *vs.* 30%; $p = 0.011$), greater reduction in number of headache (− 3.5 *vs.* − 2.4; $p = 0.022$) and in the number of days using acute medication (− 2.5 *vs.* − 1.4, $p = 0.006$). No significant differences were recorded for 7 and 21 mg erenumab compared with placebo. Improvement in quality-of-life questionnaires was greater with erenumab than with placebo.

Between 50% and 54% of subjects with erenumab and 54% with placebo experienced AEs, most commonly nasopharyngitis, fatigue, and headache. Two subjects reported treatment-unrelated SAEs: vertigo and migraine (70 mg) and ruptured ovarian cyst (21 mg). Erenumab led in 10% of subjects to the production of ADAs; only 3% had neutralizing antibodies without any impact on efficacy or safety endpoints.

Of 383 subjects who entered the open-label phase, 80% concluded 1 year of treatment with 70 mg erenumab subcutaneous injections every 4 weeks [56]. Mean monthly migraine days changed from 8.8 (± 2.6) at baseline of the double-blind phase to 6.3 (± 4.2) at the end of double-blind treatment to 3.7 (± 4.0) at week 64. Subjects formerly in the placebo, 7- and 21-mg erenumab arms achieved the same migraine day reduction after 4 weeks in the OLE compared with subjects who were in the 70-mg group in the double-blind phase. After 64 weeks, 65% of subjects reached a 50% response, 42% a 75% response, and 26% a 100% response within the last 4 weeks of treatment. Several other outcome measures also improved: severe headache days (− 4.7 ± 4.2); monthly migraine attacks (− 2.9 ± 2.5); monthly migraine hours (− 47.4 ± 57.4); monthly headache hours (− 48.9 ± 60.1); and Headache Impact Test 6 (HIT-6), Migraine-Specific Quality of Life (MSQ), and MIDAS scores. Erenumab did not lead to clinically significant changes in vitals, laboratory parameters, or ECG findings. Two serious SAEs occurred: 1 fatal coronary arteriosclerosis, considered not related to study treatment, and 1 transient exercise-induced myocardial ischemia. These cases are described in detail in the "Neurology" publication; 13.1% of subjects developed ADAs; 2.4% neutralizing antibodies. Again, ADAs did not have an impact on efficacy or safety findings. This is the first study to provide safety and efficacy results for mAbs in a long-term regimen.

In CM, 667 subjects received erenumab 70 or 140 mg in North America and Europe (NCT02066415) [57]. Randomization was done in a 3:2:2 ratio, i.e., placebo:erenumab 70 mg:erenumab 140 mg, subcutaneously monthly. This study included an initial screening and a 4-week baseline phase, 12 weeks of double-blind treatment and 12 weeks of safety

follow-up. Primary endpoint was the change in migraine days from baseline to the last month of the double-blind treatment phase (weeks 9–12). Forty percent of subjects in the study had medication overuse, and 50% of subjects have failed 2 or 3 classes of preventatives due to lack of efficacy.

At baseline, subjects reported between 17.8 and 18.2 monthly migraine days in all groups. Erenumab led to a reduction of − 6.6 migraine days in both groups with a 2.4-day benefit over placebo (− 4.2 days; $p < 0.0001$ for both erenumab groups). The 50% responder rate was also significantly greater in both erenumab groups (40% of subjects in the 70-mg group, 41% in the 140-mg group, and 23% in the placebo group). There was a significant reduction in monthly acute migraine-specific drug treatment days (− 3.5 in the 70-mg group, − 4.1 in the 140-mg group, and − 1.6 in the placebo group).

Thirty-nine percent of subjects with placebo, 44% of subjects with 70 mg, and 47% of subjects with 140 mg reported AEs, without significant differences between active and placebo. Most frequent ones were injection site pain (< 4% across groups), upper respiratory tract infection (< 3%), nausea (< 3%), and nasophyaringitis (< 6%).

Seven placebo subjects, 6 subjects with erenumab 70 mg group, and 2 subjects with 140 mg reported SAEs, and none was related to erenumab (e.g., abdominal adhesions, abdominal pain, and cartilage injury). Fourteen subjects with erenumab developed ADAs, no neutralizing antibodies were detected. ADA presence did not lead to changes in the safety or efficacy profile.

Notably, only 5% in placebo, 5% in the 70-mg, and 3% in the 140-mg erenumab groups dropped out of the trial before week 12, which is very low compared with other migraine prevention trials, e.g., with topiramate. This finding indicates a beneficial tolerability profile of erenumab. The results of an OLE (12 months) are expected.

Phase III Trials (ARISE and STRIVE)

ARISE (NCT02483585) is a randomized, double-blind, placebo-controlled study in 577 subjects with EM, followed by an open-label treatment phase. The primary endpoint was identical to phase II trials in EM [58]. Erenumab (70 mg) or placebo were subcutaneously administered once monthly in a 1:1 ratio. Subjects with erenumab experienced a significant reduction of migraine days compared with placebo (− 2.9 days *vs.* − 1.8, $p < 0.001$). The ≥ 50% responder rate was significantly higher in subjects with erenumab (40% *vs.* 30% placebo, $p = 0.010$). Monthly acute migraine-specific medication use was significantly reduced (− 1.2 *vs.* − 0.6 days, $p = 0.002$). The most common AEs in both groups were similar to those in the trials before.

The second phase III trial, STRIVE (NCT02456740), is a 6-month randomized, stratified, double-blind, placebo-controlled, parallel-group, multicenter study, followed by an active-treatment phase [59]. The study aimed to evaluate the efficacy of erenumab compared with placebo in the change of monthly migraine days in 955 subjects with EM in months 3 to 6 [59]. Subjects were randomized to receive either placebo, 70 or 140 mg of erenumab, as monthly subcutaneous injections for 6 months. STRIVE has met the primary and all secondary endpoints. Erenumab led to the reduction of mean monthly migraine days in months 4 to 6 (140 mg, − 3,7 days; 70 mg, − 3.2 days; placebo, − 1.8 days; $p < 0.001$) of the double-blind placebo-controlled treatment phase. The 50% responder rate was achieved by half the study population (50%) on erenumab 140 mg (placebo 26.6%; $p < 0.001$). Erenumab 70 and 140 mg had a beneficial effect on physical impairment and routine daily activities as daily assessed with the Migraine Physical Function Impact Diary (MPFID) [59].

Table 4 provides an overview of phases II and III erenumab trials.

Discussion

Three monoclonal antibodies against CGRP and 1 against the CGRP receptor are currently studied for the EM and CM prevention [3].

In all phase II trials, mAbs were well tolerated. AEs were mostly mild to moderate in severity. Substance class-specific AEs could not be detected and across all studies, treatment related SAEs did not occurred. Clinical phase II trials usually exclude patients with significant comorbidities. In contrast with some small molecule CGRP receptor antagonists, monoclonal antibodies did not cause relevant changes in hepatic function parameters [30].

All antibodies demonstrated efficacy as migraine preventative treatments [61]. In the phase II dose finding trials, the decrease of migraine days per month, after subtracting placebo, varied from 1 to 2.18 days [1]. Baseline migraine days were different between trials, and so were the differences between active and placebo after treatment. Several factors affect treatment response, and therefore substance efficacy differences in these phase II trials are not overly important. Of note, the mechanism of action has proven successful for the prevention of migraine [1]. Currently, available oral prophylactic medications lead to a comparable reduction of migraine days per month between 0.4 and 2.6 [62]. Phase III trials will show us whether mAbs remain in this range or show additional treatment benefit.

Monoclonal antibodies seem to act faster than older preventative medications. Fremanezumab reached a significant difference from placebo after only 3 days for daily headache hours. Migraine headache days were clearly reduced and separated from placebo in week 2 [48]. In addition to rapid onset and dose, titration is not needed [1], which we perceive as an advantage over existing preventatives. Migraine frequency varies over time and clinical practice will tell us more about speed of onset of action of mAbs. Antibodies may also be an

Table 4 Completed and ongoing phases II and III clinical trials with AMG334

NCT number	Phase	Start date	Primary completion date[a]	Condition	Population size	Arm and modality of administration	Primary endpoint—decrease from baseline (active *vs.* placebo)	Patients (%) with any AE (active *vs.* placebo)	Common AEs	Reference
NCT01952574	II	August 2013	September 2014	Episodic migraine	483	AMG334 70, 21, or 7 mg, *vs.* placebo, monthly for 3 months	MHD/28 days at weeks 9–12 (3.4 in the 70-mg group *vs.* 2.3)	54 in the 70-mg group *vs.* 54	Nasopharyngitis, fatigue, and headache	[55]
NCT02066415	II	March 2014	February 2016	Chronic migraine	667	AMG334 140 or 70 mg *vs.* placebo, monthly for 3 months	MHD/28 days at weeks 9–12 (6.6 in the 140-mg group *vs.* 4.2)	47 in the 140-mg group *vs.* 39	Injection-site pain, upper respiratory tract infection, and nausea	[57]
NCT02174861	II	June 2014	May 2017	Chronic migraine	612	AMG334 140 mg, monthly for 13 months	% of participants with AEs (NA)	NA	NA	[60]
NCT02483585	III	July 2015	July 2016	Episodic migraine	577	AMG334 70 mg *vs.* placebo, monthly for 3 months	MHD/28 days at weeks 9–12 (2.9 *vs.* 1.8)	NA	Upper respiratory tract infection, injection site pain, and nasopharyngitis	[58]
NCT02456740	III	July 2015	September 2016	Episodic migraine	955	AMG334 140 or 70 mg, *vs.* placebo, monthly for 6 months	MHD/28 days at weeks 9–12 (3.7 in the 140-mg group *vs.* 1.8)	55.5 in the 140-mg group vs. 63	Nasopharyngitis, upper respiratory tract infection, and sinusitis	[59]

AE = adverse event; MHD = migraine headache days

[a] Final data collection date for primary outcome measure

alternative for patients who do not tolerate available medication due to substance-specific AEs, such as CNS symptoms or weight gain [1].

Due to their protein nature, monoclonal antibodies are not suitable for oral administration. They have to be administered as subcutaneous or intravenous injections at relatively low frequency, usually once monthly or only every third month [30]. Fremanezumab and eptinezumab are under study for the latter dosing paradigm. Low-frequency administration of mAbs compared with current oral medication could improve therapy adherence, a problematic issue in migraine prevention [1]. Additionally, new formulations for self-administration are currently under evaluation [60] and may simplify a future large-scale application for patients with difficult access to tertiary healthcare centers.

In all studies, high placebo responses were observed, most prominent in a phase II eptinezumab trial with a 50% responder rate of 54% in the placebo arm [31]. This is most likely due to the intravenous application of eptinezumab. The particularly favorable placebo responses could also be affected by the number of study arms and by high expectations because of the novelty of this drug class [63].

Efficacy and safety of monoclonal antibodies could be challenged by the development of ADAs. However, since the examined anti-CGRP and anti-CGRP receptor antibodies are composed of entirely humanized sequences, the immunologic liability is minimized. In phase II trials, ADAs were detected in max. 18% of subjects [39] and neutralizing antibodies were observed less frequently (max. 3% of subjects with erenumab) [55]. In all studies, ADAs did not appear to affect drug concentration, efficacy, or AE profile. Phase III studies are needed to determine the role of these antibodies in long-term treatment.

Interestingly, up to 32% of subjects experienced a 100% response in the last 4 week of the observation period, suggesting that there is a subgroup of migraineurs for whom CGRP plays an essential part in the pathophysiology of migraine [31, 39]. Treatment costs with monoclonal antibodies result in the necessity to select patient groups, which are more likely to benefit from mAb therapy than others.

Long-term effects of monoclonal antibodies in a large population are still unknown, although beneficial safety data of an erenumab cohort (64-week use) are published [56]. Potential risks of inhibiting the CGRP pathway includes: medication-induced hypertension, blockage of vasodilatation in physiologically appropriate situations such as cardiac or cerebrovascular ischemia, and annulling the effect of anti-hypertensive drugs [11]. All studies conducted so far *in vitro* and *in vivo* did not show any harmful vasoconstriction [9, 64]. However, the effects of anti-CGRP antibodies in patients suffering ischemic events remain largely unknown [11].

One final issue to discuss relates to the site of action of anti-CGRP antibodies. Antibodies are large molecules, with a

molecular weight of ~150,000 Da. Therefore, they have only a minimal possibility (0.1–0.5%) to cross the blood brain barrier under physiological condition [9]. Even if a sporadic dysfunction exists, the amount of antibodies trespassing it would be too low to block CGRP effectively [9]. Consequently, antibodies are supposed to have a primary peripheral site of action, binding to the CGRP released at trigeminal nerve endings or its receptor in ganglion or dura mater. The efficacy of anti-CGRP antibodies supports the hypothesis that a peripheral component plays a pivotal role in migraine pathophysiology and migraine can be aborted by blocking peripheral mechanisms.

Conclusion

Phases I and II trials show us that mAbs, which block the CGRP pathway, are safe, tolerable, and effective treatment options. Each phase II study has produced positive efficacy results, and no safety issues have emerged. The positive results of large phase III trials in EM and CM for erenumab and fremanezumab confirm phase II data, and further long-term studies are under way to confirm their safety and efficacy profile. However, registries for use in the real world, e.g., for pregnancy, are needed. Anti-CGRP and anti-CGRP-receptor antibodies are the first effective treatment specifically developed for the prevention of migraine based on molecular pattern involved in disease pathogenesis. The efficacy of monoclonal antibodies provides further evidence for the importance of CGRP in migraine pathophysiology and the therapeutic value to antagonize its effect within the trigeminovascular system.

Compliance with Ethical Standards

Conflict of Interest BR declares no conflict of interest. UR has received honoraria for several purposes (e.g. consultation, presentations and clinical trials) from Allergan, Amgen, Autonomic Technologies, CoLucid, Eli Lilly, Electrocore, Novartis, and TEVA.

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