Ther Adv Neurol Disord
2020, Vol. 13: 1–19
DOI: 10.1177/1756286420927119

The role of erenumab in the treatment of migraine

Anna P. Andreou, Matteo Fuccaro and Giorgio Lambru

***Abstract*:** Calcitonin gene related peptide (CGRP) monoclonal antibodies (mAbs) have been the first class of specifically developed preventive treatments for migraine. Clinical trials data suggest superiority of the CGRP mAbs to placebo in terms of prevention of migraine symptoms, migraine-specific quality of life and headache related disability. Treatment-related side effects overall did not differ significantly from placebo and discontinuation rate due to side effects has been low across the clinical trials, perhaps in view of their peripheral mode of action. Along with their route and frequency of administration, these novel class of drugs may constitute an improvement compared with the established arsenal of migraine treatments. Erenumab is a fully human antibody and the only mAb acting on the CGRP pathway by blocking its receptor. It is the first of the CGRP mAb class approved by the US Food and Drug Administration (May 2018) and the European Medicines Agency (July 2018). Erenumab exists in two different doses (70 mg and 140 mg) and it is administered with monthly subcutaneous injections. This review summarises erenumab pharmacological characteristics, clinical trials data, focusing on the potential role of this treatment in clinical practice.

Keywords: CGRP, chronic migraine, erenumab, migraine, monoclonal antibodies, atogepant, rimagepant

Received: 24 February 2020; revised manuscript accepted: 23 April 2020.

Introduction

Migraine is a global disabling neurological disorder that manifests itself with recurrent episodes of head pain associated with symptoms of parasympathetic dysfunction and heightened sensitivities.[1] The pain phase is one of the phases that characterize a migraine episode. Prodromal, aura and postdromal phases often complete the migraine cycle besides the head pain.[2] Neuroimaging research has unrevealed brain networks that become dysmodulated during each of the migraine phases. Whether these brain changes initiate the migraine pain phase or whether the pain phase starts in the periphery with activation of trigeminovascular afferents is still a matter of debate.[3] Activation of dural meningeal afferents results in secretion of peptides as pituitary adenylate cyclase activating polypeptide (PACAP), substance P (SP) and calcitonin gene related peptide (CGRP),[4] the latter shown in pre-clinical and clinical experiments to have a pivotal role in migraine pathophysiology. Based on these findings, drugs directed at modulating CGRP activity in migraine have emerged as particularly promising future treatments. CGRP receptor antagonists, which compete with endogenous CGRP at the receptor binding sites, have been developed in recent years and were demonstrated to be able treat effectively acute migraine attacks. Other ways to modulate CGRP activity have been introduced recently through the development of monoclonal antibodies (mAb) against CGRP and the CGRP receptor.

Calcitonin-gene-related peptide

CGRP is found in two isoforms, αCGRP synthesized from CALC I, and βCGRP synthetized from CALC II.[5] While αCGRP expression is prevalent in the peripheral nervous system and central nervous system (CNS), βCGRP is

Correspondence to:
Giorgio Lambru
The Headache Service, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH, UK
giorgio.lambru@gstt.nhs.uk

Anna P. Andreou
The Headache Service, Guy's and St Thomas' NHS Foundation Trust, London, UK

The Wolfson, CARD, King's College London, London, UK

Matteo Fuccaro
Department of Neurology, Treviso Hospital, Treviso, Italy

synthesized and released in the enteric nervous system.[6] Within the CNS, CGRP is most abundant in the dorsal horn of the spinal cord,[7] cerebellum,[8] brainstem[9] and several hypothalamic[10] and thalamic nuclei.[11] CGRP binding sites are widely expressed throughout the brain.[12]

CGRP acts *via* a heterodimer receptor complex formed by calcitonin receptor-like receptor (CLR) and receptor activity modifying protein (RAMP)-1 (CLR/RAMP1).[13,14] Functional CLR/RAMP1 receptors require intracellular interactions with receptor component protein. The CLR/RAMP1 is a G-protein coupled receptor that induces stimulation of adenylyl cyclase and production of cAMP. More recent work has confirmed that the amylin AMY1 receptor (CTR/RAMP1 heterodimer) can respond as well to CGRP as it does to amylin.[15,16] Importantly, CGRP may exert its effects *in vivo* by activating both the CGRP and AMY1 receptors.

Within the trigeminal ganglion, the α-CGRP isoform is expressed in about 50% of neurons and is a key neuropeptide involved in both neural and vascular responses.[17–19] CGRP immunoreactive dendrites that sprout from neurons of the ipsilateral first branch of the trigeminal nerve deepen into the walls of the major cerebral arteries in the Circle of Willis, and so are widespread in rostral cerebral circulation. Sensory terminals expressing CGRP are also abundant in the dura matter and the eye and have been demonstrated in the nasal mucosa, periodontium, gingivae and the retina.[20–26]

CGRP is the most potent vasodilator when released peripherally, through direct activation of its receptor CLR/RAMP1 on smooth muscle cells.[17,27] Its release from primary trigeminal afferents innervating blood vessels of the dura matter and the cerebral circulation is part of the main mechanism of trigeminovascular activation,[17] which is believed to be involved in the pathophysiology of primary headaches.[28,29] CGRP can also induce vasodilation indirectly by activating endothelium CLR/RAMP1, resulting in a rise in cAMP[30,31] and subsequent nitric oxide (NO) production.[32] Peripheral CGRP is also involved in mediating axon-reflex mechanisms and inflammation responses.[33–35]

Centrally, CGRP is acting as a neuromodulator. On its own has either no effect on spontaneous neuronal firing or a slow excitatory effect on non-nociceptive neurons.[36,37] CGRP can also facilitate, inhibit or cause no changes to glutamate-evoked firing.[37–40] Interestingly, CGRP was shown to facilitate nociceptive-evoked firing on second order trigeminocervical neurons and CGRP antagonists to inhibit nociceptive activity.[37–40]

Rationale for developing erenumab

Erenumab is monoclonal antibody against the receptor of the neuropeptide CGRP which has been implicated in migraine pathophysiology. CGRP levels were found to be elevated during a migraine attack in plasma, saliva and CSF samples from patients.[28,41–43] Intravenous infusion of CGRP has been shown to trigger a migraine-like attack without aura in about 60% of sufferers.[44] Triptans, 5-HT1B/D receptor agonists and migraine specific treatments, have been shown to reduce CGRP plasma levels in migraine patients,[45] but not in healthy subjects[43,46] and sumatriptan administration normalize CGRP levels, resulting in resolution of the attack.[47] Furthermore, experimental activation of trigeminal ganglion cells is known to result in the release of CGRP, which is dose-dependently inhibited by 5-HT1B/D agonists, highlighting the trigeminal system as a key site that may be targeted by CGRP receptor antagonists and triptans.[47,48]

Experimental animal models provide evidence for the relevance of CGRP signalling in migraine. Stimulation of the cat superior sagittal sinus led to increased release of CGRP and VIP (vasoactive intestinal peptide) levels while SP or neuropeptide Y levels remained unchanged.[49] Electrical stimulation of dura mater in rats caused a CGRP-related dilating effect of dural blood vessels which could be inhibited by administering a CGRP receptor antagonist (CGRP8-37).[50] Significant attenuation of the neurogenic meningeal vasodilator response was similarly seen with sumatriptan.[51] Intravenous (iv) administration of CGRP also caused extracranial dural blood vessel dilation that was abolished by CGRP8-37. CGRP-induced dilation, however, was not abolished by sumatriptan, indicating that triptans act pre-junctionally to prevent CGRP release,[52] rather than on the smooth muscles of the blood vessels.[51] In the trigeminocervical complex, CGRP receptor antagonists inhibited trigeminovascular neurons activated by L-glutamate, demonstrating a possible central site of action for CGRP receptor antagonists.[39]

Based on the above clinical and pre-clinical findings, drugs directed at modulating CGRP activity in migraine have emerged as particularly promising future treatments. CGRP receptor antagonists (gepants), which compete with endogenous CGRP at the receptor binding sites, have been developed as novel anti-migraine drugs and found to be effective in the acute treatment of migraine.[53] The initial development and trials of CGRP antagonists in migraine with olcegepant (BIBN4096BS), telcagepant (MK-0974) and MK-3207, demonstrated a good efficacy for these antagonists as acute treatments for migraine: intravenously administered olcegepant was significantly superior to placebo at 2 h response rate,[54] oral telcagepant demonstrated a similar efficacy with zolmitriptan for the attack[55,56] and the superiority of gepant MK-3207 over placebo on pain resolution within 2 h after oral administration was demonstrated.[57] On the other hand, the safety profile of these molecules was rather unfavourable because of liver toxicity.[58]

Currently, three more gepants are in development for the acute and preventive treatment of migraine that seem to have an advanced safety profile and hence no serious side effects related to liver toxicity: ubrogepant (MK-1602) in recent[59–61] phase II and III trials demonstrated a positive effect regarding the two-hour pain freedom outcome without serious adverse events or relevant elevation of liver enzymes; rimegepant resulted in being superior to placebo in achieving headache freedom up to 24 h post-dose with adverse events (AEs) of only mild or moderate intensity;[62] atogepant proved to significantly reduce mean monthly migraine/probable migraine headache days and to be well tolerated, with no indications of hepatotoxicity.[63]

Despite the enthusiasm for the newer gepants in the migraine treatment, there are still several points that need to be considered. Their short half-life limits their use as an acute treatment that needs to be taken as early as possible at the onset of a migraine attack. As with other acute medications, it remains uncertain if their overuse could lead to the development of medication overuse headache. At least with the older generation of gepants, overuse is a possibility given the increased levels of aminotransferase in patients using telcagepant daily for a week.[64] Atogepant, on the other hand, has a longer half-life than other gepants, and it is developed for migraine prevention. Its use, however, will be also limited by the need of daily oral intake. Clinical experience with the use of current migraine preventives in chronic migraine (CM) shows a low percentage of long-term adherence and persistence to oral migraine-preventive medications.[65,66]

An alternative method to modulate CGRP activity that has been introduced recently is through the development of mAbs against the CGRP receptor, and the CGRP ligand. These mAbs have now been studied in clinical trials for the preventive treatment of frequent episodic migraine (EM) and CM with promising results are now approved by the US Food and Drug Administration and the European Medicines Agency. Erenumab, unlike the other CGRP mAbs for migraine prevention, is a fully human monoclonal antibody built to interact with the CGRP receptor rather than the CGRP itself. Erenumab, and the other monoclonal antibodies currently tested in headaches, have some advantages over oral preventive treatment that make them better suited for migraine prophylaxis. The slow degradation and elimination of antibodies and their long half-life allows for longer dosing intervals. This is particularly interesting as adherence and persistence to oral preventives is very low among migraine patients in the long-term.[65,66] An injectable treatment that can be self-administered may be also a more convenient treatment approach for both patients and treating physicians. Compared with the CGRP receptor antagonists for migraine prevention, their short half-life of typically a few hours will demand a daily intake, with a risk of low adherence and persistence in the long term.

Like other monoclonal antibodies, erenumab is not eliminated through hepatic, renal or biliary processes,[67] and hence it is linked with a reduced risk of drug-to-drug interactions. In addition, as mAbs are not degraded by the liver, the use of erenumab is not associated with hepatotoxicity. Hepatotoxicity was a significant problem with the use of the earlier gepants, MK-0974 and MK-3207, that led to their withdrawal from following trials.

Erenumab was hence developed as an alternative method to modulate the CGRP receptor activity, in a similar manner to CGRP antagonists, which will bypass issues such as, short-half life, overuse risk, risk of hepatotoxicity and adherence to therapy.

Development, pharmacokinetics and pharmacodynamics of erenumab

Erenumab (AMG 334) is a fully human monoclonal IgG2 antibody against the CGRP receptor developed specifically for the preventative treatment of migraine. Erenumab was produced in XenoMouse and immunized with purified polypeptides containing the N-terminal extracellular domains of human CRLR (amino acids 1–138 of GenBank accession no. AAA62158) and human RAMP1 (amino acids 1-117 of GenBank accession no. CAA04472). Erenumab selectively antagonises human and cynomolgus monkey CGRP receptor exhibiting >5000-fold higher selectivity compared with dog, rabbit and rat receptors.[68] Erenumab has been demonstrated *in vitro* to have a high affinity to human CGRP receptors (dissociation equilibrium constant KD=20 pM). It also exhibited >5000-fold higher selectivity for the CGRP receptor and had no activity even at very high concentration (10 μM) on adrenomedullin, calcitonin and amylin receptors.[68] As far as mechanism of action is concerned, erenumab is thought to bind to the CGRP receptor in as gepants. Studies with CGRP antagonists demonstrated that the CGRP receptor subunit RAMP1 governs high-affinity binding and species selectivity.[69,70]

Erenumab potently and competitively inhibited the binding of radiolabelled [125I]-CGRP to human CGRP receptors expressed in human neuroblastoma cell (SK-N-MC cells), with a Ki of 0.02 nM. Erenumab demonstrated a potent and full antagonistic effect in a competitive and reversible manner in a functional assay that assessed the reduction of cAMP production induced by erenumab this type of cells expressing CGRP receptor [half maximal inhibitory concentration (IC50) of 2.3 nM, maximal inhibition of 91.7%]. On the other hand, erenumab did not exhibit any agonist activity, even at the highest concentration tested (10 μM).

The capsaicin-induced blood flow increase model is widely used to assess the effect of drugs on the reduction of CGRP-driven vasodilation and consequent increase in blood flow. Capsaicin is a TRPV1 receptor agonist, which induces the release of neuropeptides, including CGRP, from C-fibres. When injected in the skin, capsaicin induces a marked blood flow increase, driven by the release of local CGRP from peripheral sensory fibres, that can be measured with laser doppler technology. In the capsaicin-induced blood flow increase model tested in monkeys, erenumab produced a dose-dependent reduction of capsaicin induced blood flow increase, with sustained maximal response at 4 days post-iv administration at doses of 3 mg/kg and higher. The resulting plasma concentration for monkeys dosed with 3 mg/kg iv on day 4 was approximately 36-fold in excess of the *in vitro* IC50.[68] Based on these outcomes, it was concluded that erenumab could reduce capsaicin-induced blood flow in humans at a dose around 4-fold in excess of the *in vitro* IC50 and have a maximal effect at a dose of 36-fold in excess of the *in vitro* IC50.[68] Erenumab was also found to be highly potent in inhibiting capsaicin-induced blood flow increase when injected subcutaneous (sc) in humans, with an IC50 of 255 ng/ml and non-linear PK.[71,72] The non-linear PK suggests a decreased clearance of the mAb with increased dose[72] as for other mAb therapeutics, in relation with to a target-mediated drug elimination. This suggests the presence of two parallel antibody elimination pathways with non-linear and linear clearance behavioural: the first is a rapid saturable elimination pathway related by degradation or internalization of the erenumab-receptor complex, while the second is a slow one, mediated by a non-specific mechanism in the hepatic reticuloendothelial system.[72,73]

In a phase I study sc injection of 140 mg of erenumab in migraine patients, achieved 90–95% inhibition of capsaicin-induced blood flow increase after single and repeated injections. When erenumab was injected at >70 mg sc as a single dose, detectable serum levels were observed for at least 100 days post-dose. The maximum concentration of erenumab at 140 mg injected sc in migraine patients was detected at ~11 days post-first injection and at ~7 days post third injection.[71] Based on PK modelling, the elimination half-life of erenumab for a typical 70-kg subject receiving 70 mg sc was estimated at ~21 days.[71] The estimate of SC bioavailability for erenumab was calculated at 74%,[71] which is similar to the bioavailability of other mAb therapeutics.[74]

Interestingly, although erenumab potently inhibited the capsaicin-induced blood flow increase, the basal skin perfusion was not affected.[71] In addition, in a small sample of healthy subjects and migraine patients, erenumab had no effect on

systolic or diastolic blood pressure on its own,[71] or in combination with sumatriptan.[75] Together, these data suggest that although CGRP is a major vasodilator, it does not contribute to the basal vascular tone. Although more studies are needed, blockade of the CGRP receptor with erenumab may be lacking any cardiovascular risk under resting conditions.

Erenumab mechanism of action

Erenumab as a CGRP receptor mAb blocks the CLR/RAMP1 receptor and blocks the CGRP signalling pathway. Erenumab contains 1344 amino acids with a molecular weight of approximately 150 kilodalton (KDa); this large molecular weight precludes crossing of the blood brain barrier[76] and hence its mechanism of action is limited peripherally. Given that this is a systemic treatment, erenumab could block any CGRP receptor that can be accessed in the periphery. Its efficacy in migraine is mainly attributed to the blockage of CGRP receptors expressed in the trigeminal system – both fibres and ganglia. Erenumab alters the intracellular processing in those cells with a subsequent effect the reduction of CGRP-induced cAMP production.

cAMP is an important second messenger involved in intracellular signal transduction, activation of protein kinases and regulation of ion channels.[77–79] Elucidating the role of the cAMP signalling pathway in migraine may be a field of interest for research of novel therapeutic strategies. Interestingly, cilostazol, a selective inhibitor of phosphodiesterase type 3 (an important cAMP degrading enzyme), has been shown to trigger migraine attacks in sufferers.[80,81] Cilostazol-induced migraine attacks are thought to be a consequence of intracellular cAMP accumulation. In rodents, cilosatzol induced c-fos expression in the trigeminal nucleus caudalis, light sensitivity and hyperalgesia.[82]

Possible sites of action of mAbs relevant to migraine pathophysiology are the trigeminal ganglia, and in particular cells containing the CGRP receptor, and the trigeminal fibres expressing the CGRP receptor. Although migraine pathophysiology is no longer thought to involve vasodilation as a disease mechanism, erenumab actions on cerebral and meningeal blood vessels might play some role on the efficacy of this treatment in migraine.

Within the trigeminal ganglia, erenumab may block CGRP receptors expressed on trigeminal neurons, mainly Aδ-fibres, and on satellite glial cells. Activation of CGRP receptors on glutamate expressing trigeminal fibres (Aδ-fibres) enhances the release of glutamate, contributing to peripheral and central sensitization.[83] Erenumab may block the CGRP-induced glutamate release from Aδ-fibres and reduce the potential of peripheral and central sensitization. Erenumab may also block the CGRP-induced release of inflammatory mediators and signalling molecule NO from satellite cells, further inhibiting peripheral sensitization.[84,85]

CGRP induced vasodilation is mainly through direct activation of CLR/RAMP1 on smooth muscle cells. Indirectly, CGRP induces vasodilation through endothelium NO-dependent pathways. Activation of endothelium CLR/RAMP1 by CGRP induce a rise in cAMP and NO production. The latter compound is able to spread into the smooth muscle cell, activate guanylate cyclase and induce relaxation. As NO is a signalling molecule its diffusion to nearby sensory fibres could activate the trigeminal system. Hence, there may be a role for erenumab in blocking vascular CGRP receptors. Certainly, erenumab can inhibit neurogenic vasodilation *via* the blockage of CGRP/CGRP receptor interactions on the smooth muscle, as shown in capsaicin-induced vasodilation studies.[68,72]

Safety and tolerability of erenumab

The clinical evidence published so far showed a favourable safety and tolerability profile of erenumab. Treatment-related AEs were reported in about half of patients treated with three monthly erenumab injections across the pivotal clinical trials. The proportion of patients reporting AEs after 1 year of treatment was slightly higher in the CM population.[86] These AEs were predominantly of mild-moderate severity and they were rarely responsible for treatment discontinuation. The most common AEs (⩾2%) include: nasopharyngitis, injection site pain, upper respiratory tract infections, back pain, influenza, fatigue and constipation. Table 1 summarises the safety profile of erenumab compared with placebo in EM and CM. No significant differences in the percentage of occurrence and degree of severity of AEs between active drug and placebo were detected in both clinical trials and in two recently published meta-analyses.[87,88]

Table 1. Erenumab adverse events in clinical trials.

Randomization	Phase II EM[89]				Phase III EM[90]		Phase III EM[91]			Phase IIIb EM[92]		Phase II CM[93]		
	Placebo (*n* = 153)	7 mg (*n* = 108)	21 mg (*n* = 105)	70 mg (*n* = 106)	Placebo (*n* = 291)	70 mg (*n* = 286)	Placebo (*n* = 319)	70 mg (*n* = 314)	140 mg (*n* = 319)	Placebo (*n* = 124)	140 mg (*n* = 119)	Placebo (*n* = 281)	70 mg (*n* = 188)	140 mg (*n* = 187)
Adverse events	54%	50%	51%	54%	55%	48%	63%	57%	55%	54%	55%	39%	44%	47%
Serious adverse events	0	1%	0	1%	2%	1%	2%	3%	2%	1%	2%	2%	3%	1%
Adverse events leading to treatment discontinuation	1%	2%	2%	3%	<1%	3%	3%	2%	2%	1%	0	<1%	0	1%
Adverse events occurring in >= 2% in at least one study														
Nasopharyngitis	8%	9%	5%	6%	6%	5%	10%	10%	11%	10%	4%	6%	3%	2%
Upper respiratory tract infection	2%	1%	2%	3%	5%	6%	6%	7%	5%	0	3%	1%	3%	3%
Sinusitis	/	/	/	/	2%	2%	2%	2%	3%	/	/	/	/	/
Cough	2%	2%	1%	0%	/	/	/	/	/	/	/	/	/	/
Urinary tract infection	/	/	/	/	/	/	2%	2%	2%	/	/	/	/	/
Constipation	/	/	/	/	2%	1%	1%	2%	3%	/	/	<1%	0%	4%
Diarrhoea	3%	0	1%	1%	/	/	/	/	/	/	/	/	/	/
Nausea	1%	3%	1%	3%	5%	3%	2%	2%	2%	/	/	2%	2%	3%
Fatigue	2%	5%	2%	4%	2%	4%	3%	2%	2%	2%	3%	/	/	/
Influenza	3%	1%	4%	1%	4%	4%	2%	1%	3%			/	/	/
Back pain	3%	2%	4%	1%	/	/	2%	2%	2%	2%	4%	/	/	/
Neck pain	/	/	/	/	/	/	/	/	/	0	3%	/	/	/
Arthralgia	3%	1%	0	1%	/	/	2%	2%	2%	/	/	/	/	/
Muscle spasm/ tightness	2%	0	0	0	/	/	/	/	/	/	/	1%	<1%	4%
Hypertension	/	/	/	/	/	/	3%	2%	0	/	/	/	/	/
Migraine	1%	1%	3%	3%	3%	2%	/	/	/	/	/	1%	2%	3%
Dizziness	/	/	/	/			/	/	/	2%	3%	/	/	/
Injection site pain	3%	6%	5%	5%	4%	6%	<1%	3%	<1%	6%	6%	1%	4%	4%

CM, chronic migraine; EM, episodic migraine; *n*, number.
*No statistically significant differences we demonstrated in terms of adverse events between placebo and erenumab across all studies.

Table 2. Non-cardiovascular physiological properties of CGRP in humans.

Site of action	Physiological effects	Potential implications of CGRP antagonism
Immune system[94,95]	- Inhibition of antigen presenting cell activity and pro-inflammatory cytokine secretion - Inhibition Th1 over Th2 responses - Inhibition of chemotaxis	- Immunogenic effect
Respiratory system[96,97]	- Promotion of mucus production and goblet cell hyperplasia - Modulation of local inflammatory responses and immune cells	- Worsening of COPD and asthma
Gastrointestinal system[98,99]	- Inhibition of motility - Promotion of Somatostatin secretion - Promotion of blood flow and inhibition of acid secretion - Modulation of local inflammatory responses and immune cells	- Constipation - Worsening of bowel inflammatory conditions - Worsening of gastritis and gastro-duodenal ulceration
Cutaneous tissue[100,101]	- Tissue repair mechanisms - Modulation of local inflammatory responses and immune cells	- Delayed wound healing and scare formation - Worsening of dermatitis and improvement of psoriasis
Reproductive system[102,103]	- Erectile and sperm function - Effect on pituitary hormones	- Erectile dysfunction - Infertility
Pregnancy[104,105]	- Uterine relaxation - Foetal growth - Placenta stabilization	- Risk of miscarriage
Osteo-articular system[106,107]	- Inhibition of chondrocyte hypertrophic differentiation - Inhibition of osteoclasts - Activation of osteoblasts - Joint nerve sensitization	- Worsening of osteoporosis - Improvement of arthritic-related joint pain

COPD, chronic obstructive pulmonary disease.

CGRP is a ubiquitous very potent vasodilatory peptide involved in several physiological functions. Table 2 summarises the pivotal role of CGRP in human physiology. In view of the multitude of important roles of CGRP, it would be critical to understand the short- and long-term effects of blockade of the CGRP pathway.

CGRP as a vasodilator is involved in cardiovascular regulation of blood pressure. It seems that its role under physiological circumstances may be limited,[108] but it seems to have a compensatory effect during hypertensive states.[109] A recent analysis of the vascular adverse events across the four clinical trials of erenumab and their open-label extension conducted in 2443 patients, showed a similar incidence of vascular adverse events between erenumab and placebo treatments groups. Hypertension was reported in 0.1% of erenumab group and in 0.9% of placebo group.[110]

CGRP may have a protective role against ischemia by increasing cerebral blood flow.[111] CGRP appears to be able to reduce brain injury following a stroke.[112,113] Furthermore, infusion of CGRP further has been shown to reduce vasospasm in patients with subarachnoid haemorrhage (SAH).[114,115] A recent case of a thalamic infarction following a first dose of erenumab in a young adult migraineur has been described. Stroke onset occurred during a typical migraine and a vasospasm was the postulated mechanisms after several investigations were carried out.[116]

Although the clinical trials population did not experience an excess of cardiovascular side effects while exposed to erenumab, cardiovascular safety in patients with pre-existent cardiac issues was evaluated in only one randomized, double-blind, placebo-controlled study in which erenumab effect on treadmill test performances was evaluated in patients with stable angina pectoris. No differences were demonstrated between patients receiving erenumab or placebo. Despite the study was important for trying to address an important issue, serious concerns have been raised about the methodology and hence validity of the study findings,[117] suggesting that this group of patients need to be assessed properly.

Limitations in the use of erenumab

Lack of efficacy against the amylin receptor

Recent studies suggest that CGRP acts on both the CLR/RAMP1 and CTR/RAMP1 (AMY1) receptor. This may have potential implications in the use of erenumab, a CGRP-receptor mAb, as released CGRP could still exert at least part of its effects through binding to the AMY1 receptor. Potentially, agents that block both receptors might be more effective to erenumab as well as antibodies against the CGRP ligand. Although no clinical trial ever directly compared erenumab with the CGRP mAbs, their efficacy in phase II/III studies appears to be similar. One could claim that the same limitation may apply to the small molecules of CGRP antagonists, however, if these are used at high concentrations, they show only limited selectivity between CGRP and AMY1 receptors.[118]

Anti-mAb antibodies

Unlike gepants, erenumab can trigger the immune system to produce anti-erenumab antibodies, and there is a possibility that such antibodies could be neutralizing anti-drug antibodies, reducing the efficacy of erenumab. Although this possibility is reduced since erenumab is a human immunoglobulin, anti-drug antibodies have been reported in clinical trials. In the clinical trials of erenumab, including those with long-term treatment, 2–8% of patients developed anti-drug antibodies.[90,91,93,119] Only a small percentage of patients were reported to have neutralising anti-erenumab antibodies at least on one occasion, but that did not seem to result in reduced efficacy or increased rate of adverse events. Long-term studies looking at anti-drug antibodies that may develop over a longer time of treatment, are needed.

How does erenumab compare with other CGRP antagonists?

Very limited data are available for the comparison of erenumab and CGRP antagonists, and these are mostly limited to the earlier oral gepants. Unlike telcagepant which was modestly selective over the AMY1 receptor, erenumab appears to be more specific over the CGRP receptor.[15,120] As discussed earlier though, this may be a peculiarity of erenumab, as CGRP appears to act on both the CGRP and AMY1 receptor.[15] In addition, erenumab appears to be more potent than telcagepant in competing with [125I]-CGRP binding (Ki of 0.02 nM *versus* 0.77 nM, respectively).[68] The higher affinity of erenumab may be attributed to the multiple surface binding interactions of the mAb with the CGRP receptor. In the capsaicin-induced blood flow increase studies in humans, erenumab displayed an IC50 of 1.7 nM,[68] which was very similar to the potency of the CGRP antagonist MK-3207,[121] but was significantly more potent than telcagepant which had an IIC50 of 101 nM.[122] Interestingly, both erenumab and the small CGRP antagonists do not seem to affect resting tissue blood perfusion.

Beyond the pharmacodynamic and pharmacokinetic differences, the prolonged plasma half-life of erenumab allows longer dosing intervals and not daily intake like with CGRP antagonists used for prevention, a property that is expected to offer higher adherence to treatment. Of course, the nature of erenumab as a mAb limits its route of treatment as sc injections, compared with orally active CGRP antagonist. Of course, should side effects appear or treatment discontinuation is needed for any other clinical reason, for example, in pregnancy, the long

half-life of erenumab may come as a limitation compared with stopping an orally active CGRP antagonist. In addition, unlike the CGRP receptor antagonists, erenumab is not degraded by the liver, and hence is unlikely to show any hepatotoxicity compared with telcagepant and MK-3207.

Erenumab: clinical data in migraine

Episodic migraine

A dose-finding phase II clinical trial of erenumab *versus* placebo for the prevention of EM demonstrated that erenumab only at the dose of 70mg administered sc every 4 weeks met the primary endpoint of reduction of mean monthly migraine days (MMD) from baseline compared with placebo in weeks 8–12 after randomization (–3.4 *versus* –2.3 $p < 0.021$). Furthermore, some secondary endpoints were also met, namely 50% responder rate (46% in the erenumab 70 mg arm *versus* 30% in the placebo arm, $p < 0.011$) and reduction in headache days/month (–3.5 *versus* –2.4 $p < 0.022$). No significant differences emerged on migraine specific disability and quality of life scales. Frequency of occurrence of adverse events were comparable between active groups and placebo. Severe adverse events were not related to the treatment.[89] Subsequently two phase III and a phase IIIb trial tested the efficacy of erenumab in EM.[90–92]

ARISE is the first phase III trial that demonstrated clinical superiority of erenumab 70 mg/month compared with placebo in EM. Adults with EM aged between 18 and 65 years, with less than three previous preventive drugs failures, were randomized to placebo or erenumab 70 mg/month for 12 weeks. After 12 weeks, MMD was significantly improved in the active arm than compared with the placebo arm (–2.9 *versus* 1.8 $p < 0.001$). Erenumab resulted in being superior to placebo in the proportion of patients, obtaining at least 50% reduction of MMD (39.7% *versus* 29.5% $p < 0.010$) and in reduction of migraine specific drug days/month (–1.2 *versus* 0.6 $p = 0.002$).[90]

STRIVE was a 24-week long phase III trial testing efficacy of erenumab 70 mg and 140 mg/month *versus* placebo in EM. Adults with EM, with a maximum of two previous migraine preventive drug failures and no medication overuse, were randomized to either placebo, erenumab 70 mg/month or erenumab 140 mg/month. The trial demonstrated that from month 4 through month 6, erenumab led to a greater reduction in MMD from baseline compared with placebo (erenumab 70 mg –3.2 and erenumab 140 mg –3.7 *versus* –1.8 $p < 0.001$), a greater reduction in migraine specific painkiller days/month in both active treatment arms compared with placebo (erenumab 70 mg –1.1 and erenumab 140 mg –1.6 *versus* –0.2 $p < 0.001$). The results also showed a higher percentage of 50% responders in patients treated with erenumab compared with placebo (erenumab 70 mg 43.3% and erenumab 140 mg 50.0% *versus* 26.6% $p < 0.001$).[91] The trials' methodological differences and efficacy endpoints are summarised in Table 3.

Long term data in episodic migraine

Long term data from the phase II trial were collected aiming to assess long-term safety of erenumab administered at the dose of 70 mg/month for 5 years. The 1 year interim analysis conducted in 307 of the initial 472 patients' cohort showed a safety profile of erenumab similar to that in the double-blind phase and no new safety concerns had emerged. Only 13% ($n = 14/107$ participants) of participants discontinued erenumab due to adverse events. Participants exposed to erenumab 70 mg for a year reported a mean reduction in MMD from 8.8 [Standard deviation (SD): 2.6] at baseline to 3.7 (SD: 4.0) at week 64, with a mean change from baseline of 5.0 days.[86]

The three-year interim analysis of the same phase II trial assessed safety, tolerability and efficacy of erenumab at the increased dose of 140 mg/month. At the time of this analysis 236 participants out of 383 who continued to the 1 year open label extension were included in this study. Out of the subjects who discontinued the trial for personal reasons, only one participant did so due to adverse events. Erenumab administered at the dose of 140 mg demonstrated no new safety concerns including cardiovascular problems. The most frequent side effects reported in this study included viral upper respiratory tract and sinus infection, flu-like syndrome and back pain. Serious adverse events were rare and similar to the placebo group. No cases of hepatotoxicity were detected. Two patients on erenumab 140 mg (0.8%) had increased liver enzymes. No efficacy outcomes were reported in this study.[123]

Table 3. Methodologies and outcomes of clinical trials of erenumab in episodic migraine.

	ARISE[90]	STRIVE[91]	LIBERTY[92]
Number of participants	577	955	246
Erenumab dose	70 mg	70 mg and 140 mg	140 mg
Number of preventive treatments failed	<3 treatments	<3 treatments	2–4 treatments
Trial duration	12 weeks	24 weeks	12 weeks
Change in mean MMD	−2.9 days	−3.2 days (70 mg) −3.7 days (140 mg)	−1.8 days
Therapeutic gain	−1.1 days	−1.4 days (70 mg) −1.9 days (140 mg)	−1.6 days
Change in acute medication days/month	−1.2	−1.1 (70 mg) −1.6 (140 mg)	−1.3
Rate of 50% responders	39.7%	43.3.% (70 mg) 50.0% (140 mg)	30%
HIT-6	−4.9 (gain: −2.3)	Not used	Not used
Discontinuation rate due to side effects	1.8%	2.2% (70 mg) 2.2% (140 mg)	0%

MMD, monthly migraine days.

Chronic migraine

The safety and efficacy of erenumab in the prevention of CM were evaluated in a double-blind, placebo-controlled, phase II clinical trial.[93] Patients were randomized (3:2:2) to placebo, erenumab 70 mg or 140 mg and administered every 4 weeks for 12 weeks. The reduction in MMD from baseline to weeks 9–12 was the primary endpoint. Secondary endpoints included the percentage of participants achieving 50% reduction in MMD, change in the use of monthly acute migraine treatments and change in cumulative headache hours from baseline. The mean monthly migraine days at baseline ranged between 17.8 and 18.2 days. Erenumab 70 mg and 140 mg reduced monthly migraine days by 6.6 days compared with 4.2 days of placebo [95% confidence interval (CI) −3·5 to −1·4, $p < 0{\cdot}0001$]. At the end of the double-blind treatment phase, 40% of patients in the erenumab 70 mg group and 41% of patients in the erenumab 140 mg group achieved a 50% or more reduction from baseline in monthly migraine days compared with 23% of patients in the placebo arm.

Responders rate analysis in chronic migraine

The responder rate analysis has been considered a valid secondary endpoint outcome aiming to enforce the meaning of a reduction in mean migraine days, which has been used as a primary endpoint in all clinical trials testing the mAbs. This efficacy outcome is also useful in clinical practice to present to the patients the likely magnitude of effect of a treatment that they have been offered. A *post hoc* analysis of the overall population treated in the erenumab CM trial evaluated the 50% (pre-specified secondary endpoint), 75% (*post hoc* analysis), and 100% (*post hoc* analysis) reduction in MMD from baseline to Month 3. In addition, the percentage of patients with no response to treatment, defined as no change or worsening of MMD, was assessed. At month 3, 39.9% and 41.2% of patients on erenumab 70 and 140 mg, respectively, achieved 50% response *versus* placebo (23.5%). Similarly, at month 3, 17.0% and 20.9% of patients on erenumab 70 and 140 mg, respectively, achieved 75% response *versus* placebo (7.8%). The proportion of patients who achieved a 100% response at month 3 in the placebo, erenumab 70 mg, and 140 mg groups

were 0.4% (n = 1/281), 4.3% (n = 8/188), and 2.7% (n¼ 5/187), respectively. Overall, 28.1%, 16.3% and 20.9% of patients reported no change/worsening in the placebo, erenumab 70 mg and 140 mg groups, respectively.[124]

Chronic migraine and medication overuse

Evidence of efficacy of erenumab in patients with CM and medication overuse headache (MOH) come from a subgroup analysis of the phase II trial.[125] Of all participants, 41% fulfilled the criteria for MOH. At month 3, there was an average reduction of 6.6 migraine days with both erenumab doses compared with 3.5 days migraine days reduction in the placebo arm (treatment difference of –3.1 days, 95% CI –4.8 to –1.4). Furthermore, the ⩾50% responder rates in the MOH group were superior for the group treated with erenumab 70 mg (36%) and with 140 mg (35%), compared with the placebo group (18%). There was a significant reduction acute migraine-specific medication use days in the medication overuse subgroup treated with erenumab 70 mg (–5.4 days) and 140 mg (–4.9 days) compared with the placebo group (–2.1 days).

A significantly greater proportion of patients in the erenumab 70 mg and 140 mg groups transitioned from medication overusers to non-medication overusers at month 3, regardless of the abortive treatments overused (simple analgesics, triptans or combination). More than 50% of patients overusing simple analgesics or triptan switched to non-MOH already at month 1.

The reduction in migraine days and painkillers intake led to a reduction of the disability and to an improvement of the quality of life scores.[125]

Difficult-to-treat migraine

Participants enrolled in the initial clinical trials of erenumab were naïve or almost naïve to treatments, which may reflect the population of migraine patients assessed in primary care but not in secondary or tertiary care, where either EM or CM patients are normally more difficult to treat. One study and two subgroup analysis of already published studies tried to address the question on whether erenumab was superior to placebo also in difficult-to-treat EM and CM patients.

A subgroup analysis of the STRIVE study assessed the effect of erenumab in EM patients who failed ⩾1 or ⩾2 preventive treatments. The analysis showed consistency of effect of erenumab regardless of the number of preventive treatment failures.[126] Subsequently, a clinical trial was specifically designed to assess the efficacy of erenumab 140 mg/month for three months *versus* placebo in patients who failed to respond or tolerate 2–4 preventive treatments. The LIBERTY trial included participants who had previously failed two (39%), three (38%) and four preventive medications (23%). At week 12 of the randomised phase, erenumab led 30% of the patients to at least 50% reduction in the mean number of monthly migraine days, compared with 14% in the placebo group [odds ratio 2·7 (95% CI 1·4–5·2); $p = 0{\cdot}002$].[92] Despite being superior to placebo, the 50% responder rate of this trial was less impressive compared with the rate displayed in the other trials conducted in EM patients who failed two or less preventive treatments (>40%). This discrepancy may confirm that patients who fail several previous preventive treatments are a more difficult to treat group. An open-label extension of this placebo-controlled trial phase was conducted to evaluate long-term safety and efficacy of erenumab in EM. The results of an interim analysis were presented during the 2019 European Headache Federation (EHF) conference in Athens. A total of 240 patients of the placebo-controlled trial continued in the open-label phase and were treated with erenumab 140 mg/month. In total, 202 patients completed a 52-week treatment and follow up. The analysis confirmed the efficacy of erenumab and displayed a slight improvement in the efficacy outcomes compared with the placebo-controlled phase with 48% of patients obtaining a 50% response rate and with a mean reduction in migraine days/month of 3.6 days/month. This improvement was translated into a reduction of migraine-related disability according to the Headache Impact Test (HIT-6) score and Migraine Physical Function Impact Diary-Every day activity domain (MPFID-EA) or physical-impairment domain (PI) score.[127]

A subgroup analysis of the pivotal CM trial assessed the efficacy of erenumab in difficult-to-treat patients. The study included patients who failed at least one preventive drug (70%), at least two drugs (almost 50%) and at least three drugs (35%). For both dosages (but particularly for 140 mg), erenumab was superior to placebo in those who failed at least one treatment: erenumab 70 mg *versus* placebo –2.5 MMD, $p < 0.001$;

erenumab 140 mg *versus* placebo –3.3 MMD, $p < 0.001$. Similar results were obtained by those who failed at least two treatments: erenumab 70 mg *versus* placebo, –2.7 migraine days, $p < 0.001$; erenumab 140 mg *versus* placebo –4.3 MMD, $p < 0.001$; and at least three treatments: erenumab 70 mg *versus* placebo, –2.5 MMD, $p < 0.005$; and erenumab 140 mg *versus* placebo, –4.1 MMD. This analysis supported the clinical usefulness of erenumab in difficult cases of CM which are often encountered in clinical practice.[128]

Migraine-related disability and quality of life scales in erenumab trials

The aim of migraine preventive treatments is ultimately to provide improvement of quality of life and to reduce migraine-related disability for sufferers. Several scales have been used in the erenumab clinical trial programmes to evaluate any change in quality of life and disability outcomes in migraine patients. The phase II trial in EM[89] the Migraine Disability Assessment Questionnaire (MIDAS), HIT-6 were used, along with the Patient Reported Outcomes Measurement Information System (PROMIS) and some domains of the Migraine-Specific Quality of Life Questionnaire (MSQ). However, the study was not designed to detect a significant difference for these endpoints. Hence, the main data on migraine-related disability and quality of life have come from ARISE and STRIVE trials. In the ARISE trial, the established HIT-6 (modified version), MIDAS and MSQ were used. Migraine-related physical impairment was tested using the Migraine Physical Function Impact Diary (MPFID-PI), and achievement of at least a 5-point reduction in monthly average Impact on Everyday Activities (MPFID-EA) domain score was considered clinically meaningful. There was no statistically significant difference in the two domains of the MPFID score between erenumab 70 mg and placebo. However, the improvements in MSQ and HIT-6 scores were statistically greater in the erenumab group than in placebo at month 3.[90]

The migraine-related disability and quality of life measures utilised in the STRIVE trial include: MIDAS and HIT-6 score as well as the MSQ. Overall, erenumab treatment *versus* placebo resulted in a greater reduction in migraine-related disability. Separation between the erenumab and placebo groups occurred as early as month 1, and reductions in scores remained consistently greater for erenumab throughout the 6 months of treatment. There was a reduction of the proportion of patients with severe and very severe migraine-related disability as per MIDAS in patients receiving erenumab 70 and 140 mg over months 4–6 compared with those receiving placebo.[91] Similarly, erenumab treatment resulted in greater reductions of HIT-6 scores compared with placebo. There was no significant difference between the 70 mg and 140 mg doses. A clinically meaningful 5-point reduction (improvement) from baseline in HIT-6 over months 4–6 after receiving 70 mg and 140 mg was 56.4% and 49.7%, respectively, compared with placebo (39.9%). Moreover, in patients receiving both erenumab 70 mg and 140 mg, a clinically meaningful improvement of MSQ was evident.

Erenumab: future directions and conclusions

Findings from rigorous clinical trials have all pointed towards the clinical efficacy, safety and good tolerability of erenumab in the prevention of EM and CM.[89–93,123,127]

These promising data will need to be confirmed in the real-world migraine population, which is considered often more difficult to treat compared with the clinical trials participants predominantly for two reasons: a greater number of preventive treatments failed and the greater number of comorbidities. Such data will also be relevant in the context of healthcare economic aspects. Indeed, the mAbs are considered costly treatments and, due to cost-effectiveness reasons, their use may be limited to CM instead of EM and to those CM who are refractory to medical treatments, having failed three classes of preventive medications. Indeed, initial cost-effective analysis conducted in the USA have concluded that erenumab may be a cost-effective approach in CM[129] but not in EM. In Europe, a recent cost analysis of erenumab and BoNT/A have highlighted that erenumab could be as cost-effective as BoNT/A either at a lower compared to the current one or in patients who failed to respond to BoNT/A.[130] Hence, future studies will need to establish the effectiveness of mAbs in this subgroup of complex CM refractory to medications.

At the time of writing, the only real-world report published so far on erenumab includes a small

cohort of migraine patients (13 episodic and 65 chronic) treated with erenumab 70 mg/month for mostly 2 months. Results at 4 and 8 weeks showed a 50% response rate in the CM group of 68.2% after the first dose and of 87.5% after the second dose. The proportion of 75% responders was 40.5% and 37.5% after the first and the second dose, respectively. There was a clinically meaningful reduction of the HIT-6 score of almost 10 points after the first month and of almost 12 points after the second. The reduction in migraine days led to a reduction in painkillers intake in responders. Similar outcomes were noticed in the EM group. The treatment was overall tolerated well with only one patient reporting injection site pain.[131]

Migraine often occurs in comorbidity with other conditions including pain, sleep and psychiatric comorbidities.[132] Patients with migraine and one or more of these comorbidities suffer from a high degree of disability and display a greater level of management complexity. Established migraine oral preventive treatments are normally chosen or dismissed based upon the presence and type of comorbidities. Studies that aim to test the efficacy of anti-CGRP mAbs in patients with migraine and other pain and psychiatric comorbidities will help clarifying the role of this class of medications in this complex population which is often found challenging to be managed both primary care and in specialist headache clinics.

The outcomes of clinical trials and the pharmacodynamic properties of erenumab suggest a quick onset of action, normally within 1–2 weeks. This drug property has led the EHF to recommend a 3-month trial of mAbs for 3 months before assessing their effectiveness.[133] Given the complexity and refractoriness of certain migraine patients seen in tertiary referral centres, it is plausible to postulate that a subgroup of these patients may need 6 months of treatment before assessing whether to continue or discontinue a treatment with erenumab. In patients obtaining a clinically meaningful response, it is unclear how long the therapy should be continued. In clinical practice, an attempt to stop preventive therapy, in order to evaluate if the improvement may be sustained and to minimize the risk of adverse events, can be made if migraines become infrequent and not debilitating. None of the trials assessed the persistency of effect and risk of rebound headache after erenumab discontinuation. Currently, the EHF guidelines suggest to evaluate possible discontinuation after 6 or 12 months,[133] however, duration of trials with erenumab and the other mAbs may be dictated by the degree of response: 12 months in those with >50% response, which may no longer display a CM pattern, longer than 12 months in those with 30–50% response and 6 months in those with some degree of improvement but <30%. Post-market and real-world data will need to address these and other critical questions on this novel therapy to better shape the place of this novel treatment in the arsenal of medical options for migraine treatment.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

APA has received speaker honoraria, funding for travel, and honoraria for participation in advisory boards sponsored by eNeura, Allergan, Lilly and Novartis. MF has nothing to declare. GL has received speaker honoraria, funding for travel, and honoraria for participation in advisory boards sponsored by Allergan, TEVA, Lilly and Novartis. He has received speaker honoraria and funding for travel from electroCore, Nevro Corp, and Autonomic Technologies.

ORCID iD

Giorgio Lambru https://orcid.org/0000-0002-2780-4776

References

1. The International Classification for Headache Disorders, 3rd edition (beta version). Headache classification committee of the international headache society (IHS). *Cephalalgia* 2013; 33: 629–808.
2. Dodick DW. A phase-by-phase review of migraine pathophysiology. *Headache* 2018; 58(Suppl. 1): 4–16.
3. Burstein R, Noseda R and Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci* 2015; 35: 6619–6629.
4. Edvinsson L, Mulder H, Goadsby PJ, *et al.* Calcitonin gene-related peptide and nitric oxide in the trigeminal ganglion: cerebral vasodilatation from trigeminal nerve stimulation involves mainly calcitonin gene-related peptide. *J Auton Nerv Syst* 1998; 70: 15–22.

5. Amara S, Arriza J, Leff S, *et al*. Expression in brain of a messenger RNA encoding a novel neuropeptide homologous to calcitonin gene-related peptide. *Science* 1985; 229: 1094–1097.
6. Mulderry PK, Ghatei MA, Spokes RA, *et al*. Differential expression of alpha-CGRP and beta-CGRP by primary sensory neurons and enteric autonomic neurons of the rat. *Neuroscience* 1988; 25: 195–205.
7. Moussaoul S, Duval P, Lenoir V, *et al*. CGRP in the trigeminal nucleus, spinal cord and hypothalamus: effect of gonadal steroids. *Neuropeptides* 1996; 30: 546–550.
8. Edvinsson L, Eftekhari S, Salvatore C, *et al*. Cerebellar distribution of calcitonin gene-related peptide (CGRP) and its receptor components calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1) in rat. *Mol Cell Neurosci* 2011; 46: 333–339.
9. Tajti J, Uddman R and Edvinsson L. Neuropeptide localization in the "migraine generator" region of the human brainstem. *Cephalalgia* 2001; 21: 96–101.
10. Takahashi K, Mouri T, Sone M, *et al*. Calcitonin gene-related peptide in the human hypothalamus. *Endocrinol Jpn* 1989; 36: 409–415.
11. Summ O, Charbit AR, Andreou AP, *et al*. Modulation of nocioceptive transmission with calcitonin gene-related peptide receptor antagonists in the thalamus. *Brain* 2010; 133: 2540–2548.
12. Van Rossum D, Menard DP, Fournier A, *et al*. Binding profile of a selective calcitonin gene-related peptide (CGRP) receptor antagonist ligand, [125I-Tyr]hCGRP8-37, in rat brain and peripheral tissues. *J Pharmacol Exp Ther* 1994; 26: 846–853.
13. Mclatchie LM, Fraser NJ, Main MJ, *et al*. RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor. *Nature* 1998; 393: 333–339.
14. Evans BN, Rosenblatt M, Mnayer LO, *et al*. CGRP-RCP, a novel protein required for signal transduction at calcitonin gene-related peptide and adrenomedullin receptors. *J Biol Chem* 2000; 275: 31438–31443.
15. Walker CS, Eftekhari S, Bower RL, *et al*. A second trigeminal CGRP receptor: function and expression of the AMY1 receptor. *Ann Clin Transl Neurol* 2015; 2: 595–608.
16. Hay DL, Garelja ML, Poyner DR, *et al*. Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. *Br J Pharmacol* 2018; 175: 3–17.
17. Uddman R, Edvinsson L, Ekman R, *et al*. Innervation of the feline cerebral vasculature by nerve fibers containing calcitonin gene-related peptide: trigeminal origin and co-existence with substance P. *Neurosci Lett* 1985; 62: 131–136.
18. Tajti J, Uddman R, Moller S, *et al*. Messenger molecules and receptor mRNA in the human trigeminal ganglion. *J Auton Nerv Syst* 1999; 76: 176–183.
19. Eftekhari S, Salvatore CA, Calamari A, *et al*. Differential distribution of calcitonin gene-related peptide and its receptor components in the human trigeminal ganglion. *Neuroscience* 2010; 169: 683–696.
20. Wahlestedt C, Beding B, Ekman R, *et al*. Calcitonin gene-related peptide in the eye: release by sensory nerve stimulation and effects associated with neurogenic inflammation. *Regul Pept* 1986; 16: 107–115.
21. Tsai SH, Tew JM, McLean, *et al*. Cerebral arterial innervation by nerve fibers containing calcitonin gene-related peptide (CGRP): I. Distribution and origin of CGRP perivascular innervation in the rat. *J Comp Neurol* 1988; 271: 435–444.
22. Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache* 2017; 57(Suppl. 2): 47–55.
23. Silverman JD and Kruger L. An interpretation of dental innervation based upon the pattern of calcitonin gene-related peptide (CGRP)-immunoreactive thin sensory axons. *Somatosens Res* 1987; 5: 157–175.
24. Luthman J, Johansson O, Ahlstrom U, *et al*. Immunohistochemical studies of the neurochemical markers, CGRP, enkephalin, galanin, gamma-MSH, NPY, PHI, proctolin, PTH, somatostatin, SP, VIP, tyrosine hydroxylase and neurofilament in nerves and cells of the human attached gingiva. *Arch Oral Biol* 1988; 33: 149–158.
25. Takeda N, Kalubi B and Abe Y. Neurogenic inflammation in nasal allergy: histochemical and pharmacological studies in guinea pigs. A review. *Acta Otolaryngol Suppl* 1993; 501: 21–24.
26. Blixt FW, Radziwon-Balicka A, Edvinsson L, *et al*. Distribution of CGRP and its receptor components CLR and RAMP1 in the rat retina. *Exp Eye Res* 2017; 161: 124–131.

27. Brain SD, Williams TJ, Tippins JR, *et al.* Calcitonin gene-related peptide is a potent vasodilator. *Nature* 1985; 313: 54–56.
28. Edvinsson L and Goadsby PJ. Neuropeptides in the cerebral circulation: relevance to headache. *Cephalalgia* 1995; 15: 272–276.
29. Edvinsson L and Uddman R. Adrenergic, cholinergic and peptidergic nerve fibres in dura mater–involvement in headache? *Cephalalgia* 1981; 1: 175–179.
30. Edvinsson L, Fredholm BB, Hamel E, *et al.* Perivascular peptides relax cerebral arteries concomitant with stimulation of cyclic adenosine monophosphate accumulation or release of an endothelium-derived relaxing factor in the cat. *Neurosci Lett* 1985; 58: 213–217.
31. Edvinsson L, Ekman R, Jansen I, *et al.* Calcitonin gene-related peptide and cerebral blood vessels: distribution and vasomotor effects. *J Cereb Blood Flow Metab* 1987; 7: 720–728.
32. Bull HA, Hothersall J and Chowdhury N. Neuropeptides induce release of nitric oxide from human dermal microvascular endothelial cells. *J Invest Dermatol* 1996; 106: 655–660.
33. Couture R and Cuello AC. Studies on the trigeminal antidromic vasodilatation and plasma extravasation in the rat. *J Physiol* 1984; 346: 273–285.
34. Foreman JC. Peptides and neurogenic inflammation. *Br Med Bull* 1987; 43: 386–400.
35. Foreman JC. Substance P and calcitonin gene-related peptide: effects on mast cells and in human skin. *Int Arch Allergy Appl Immunol* 1987; 82: 366–371.
36. Miletic V and Tan H. Iontophoretic application of calcitonin gene-related peptide produces a slow and prolonged excitation of neurons in the cat lumbar dorsal horn. *Brain Res* 1988; 446: 169–172.
37. Biella G, Panara C, Pecile A, *et al.* Facilitatory role of calcitonin gene-related peptide (CGRP) on excitation induced by substance P (SP) and noxious stimuli in rat spinal dorsal horn neurons. An iontophoretic study in vivo. *Brain Res* 1991; 559: 352–356.
38. Leem JW, Gwak YS, Lee EH, *et al.* Effects of iontophoretically applied substance P, calcitonin gene-related peptide on excitability of dorsal horn neurones in rats. *Yonsei Med J* 2001; 42: 74–83.
39. Storer RJ, Akerman S and Goadsby PJ. Calcitonin gene-related peptide (CGRP) modulates nociceptive trigeminovascular transmission in the cat. *Br J Pharmacol* 2004; 142: 1171–1181.
40. Yu Y, Lundeberg T and Yu LC. Role of calcitonin gene-related peptide and its antagonist on the evoked discharge frequency of wide dynamic range neurons in the dorsal horn of the spinal cord in rats. *Regul Pept* 2002; 103: 23–27.
41. Bellamy LL, Cady RK and Durham PL. Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients. *Headache* 2006; 46: 24–33.
42. Juhasz G, Zsombok T, Modos EA, *et al.* NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. *Pain* 2003; 106: 461–470.
43. Hansen JM, Petersen J, Wienecke T, *et al.* Sumatriptan does not change calcitonin gene-related peptide in the cephalic and extracephalic circulation in healthy volunteers. *J Headache Pain* 2009; 10: 85–91.
44. Hansen JM, Hauge AW, Olesen J, *et al.* Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia* 2010; 30: 1179–1186.
45. Goadsby PJ and Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 1993; 33: 48–56.
46. Juhasz G, Zsombok T, Jakab B, *et al.* Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. *Cephalalgia* 2005; 25: 179–183.
47. Durham PL and Russo AF. Regulation of calcitonin gene-related peptide secretion by a serotonergic antimigraine drug. *J Neurosci* 1999; 19: 3423–3429.
48. Williamson DJ, Shepheard SL, Hill RG, *et al.* The novel anti-migraine agent rizatriptan inhibits neurogenic dural vasodilation and extravasation. *Eur J Pharmacol* 1997; 328: 61–64.
49. Zagami AS, Goadsby PJ and Edvinsson L. Stimulation of the superior sagittal sinus in the cat causes release of vasoactive peptides. *Neuropeptides* 1990; 16: 69–75.
50. Williamson DJ, Hargreaves RJ, Hill RG, *et al.* Intravital microscope studies on the effects of neurokinin agonists and calcitonin gene-related peptide on dural vessel diameter in the anaesthetized rat. *Cephalalgia* 1997; 17: 518–524.

51. Williamson DJ, Hargreaves RJ, Hill RG, *et al.* Sumatriptan inhibits neurogenic vasodilation of dural blood vessels in the anaesthetized rat–intravital microscope studies. *Cephalalgia* 1997; 17: 525–531.

52. Goadsby PJ and Edvinsson L. Joint 1994 Wolff Award Presentation. Peripheral and central trigeminovascular activation in cat is blocked by the serotonin (5HT)-1D receptor agonist 311C90. *Headache* 1994; 34: 394–399.

53. Lambru G, Andreou AP, Guglielmetti M, *et al*. Emerging drugs for migraine treatment: an update. *Expert Opin Emerg Drugs* 2018; 23: 301–318.

54. Olesen J, Diener HC, Husstedt IW, *et al.* Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *N Engl J Med* 2004; 350: 1104–1110.

55. Ho TW, Mannix LK, Fan X, *et al*. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. *Neurology* 2008; 70: 1304–1312.

56. Ho TW, Ferrari MD, Dodick DW, *et al*. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet* 2009; 372: 2115–2123.

57. Hewitt DJ, Aurora SK, Dodick DW, *et al.* Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. *Cephalalgia* 2011; 31: 712–722.

58. Ho TW, Connor KM, Zhang Y, *et al*. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology* 2014; 83: 958–966.

59. Voss T, Lipton RB, Dodick DW, *et al*. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. *Cephalalgia* 2016; 36: 887–898.

60. Lipton RB, Dodick DW, Ailani J, *et al*. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial. *JAMA* 2019; 322: 1887–1898.

61. Dodick DW, Lipton RB, Ailani J, *et al.* Ubrogepant for the treatment of migraine. *N Engl J Med* 2019; 381: 2230–2241.

62. Marcus R, Goadsby PJ, Dodick D, *et al*. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia* 2014; 34: 114–125.

63. Chan C and Goadsby PJ. Recent advances in pharmacotherapy for episodic migraine. *CNS Drugs* 2019; 33: 1053–1071.

64. Ho TW, Ho AP, Ge YJ, *et al*. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. *Cephalalgia* 2016; 36: 148–161.

65. Hepp Z, Dodick DW, Varon SF, *et al.* Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. *Cephalalgia* 2017; 37: 470–485.

66. Hepp Z, Dodick DW, Varon SF, *et al*. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia* 2015; 35: 478–488.

67. Zhou H and Mascelli MA. Mechanisms of monoclonal antibody-drug interactions. *Annu Rev Pharmacol Toxicol* 2011; 51: 359–372.

68. Shi L, Lehto SG, Zhu DX, *et al*. Pharmacologic characterization of AMG 334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. *J Pharmacol Exp Ther* 2016; 356: 223–231.

69. Salvatore CA, Hershey JC, Corcoran HA, *et al.* Pharmacological characterization of MK-0974 [N-[(3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl) piperidine-1-carboxamide], a potent and orally active calcitonin gene-related peptide receptor antagonist for the treatment of migraine. *J Pharmacol Exp Ther* 2008; 324: 416–421.

70. Mallee JJ, Salvatore CA, Lebourdelles B, *et al.* Receptor activity-modifying protein 1 determines the species selectivity of non-peptide CGRP receptor antagonists. *J Biol Chem* 2002; 277: 14294–14298.

71. De Hoon J, Van Hecken A, Vandermeulen C, *et al*. Phase I, Randomized, double-blind, placebo-controlled, single-dose, and multiple-dose studies of erenumab in healthy subjects and patients with migraine. *Clin Pharmacol Ther* 2018; 103: 815–825.

72. Vu T, Ma P, Chen JS, *et al*. Pharmacokinetic-pharmacodynamic relationship of erenumab (AMG 334) and capsaicin-induced dermal blood flow in healthy and migraine subjects. *Pharm Res* 2017; 34: 1784–1795.

73. Ryman JT and Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol* 2017; 6: 576–588.

74. Lobo ED, Hansen RJ and Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* 2004; 93: 2645–2668.

75. De Hoon J, Van Hecken A, Vandermeulen C, *et al*. Phase 1, randomized, parallel-group, double-blind, placebo-controlled trial to evaluate the effects of erenumab (AMG 334) and concomitant sumatriptan on blood pressure in healthy volunteers. *Cephalalgia* 2019; 39: 100–110.

76. Tabrizi M, Bornstein GG and Suria H. Biodistribution mechanisms of therapeutic monoclonal antibodies in health and disease. *AAPS J* 2010; 12: 33–43.

77. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. *Annu Rev Pharmacol Toxicol* 2015; 55: 533–552.

78. Benschop RJ, Collins EC, Darling RJ, *et al*. Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. *Osteoarthritis Cartilage* 2014; 22: 578–585.

79. Lima WG, Marques-Oliveira GH, Da Silva TM, *et al*. Role of calcitonin gene-related peptide in energy metabolism. *Endocrine* 2017; 58: 3–13.

80. Butt JH, Rostrup E, Hansen AS, *et al*. Induction of migraine-like headache, but not aura, by cilostazol in patients with migraine with aura. *Brain* 2018; 141: 2943–2951.

81. Guo S, Olesen J and Ashina M. Phosphodiesterase 3 inhibitor cilostazol induces migraine-like attacks via cyclic AMP increase. *Brain* 2014; 137: 2951–2959.

82. Christensen SL, Petersen S, Sorensen DB, *et al*. Cilostazol induces C-fos expression in the trigeminal nucleus caudalis and behavioural changes suggestive of headache with the migraine-like feature photophobia in female rats. *Cephalalgia* 2018; 38: 452–465.

83. Marvizon JC, Perez OA, Song B, *et al*. Calcitonin receptor-like receptor and receptor activity modifying protein 1 in the rat dorsal horn: localization in glutamatergic presynaptic terminals containing opioids and adrenergic α_{2C} receptors. *Neuroscience* 2007; 148: 250–265.

84. Eftekhari S and Edvinsson L. Possible sites of action of the new calcitonin gene-related peptide receptor antagonists. *Ther Adv Neurol Disord* 2010; 3: 369–378.

85. Afroz S, Arakaki R, Iwasa T, *et al*. CGRP induces differential regulation of cytokines from satellite glial cells in trigeminal ganglia and orofacial nociception. *Int J Mol Sci* 2019; 20: 711.

86. Tepper SJ, Ashina M, Reuter U, *et al*. Long-term safety and efficacy of erenumab in patients with chronic migraine: results from a 52-week, open-label extension study. *Cephalalgia*. Epub ahead of print 26 March 2020. DOI: 10.1177/0333102420912726.

87. Lattanzi S, Brigo F, Trinka E, *et al*. Erenumab for preventive treatment of migraine: a systematic review and meta-analysis of efficacy and safety. *Drugs* 2019; 79: 417–431.

88. Xu D, Chen D, Zhu LN, *et al*. Safety and tolerability of calcitonin-gene related peptide binding monoclonal antibodies for the prevention of episodic migraine – a meta-analysis of randomized controlled trials. *Cephalalgia* 2019; 39: 1164–1179.

89. Sun H, Dodick DW, Silberstein S, *et al*. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomized, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol* 2016; 15: 382–390.

90. Dodick DW, Ashina M, Brandes JL, *et al*. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018; 38: 1026–1037.

91. Goadsby PJ, Reuter U, Hallstrom Y, *et al*. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017; 377: 2123–2132.

92. Reuter U, Goadsby PJ, Lanteri-Minet M, *et al*. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomized, double-blind, placebo-controlled, phase 3b study. *Lancet* 2018; 392: 2280–2287.

93. Tepper S, Ashina M, Reuter U, *et al*. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo–controlled phase 2 trial. *Lancet Neurol* 2017; 16: 425–434.

94. Holzmann B. Anti-inflammatory activities of CGRP modulating innate immune responses in health and disease. *Curr Protein Pept Sci* 2013; 14: 268–274.

95. Levite M. Neurotransmitters activate T-cells and elicit crucial functions via neurotransmitter receptors. *Curr Opin Pharmacol* 2008; 8: 460–471.

96. Rochlitzer S, Veres TZ, Kühne K, *et al*. The neuropeptide calcitonin gene-related peptide affects allergic airway inflammation by modulating dendritic cell function. *Clin Exp Allergy* 2011; 41: 1609–1621.

97. Li M, Wetzel-Strong SE, Hua X, *et al*. Deficiency of RAMP1 attenuates antigen-induced airway hyperresponsiveness in mice. *PLoS One* 2014; 9: e102356.

98. Straub RH, Wiest R, Strauch UG, *et al*. The role of the sympathetic nervous system in intestinal inflammation. *Gut* 2006; 55: 1640–1649.

99. Holzer P. Implications of tachykinins and calcitonin gene-related peptide in inflammatory bowel disease. *Digestion* 1998; 59: 269–283.

100. Granstein DR, Wagner AJ, Stohl LL, *et al*. Calcitonin gene-related peptide: key regulator of cutaneous immunity. *Acta Physiol (Oxf)* 2015; 3: 586–594.

101. Toda M, Suzuki T, Hosono K, *et al*. Roles of calcitonin gene-related peptide in facilitation of wound healing and angiogenesis. *Biomed Pharmacother* 2008; 62: 352–359.

102. Balkan W, Oates EL, Howard GA, *et al*. Testes exhibit elevated expression of calcitonin gene-related peptide receptor component protein. *Endocrinology* 1999; 40: 1459–1469.

103. Bivalacqua TJ, Champion HC, Abdel-Mageed AB, *et al*. Gene transfer of prepro-calcitonin gene-related peptide restores erectile function in the aged rat. *Biol Reprod* 2001; 65: 1371–1377.

104. Dong YL, Fang L, Kondapaka S, *et al*. Involvement of calcitonin gene-related peptide in the modulation of human myometrial contractility during pregnancy. *J Clin Invest* 1999; 104: 559–565.

105. Thota C, Gangula PR, Dong YL, *et al*. Changes in the expression of calcitonin receptor-like receptor, receptor activity-modifying protein (RAMP) 1, RAMP2, and RAMP3 in rat uterus during pregnancy, labor, and by steroid hormone treatments. *Biol Reprod* 2003; 69: 1432–1437.

106. McMurdo L, Lockhart JC and Ferrell WR. Modulation of synovial blood flow by the calcitonin gene-related peptide (CGRP) receptor antagonist, CGRP(8-37). *Br J Pharmacol* 1997; 121: 1075–1080.

107. Schinke T, Liese S, Priemel M, *et al*. Decreased bone formation and osteopenia in mice lacking alpha-calcitonin gene-related peptide. *J Bone Miner Res* 2004; 19: 2049–2056.

108. Smillie SJ and Brain SD. Calcitonin gene-related peptide (CGRP) and its role in hypertension. *Neuropeptides* 2011; 45: 93–104.

109. Smillie SJ, King R, Kodji X, *et al*. An ongoing role of α-calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress. *Hypertension* 2014; 63: 1056–1062.

110. Kudrow D, Pascual J, Winner PK, *et al*. Vascular safety of erenumab for migraine prevention. *Neurology*. Epub ahead of print 18 December 2019. DOI: 10.1212/WNL.0000000000008743.

111. Zhang JY, Yan GT, Liao J, *et al*. Leptin attenuates cerebral ischemia/reperfusion injury partially by CGRP expression. *Eur J Pharmacol* 2011; 671: 61–69.

112. Chai W, Mehrotra S, Jan Danser AH, *et al*. The role of calcitonin gene-related peptide (CGRP) in ischemic preconditioning in isolated rat hearts. *Eur J Pharmacol* 2006; 531: 246–253.

113. Maassenvandenbrink A, Meijer J, Villalon CM, *et al*. Wiping out CGRP: potential cardiovascular risks. *Trends Pharmacol Sci* 2016; 37: 779–788.

114. Juul R, Edvinsson L, Gisvold SE, *et al*. Calcitonin gene-related peptide-LI in subarachnoid haemorrhage in man. Signs of activation of the trigemino-cerebrovascular system? *Br J Neurosurg* 1990; 4: 171–179.

115. Juul R, Hara H, Gisvold SE, *et al*. Alterations in perivascular dilatory neuropeptides (CGRP, SP, VIP) in the external jugular vein and in the cerebrospinal fluid following subarachnoid haemorrhage in man. *Acta Neurochir (Wien)* 1995; 132: 32–41.

116. Aradi S, Kaiser E and Cucchiara B. Ischemic stroke associated with calcitonin gene-related peptide inhibitor therapy for migraine: a case report. *J Stroke Cerebrovasc Dis* 2019; 28: 104286.

117. Maassenvandenbrink A, Terwindt GM and Van Den Maagdenberg AMJM. Calcitonin gene-related peptide (receptor) antibodies: an exciting avenue for migraine treatment. *Genome Med* 2018; 10: 10.

118. Hay DL and Walker CS. CGRP and its receptors. *Headache* 2017; 57: 625–636.

119. Ashina M, Dodick D, Goadsby PJ, *et al*. Erenumab (AMG 334) in episodic migraine: interim analysis of an ongoing open-label study. *Neurology* 2017; 89: 1237–1243.

120. Moore EL and Salvatore CA. Targeting a family B GPCR/RAMP receptor complex: CGRP receptor antagonists and migraine. *Br J Pharmacol* 2012; 166: 66–78.

121. Li CC, Vermeersch S, Denney WS, *et al.* Characterizing the PK/PD relationship for inhibition of capsaicin-induced dermal vasodilatation by MK-3207, an oral calcitonin gene related peptide receptor antagonist. *Br J Clin Pharmacol* 2015; 79: 831–837.

122. Sinclair SR, Kane SA, Van Der Schueren BJ, *et al.* Inhibition of capsaicin-induced increase in dermal blood flow by the oral CGRP receptor antagonist, telcagepant (MK-0974). *Br J Clin Pharmacol* 2010; 69: 15–22.

123. Ashina M, Goadsby PJ, Reuter U, *et al.* Long-term safety and tolerability of erenumab: three-plus year results from a five-year open-label extension study in episodic migraine. *Cephalalgia* 2019; 39: 1455–1464.

124. Brandes JL, Diener HC, Dolezil D, *et al.* The spectrum of response to erenumab in patients with chronic migraine and subgroup analysis of patients achieving ⩾50%, ⩾75%, and 100% response. *Cephalalgia* 2020; 40: 28–38.

125. Tepper SJ, Diener HC, Ashina M, *et al.* Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. *Neurology* 2019; 92: e2309–e2320.

126. Goadsby PJ, Paemeleire K, Broessner G, *et al.* Efficacy and safety of erenumab in episodic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2019; 39: 817–826.

127. Reuter U, Goadsby PJ, Lanteri-Minet M, *et al.* Long-term efficacy and safety of erenumab: results from 64 weeks of the LIBERTY study. Presented at 13th European Headache Federation Congress, Athens, Greece, May 2019.

128. Ashina M, Tepper S, Brandes JL, *et al.* Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2018; 38: 1611–1621.

129. Sussman M, Benner J, Neumann P, *et al.* Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: results from the US societal and payer perspectives. *Cephalalgia* 2018; 38: 1644–1657.

130. Giannouchos TV, Mitsikostas DD, Ohsfeldt RL, *et al.* Cost-effectiveness analysis of erenumab versus onabotulinumtoxinA for patients with chronic migraine attacks in Greece. *Clin Drug Investig* 2019; 39: 979–990.

131. Barbanti P, Aurilia C, Egeo G, *et al.* Erenumab: from scientific evidence to clinical practice-the first Italian real-life data. *Neurol Sci* 2019; 40: 177–179.

132. Buse DC, Reed ML, Fanning KM, *et al.* Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. *J Headache Pain* 2020; 21: 23.

133. Sacco S, Bendtsen L, Ashina M, *et al.* European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain* 2019; 20: 6.