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Review article

Are antimigraine drugs that influence CGRP levels justified?

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ABSTRACT

Migraine is one of the most common disorders found in everyday clinical practice. Although migraines are not directly life-threatening or permanently disabling, the severity of the pain and symptoms that characterize a migraine attack often prevent normal work and cause difficulties in everyday life. Migraines also affect the patient's family, who often experience stress and depression in response to the patient's condition. Available therapy, used in both acute and chronic treatments, might not provide sufficient improvement. Due to problems like therapy inefficacy, side effects, and intolerance, patients often stop treatments. Recent studies have indicated that drugs that act through calcitonin gene-related peptide (CGRP) can significantly improve migraine therapy. Here, we review results from currently available clinical trials on CGRP receptor antagonists and anti-CGRP monoclonal antibodies.

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Migraine – a social and clinical issue

Migraine is a disorder that largely limits social functioning. It is characterized by a pulsating, repetitive headache that lasts 4–72 h, and it is associated with nausea, vomiting, photophobia, and phonophobia. Migraine headaches may also be accompanied by the so-called aura, which most frequently manifests as scotomas, flashing lights, zig-zags, visual focus disorders, or visual impairment. Worldwide, 11.6% of the population is affected by migraine. Its incidence in Europe is 11.4%. The highest migraine frequency is observed in Central and South America (16.4%), and the lowest frequency is observed in North America (9.7%). Women are about twice as likely as men to experience migraines (13.8% women and 6.9% men), and the highest susceptibility is in the third decade of life. It was shown that migraines were more widespread among inhabitants of cities and towns than among residents of rural areas (11.2% *vs.* 8.4%) [1].

Patients with migraines have a low health-related quality of life (HRQoL), and HRQoL decreases with increases in the frequency and severity of migraine attacks [2]. Compared to healthy individuals, patients with migraines are twice as likely to experience low sleep quality and short sleep durations ($\leq$ 7 h), and they are more likely to experience sleepiness during the day. These patients also have other sleep related issues; for example, they require more time to fall asleep, have low sleep efficacy, frequently experience night sweats, and take sedatives more often, compared to healthy individuals [3,4]. At the same time, some 50–60% of patients with migraines complain of concurrent anxiety or depression. Migraines

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are strongly tied to chronic stress, affective bipolar disorder, adult attention-deficit hyperactivity disorder (adult ADHD), overweight status, epilepsy, and stroke [5,6].

Among neurological disorders, migraine is one of the most burdensome. A migraine attack largely disturbs the daily functioning of the patient. The Eurolight test showed that, over a period of 3 months, some 28% of women and 17.7% of men lost >10% of daily personal activities due to migraines, including 3.2 working days, 4.6 days of work at home, and 2.1 days of social interactions. The International Burden of Migraine Study showed that as many as 23.3% of patients with migraine episodes (<15 headache days per month) and 78% of patients with chronic migraines (≥15 headache days per month) reported heavy or extremely heavy impairments due to headache, during the 3 months preceding the test. These impairments made it impossible for patients to perform housework/paid employment, household duties, and activities that were not work-related [2]. The American Migraine Prevalence and Prevention (AMPP) study examined over 18,000 patients with migraines, and found that migraine frequently caused limitations in functioning. The majority of patients reported that some limitation of function usually occurred, and over half of the patients reported significant impairments or a need to stay in bed [7,8].

When patients are incapacitated with migraines, their ability to perform daily activities is largely disturbed, which contributes to significant economic and social burdens. The annual cost of migraine therapy in Europe is 18–27 trillion Euro, and 77 to 93% of the total cost comprises secondary costs, of which 2/3 is due to reduced work efficiency [9–11]. Migraine is a factor that contributes to disability in both the countries with low, and with high income levels. Steiner et al. [12] believe that further research should be carried out to assess the significance of headaches for the global public health, which could also monitor the benefits stemming from improved headache care, new treatments and social changes.

During migraine attacks, patients typically resort to emergency medications, most often non-steroid anti-inflammatory drugs or triptans. People whose daily activities are affected due to the frequency or acuteness of migraine have the option of prophylactic treatment, including – among others – propranolol, metoprolol, topiramate, valproate, flunarizine, amitriptyline, frovatriptan (for short-term preventive treatment of menstrual migraine) or botulinum toxin. Unfortunately, some 2/3 of patients that qualify for prophylactic migraine treatment do not receive it. Even when patients decide to start prophylactic treatment, some 80% stop it, due to drug intolerance, adverse effects, and limited therapeutic efficacy [7,13].

These factors justify the search for new therapeutic strategies with improved efficiency, both in treating migraine attacks and in prophylaxis.

The role of calcitonin gene related peptide (CGRP) in the pathophysiology of migraine

In recent years, discussions on the pathophysiology of migraine are frequently directed to the role of the trigeminovascular system. During a migraine attack, nociceptors located in the dilated vessels of the meninges are stimulated, and this signal is transmitted by the trigeminal nerve to the trigeminal ganglion, then to the brainstem and sensory cortex [14,15]. The trigeminal nerve terminals release different neuropeptides, including calcitonin, CGRP, neurokinin A, and neuropeptide Y, which may lead to neurogenic inflammation. CGRP is one of the crucial agents in the pathophysiology of migraine. CGRP is expressed in 35 to 50% of neurons in the trigeminal nerve ganglion [16,17]. The CGRP neuropeptide consists of 37 amino acids, an N-terminal disulfide bond, and an amidated C terminus. The two latter moieties are required to activate the receptor. In humans, CGRP is found in alpha and beta isoforms. The alpha isoform is found mainly in the axons of the trigeminal nerve, and the beta isoform is found in the nervous systems of the intestines and the pituitary gland [18]. The CGRP receptor is found both in central and in peripheral nervous systems. This G protein coupled receptor operates in a complex of three elements: the calcitonin-like receptor, a receptor activity-modifying protein 1 (RAMP1), and a receptor component protein [19]. CGRP is released from trigeminal cells of the meningeal tissue and in the first synapse in the spinal trigeminal nucleus. In peripheral tissues, the CGRP receptors can be found on the walls of the arteries, mononuclear immune cells and also likely in the Schwann cells. On the other hand, within the trigeminal ganglion, they are found on neurons and glial cells, and in the median ends of afferent trigeminal cells of the spinal trigeminal nucleus. It is believed that CGRPs, as relatively large molecules, do not pass through the blood-brain barrier easily. In the trigeminal ganglion, these molecules are likely to affect the production of substances that are transported along central ends to the spinal trigeminal nucleus [20].

Studies have shown that, during both a spontaneous and a nitric oxide-triggered migraine attacks, CGRP concentrations are elevated in the serum and saliva of patients [21,22]. The administration of triptans, commonly used to treat migraines, lowers the CGRP concentrations in serum [23,24]. CGRP plays crucial roles in several pathological mechanisms of migraine and pain. Among other actions, it causes vessel dilatation, neurogenic inflammation, mast cell degranulation, sensory signalling pathway activation, and peripheral sensitization [25]. Ohlsson et al. [26] have demonstrated that fremanezumab, a monoclonal antibody directed against calcitonin-related polypeptides, effectively and selectively blocks vasomotor responses to CGRP in human intracranial and peripheral arteries. CGRP receptor antagonists and anti-CGRP monoclonal antibodies were shown to be efficient in the treatment of migraine symptoms.

Table 1
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of olcegepant ((BIBN 4096 BS).

Author date of publication	Study	Dosage	Patients	Results
[28] Olesen et al. 2004	International, multicenter, double-blind, randomized clinical trial	Olcegepant *iv* – 0.25, 0.5, 1, 2.5, 5, or 10 mg; placebo	126 patients with an acute migraine attack	Pain aborted in case of 60% treated patients. Highest efficacy was observed for 5 mg dose 75%, lower for the remaining doses: 0.5 mg – over 20%, 1 mg – over 40%, 2.5 mg – 66%, 10 mg – over 60% and after placebo – 27%. The examined patients also demonstrated reduction in symptoms accompanying migraine: nausea, phono- and photophobia, and improvement of general functioning. The recurrence frequency amounted 20% for patients receiving olcegepant and 46% for patients receiving placebo. Side effects: olcegepant – 20% patients, placebo – 12% patients; most frequent – paraesthesias.

Table 2
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of telcagepant (MK-0974).

Author date of publication	Study	Dosage	Patients	Results
Ho et al. 2008a [29]	Randomized, double-blind, parallel-group, clinical trial with a two-stage	Telcagepant *po*: 25, 50, 100, 200, 300, 400, or 600 mg; rizatriptan *po* 10 mg; placebo	333 treated patients with moderate or severe migraine attack	Due to no effect of the 25-200 mg doses their administration was not continued. The pain relief at 2 hours: telcagepant at doses -300 mg, 400 mg, and 600 mg and rizatriptan demonstrated significance *vs.* placebo. The estimated pain relief values at 2 h were: 300 mg – 68.1%, 400 mg -48.2%, 600 mg – 67.5%, rizatriptan – 69.5%, and placebo – 46.3%. Telcagepant was generally well tolerated, side effects – nausea, dizziness, and somnolence.
Ho et al. 2008b [30]	Randomised, parallel-treatment, placebo-controlled, double-blind	Telcagepant *po* – 150 mg (n = 333) or 300 mg (n = 354); zolmitriptan 5 mg (n = 345), or placebo (n = 348).	1300 patients with moderate or severe migraine attack	Telcegepant (150 and 300 mg) and rizatriptan were more effective than placebo in pain relief, pain abortion and absences of phono-, photohobia and nausea at 2 h after treatment. Efficacy of telcagepant 300 mg and zolmitriptan 5 mg were much the same, and both were more effective than telcagepant 150 mg. Adverse effects occured with the following frequencies: telcagepant 150 mg – 31%, telcagepant 300 mg – 37%, zolmitriptan – 51%, and placebo – 32%. The most frequent ones included nausea, dizziness, dry mouth, somnolence, dizziness, nausea, fatigue.
Connor et al. 2009 [31]	Randomized, double-blind, placebo controlled, parallel-group–phase 3	Telcagepant *po* – 50 mg (n = 177), 150 (n = 381) or 300 mg (n = 371) or placebo (n = 365)	1294 patients with moderate or severe migraine attack	Groups of patients who received larger doses of telcagepant differed, statistically significantly, from the control group, in all parameters evaluated, i.e. pain freedom, pain relief, absence of photophobia, absence of phonophobia, and absence of nausea, all at 2 hours postdose and 2–24 hour sustained pain freedom (300 mg, $p \leq 0.001$; 150 mg, $p \leq 0.05$). Adverse effects of telcagepant included: fatigue, dizziness, nausea, upper abdominal pain, somnolence, and vomiting.
Connor et al. 2011 [32]	Randomized, double-blind, active-controlled, parallel-group, 18-month trial	Telcagepant *po* – 280 mg/300 mg (n = 712), or rizatriptan (n = 356)	1068 patients with acute mild, moderate, or severe migraine. A second dose within 2-24 hours for nonresponse or migraine recurrence.	Clinical examination evaluated telcagepant and rizatriptan tolerance during a 18-month treatment period. In case of lack of improvement or recurrence of migraine the patients were allowed to take another does within next 2-24 hours. It was proven, that the group treated with telcagepant experienced fewer triptan-related adverse events (difference:-6.2%; 95% CI -10.4,-2.6; $p<0.001$) and drug-related adverse events (difference: -15.6%; 95% CI -22.2, -9.0), than the group the one treated with rizatriptan.
Ho et al. 2014 [33]	Randomized, double-blind, placebo-controlled, multicenter trial	Telcagepant: 140 mg (n = 265), 280 mg (n = 264); placebo (n = 131)	660 patients experiencing 3–14 migraine days during a 4-week period	Mean monthly headache days decreased in all tested groups, respectively: telcegapant 140 mg by 2.9 days, telcegapant 280 mg by 3.1 days, and by 1.7 days for placebo; $p<0.05$. The plan was to administer the drug in 140 mg and 280 mg doses twice a day for 12 weeks, but due to its hepatotoxicity the test was halted. The average treatment duration was 48 to 50 days. At least triple increase in alanine aminotransferase (ALT) and aspargine aminotransferase (AST) levels, above the upper reference limit was recorded in 13 and 7 patients, respectively, who received telcagepent treatment. None of the patients of the control group demonstrated increased levels of hepatic enzymes.
Ho et al. 2016 [34]	Randomized, double-blind, placebo-controlled, parallel-group study	Telcagepant 140 mg (n = 3018); placebo (n = 1502)	4520 women with migraine for 3 months who experienced perimenstrual headaches	Telcagepant (140 mg) was administered for 7 consecutive days to women in perimenstrual period. Telcagepant did not reduce monthly headache ($\geq$5 moderate or severe migraine headaches per month) and reduced on-drug headache days. Due to adverse effects of the treatment 2.5% patients receiving telcagepant, and 2.7% of those who received placebo, was halted. Increased ALT activity over 3 times the upper limit of normal was observed in 0.6% of

Table 2 (*Continued*)

Author date of publication	Study	Dosage	Patients	Results
				women who received telcagepant, and 0.4% from the control group.
Hewitt et al. 2011a [35]	Randomized, double-blind, placebo-controlled study	Telcagepant 280 mg + ibuprofen 400 mg (n = 171), telcagepant 280 mg + acetaminophen 1000 mg (n = 171), telcagepant 280 mg (n = 170), or placebo (n = 171).	683 patients with moderate or severe migraine headache	Every group that received active treatment demonstrated higher efficacy than the control group with 2-hour pain freedom ($p<0.001$): telcagepant + ibuprofen - 35.2%, telcagepant + acetaminophen-38.3%, telcagepant-31.2%, placebo-10.9%. Faster pain freedom was observed in the group treated with combination therapy, when compared to the group treated with telcagepant monotherapy (1 h *vs.* 1.5 h).

Table 3
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of MK-3207.

Author date of publication	Study	Dosage	Patients	Results
Hewitt et al. 2011b [36]	Multicenter, randomized, double-blind, placebo controlled, parallel-group study	MK-3207: 2.5 mg (n = 33), 5 mg (n = 47), 10 mg (n = 67), 20 mg (n = 67), 50 mg (n = 68), 100 mg (n = 62), 200 mg (n = 63), or placebo (n = 140)	547 patients with moderate/severe migraine headache	During the first chase of the test the patient received MK-3207 in doses of: 2.5, 5, 10, 20, 50, 100 mg, during the subsequent phase the 200 mg dose was added. The statistically significant differences were recorded for the following parameters (*vs.* placebo): pain freedom at 2 h – 200 mg ($p<0.001$), 10 mg or 100 mg ($p<0.05$); the pain relief at 2 h – 10 mg, 20 mg ($p<0.01$), 100 mg ($p<0.05$), 50 mg, 200 mg ($p<0.001$); no photophobia, phonophobia and nausea at 2 hour, 2–24 hour sustained pain freedom – 200 mg *vs.* placebo. Only the highest dose of MK-3207 proved higher efficacy in comparison with placebo in all the investigated parameters: pain freedom and pain relief at 2 hour, no photophobia, phonophobia and nausea at 2 hour, 2–24 and 2-48 hour sustained pain freedom. The most frequent adverse effects included: nausea, dizziness, fatigue, dry mouth and sleepiness, one of the patients treated with MK-3207 demonstrated over a triple increase in hepatic enzymes levels.

Table 4
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of rimegepant (BMS-927711).

Author date of publication	Study	Dosage	Patients	Results
Marcus et al. 2014 [37]	Randomized, double-blind, placebo controlled, dose-ranging study	BMS-927711: 10 mg (n = 85), 25 mg (n = 68), 75 mg (n = 91), 150 mg (n = 90), 300 mg (n = 121), 600 mg (n = 92), sumatriptan 100 mg (n = 109), or placebo (n = 229)	885 patients with moderate to severe migraine headache	It was proven that both sumatriptan, and the 3 tested doses of BMS-927711 (75 mg, 150 mg, 300 mg) were more effective than placebo in the primary endpoint -pain freedom at two hours post-dose. Significantly more patients had pain freedom at two hours post-dose *vs.* placebo (BMS-927711: 75 mg – 31.4%, 150 mg – 32.9%, 300 mg – 29.7%; the sumatriptan – 35%, and placebo – 15.3%). Improvement of clinical condition in secondary endpoints, such as: 2-24 hour the sustained pain relief and 2-24 hour the sustained pain freedom was observed after administration of BMS-927711 in doses of 75-600 mg and in case of sumatriptan. The most frequent adverse effect of BMS-927711 was nausea, with its frequency of occurrence increasing with the growing dose of medication.

CGRP receptor antagonists (called gepants)

CGRP receptor antagonists are mainly used in emergency treatments of migraine. However, in the literature, some studies have described the use of these drugs in migraine prophylaxis.

The first CGRP receptor antagonist to enter the clinical trial stage was olcegepant (BIBN 4096 BS). It is a strong, non-peptide CGRP receptor antagonist that binds specifically to the RAMP1 external receptor region and competes for binding with endogenous CGRP [27]. It was administered intravenously to patients with acute migraine attacks. However, although its clinical efficacy was

Table 5
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of BI 44370 TA.

Author date of publication	Study	Dosage	Patients	Results
Diener et al. 2011 [38]	Randomised, double-blind, double-dummy, placebo- and active-controlled, parallel-group	BI 44370 TA: 50 mg (n = 64), 200 mg (n = 65), 400 mg (n = 73), eletriptan 40 mg (n = 69), placebo (n = 70)	341 patients with acute migraine attacks	Both eletriptan and BI 44370TA proved higher efficacy than placebo in pain freedom after 2 h (BI 44370 TA 400 mg- 27.4%, eletriptan- 34.8%, placebo- 8.6% ($p = 0.0016$), and in relieving symptoms such as: photophobia, phonophobia, and vomiting. After administration of 200 mg lowered pain was observed in 2 hours, 2-24 hours and 2-48 hours after dose and no significant influence on other migraine symptoms. Frequency of adverse effects was low, and the most frequent ones included diarrhoea and fatigue. One of the patients treated with the highest dose of the tested drug demonstrated largely increased activity of hepatic enzymes.

Table 6
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of ubrogepant.

Author date of publication	Study	Dosage	Patients	Results
Voss et al. 2016 [39]	Multicenter, randomized, double-blind, placebo-controlled trial	Ubrogepant: 1 mg (n = 138), 10 mg (n = 139), 25 mg (n = 139), 50 mg (n = 139), 100 mg (n = 140), placebo (n = 139)	834 patients with moderate or severe migraine attacks	At 2 hours after administration, the 100 mg dose demonstrated the higher pain freedom efficacy, which was statistically significant in comparison to placebo (25.5% *vs.* 8.9%, $p = 0.003$). Other doses also proved higher efficacy than placebo: 25 mg (21.4% *vs.* 8.9%, $p = 0.013$) and 50 mg (21.0% *vs.* 8.9%, $p = 0.020$). Ubrogepant in the 100 mg dose also relieved other symptoms (phonophobia, photophobia and persistent pain up to 48 h) and demonstrated no influence on the nausea accompanying migraine. The 25 mg and 50 mg doses also influenced the symptoms of migraine, yet to a lesser extent than the highest dose. The most frequent adverse effects included: dry mouth, nausea, fatigue, dizziness, and somnolence. One patient demonstrated increased AST activity (>3ULN, in the 50 mg group).

validated, further research was halted, due to the inconvenient path of administration.

Other types of CGRP antagonists are available in oral formulations. These include: telcagepant (MK0974), MK-3207, rimegepant (BMS-927711), BI 44370 TA, and ubrogepant.

It was shown that CGRP receptor antagonists were more efficient than placebo in treating acute migraine attacks, and they demonstrated efficacy similar to that of various triptans (i.e. rizatriptan, eletriptan, zolmitriptan, and sumatriptan). The greatest benefit of CGRP antagonists was the relief or reduction of headache within 2 h from administration. Depending on the dose used, other symptoms were improved, including the 24-h relief or reduction of headache and the alleviation of phono- and photophobia. Generally, once the appropriate dose was determined, good drug tolerance was observed. The most frequent adverse effects involved the gastrointestinal system, followed by dry mouth, dizziness, somnolence, and fatigue. Nevertheless, in single cases, patients treated with some CGRP receptor antagonists (e.g., MK-3207, rimegepant, ubrogepant) exhibited elevated levels of hepatic enzymes (Tables 1–6). The influence of CGRP receptor antagonists on the activity of hepatic enzymes was confirmed, when telcagepant was administered for long periods of time as a migraine prophylaxis. In studies by Ho et al. [33,34], despite the observed treatment efficacy in mitigating migraine headaches, during long-term therapy trials, the tests were halted, due to hepatotoxicity (Tables 1–6).

Despite their potential adverse effects on liver enzymes, two of the CGRP receptor antagonists, i.e. ubrogepant and rimegepant, were further investigated in cases of episodic migraine, forming part of clinical trials (clinicaltrials.gov/show/NCT02867709, clinicaltrials.gov/show/NCT02828020, clinicaltrials.gov/show/NCT02873221, clinicaltrials.gov/show/NCT03266588, clinicaltrials.gov/show/NCT03235479, clinicaltrials.gov/show/ NCT03237845) [40–45].

Preliminary results demonstrated that both ubrogepant and rimegepant were effective in alleviating or relieving headaches during acute migraine attacks, as well as in reducing the annoying symptoms associated with migraine, i.e. photophobia, phonophobia, and nausea. Even with the initial concerns of their hepatotoxicity, they have proven to be well tolerated drugs with good safety profile. Based on these positive results, the manufacturer of ubrogepant plans to submit a new drug application to the US Food and Drug Administration in the first part of 2019. What is also of particular interest of the research on the new, rapid action form of rimegepant, which has sublingual route of administration and does not require administration of fluids. This form of therapy would overcome fears of nausea and vomiting during oral administration [46]. The search for new, effective migraine drugs, with a good safety profile is well justified.

Monoclonal antibodies

Monoclonal antibodies against CGRP are the only drugs that are not used in other diseases; these antibodies are reserved solely for the prevention of migraine. They are characterized by their long effective period (20–45 days), which enables less frequent drug administration. Compared to gepants, they exhibit much lower risks of hepatotoxic activity and drug interactions, because they are not substrates for cytochrome P450 enzymes. Instead, they are

Table 7
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of anti-CGRP monoclonal antibodies - erenumab.

Author date of publication	Study	Dosage	Patients	Results
Sun et al. 2016 [49]	Multicentre, randomised, double-blind, placebo-controlled study	AMG334 *sc*: 7 mg (n = 108), 21 (n = 108), 70 mg (n = 107); placebo (n = 160)	483 patients with 4 to 14 migraine days per month; 12 weeks	After 12 weeks of treatment a statistically significant lowering of the mean change in monthly migraine days between the group receiving the highest dose and that receiving placebo was demonstrated (3.4 ± 0.4 *vs.* 2.3 ± 0.3). The group receiving dose 70 mg demonstrated lowering of the number of days using acute medication (2.5 ± 0.3 *vs.* 1.2 ± 0.3) and migraine specific medication (1.6 ± 0.3 *vs.* 0.7 ± 0.2). The most frequent adverse effects included nasopharyngitis, fatigue, and headache. 3% of patients were found to produce neutralising antibodies.
Tepper et al. 2017 [50]	Multicentre, randomised, double-blind, placebo-controlled, study	Erenumab every 4 weeks, *sc*: 70 mg (n = 191), 140 mg (n = 190); placebo (n = 286)	667 patients with chronic migraine; 12 weeks	Both doses of medication decreased monthly migraine days versus placebo (for both doses of erenumab: 6.6 days and 4.2 days for placebo). During the last 4 weeks of the trial at least 50% reduction of monthly migraine headache from baseline was observed in significantly larger group of patients who received erenumab, in comparison with placebo [erenumab: 70 mg – 75 (40%) patients, 140 mg -77 (41%) patients, placebo – 66 (23%) patients]. The most frequent adverse events were injection-site pain, upper respiratory tract infection, and nausea. There were 14 incidences of binding antibodies in the erenumab groups, but no anti-erenumab neutralising antibodies were found.
Ashina et al. 2017 [51]	12-week, double-blind, placebo-controlled clinical trial, open-label extension (OLE) study up to 5 years	Erenumab (7, 21, 70 mg *sc* every 4 weeks) for 12 weeks (parent study), in OLE study erenumab (70 mg, *sc* every 4 weeks); placebo	472 patients with episodic migraine in the parent study and 383 in the OLE	After 64 weeks of treatment a decrease in headaches was observed in trial groups (8.8 ± 2.6 in the parent study, 6.3 ± 4.2 at week 12, and 3.7 ± 4.0 at week 64). After 64 weeks of treatment a significant reduction in monthly migraine days was observed [50% reduction -184 (65%) patients, 75% reduction 119 (42%) patients and 100% reduction – 73 (26%) patients]. After 64 weeks of treatment a significant a mean reduction of 2.4 monthly migraine-specific medication days was observed. HIT-6 (Headache Impact Test) score for determination of headache intensity and change of clinical condition of the patient decreased from 60.2 ± 6.3 at baseline to 51.7 ± 9.2 at week 64 After 64 weeks of treatment better scores at the MSQ (Migraine-Specific Quality of Life). MIDAS (Migraine Disability Assessment) were recorded, total score was reduced, which proves the lowering of the number of days lost at work, at home and in social life. The safety of erenumab was comparable to placebo.
de Hoon et al. 2018 [52]	Randomized, double-blind, placebo-controlled, single-dose, and multiple-dose studies	Erenumab in single dose: 1, 7, 21, 70, 140, 210 mg *sc*, 240 mg *iv* (healthy subject), 140 mg *sc* (patients with migraine). Erenumab in multiple doses: 21, 70, 140, or 280 mg (first dose), 210 mg (second dose)/, 210 mg (third dose) mg *sc* (healthy subject), 21, 140 mg *sc* (patients with migraine)	80 healthy volunteers 28 migraine patients	Erenumab in the doses of 1-70 mg demonstrates a non-linear pharmacokinetics, and in the 70-210 doses a linear type of pharmacokinetics. There were no statistically significant differences in the pharmacokinetic parameters between the healthy volunteers and migraine patients, apart from T_{max} (erenumab 140 mg *sc*: 11.0 days in migraine patients *vs.* 5.5 days in healthy volunteers). In case of patients receiving repeated doses of drug there were no correlations observed between the blood concentration of erenumab and the systolic and diastolic blood pressure of healthy volunteers and migraine patients. Erenumab was well tolerated. Most frequent adverse effects after administration of a single dose included: headaches, nasopharyngitis, arthralgia, and influenza-like illness. After multiple doses the most frequent adverse effects included: nasopharyngitis, leukocyturia, hematuria and oropharyngeal pain.

Table 7 (*Continued*)

Author date of publication	Study	Dosage	Patients	Results
Goadsby et al. 2017 [53]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Erenumab: 70 mg (n = 317), 140 mg (n = 319); placebo (n = 319) – monthly for 6 months.	955 patients with episodic migraine	After 3 months of treatment a reduction in mean migraine days per month (70 mg – 3.2 days, 140 mg – 3.7 days, placebo–1.8 days; $p<0.001$ for each dose *vs.* placebo) was observed. After 4-6 months at least 50% reduction in mean migraine days per month was observed in 43.3% of patients in the 70 mg group, 50.0% of patients in the 140 mg group, and 26.6% in the placebo group. After 3 months of treatment the mean number of days of use of acute migraine–specific medication per month decreased in statistically significant manner (70 mg – 1.1days, 140 mg – 1.6 days, placebo–0.2 days). The group on erenumab demonstrated improvement of physical-impairment scores (70 mg – 4.2 points, 140 mg – 4.8 points, 2.4 points–placebo), and everyday-activities scores (70 mg-5.5 points, 140 mg-5.9 points, 3.3 points-placebo). There was a similar number of adverse effects in both the trial and the control group.
Giamberardino et al. 2017 [54]	Randomized, double-blind, placebo-controlled, multicenter study	Erenumab: 7 mg (n = 108); 21 mg (n = 108), 70 mg (n = 107), placebo (n = 160) – *sc* once a month for 12 weeks	483 patients with episodes of migraine	The main change in monthly migraine days between erenumab (70 mg) and placebo (3.4 ± 0.4 *vs*. 2.3 ± 0.3 days) from baseline was observed to the last 4 weeks of the 12-week. Lower doses had no statistically significant effects. The most common reported AEs were headache, nasopharyngitis, and fatigue.
	Multicenter, randomized double-blind, placebo-controlled study	Erenumab: 70 mg (n = 317), 140 mg (n = 319), placebo (n = 319) –*sc* once a month for 24 weeks.	955 patients with episodes of migraine	During the last 3 months of treatment a reduction of monthly migraine days (erenumab: 70 mg – 3.2 days, 140 mg – 3.7 days, placebo-1.8 days) and migraine-specific medication days for the acute attack (erenumab: 70 mg – 1.1 days, 140 mg – 1.6 days, placebo-0.2 days) was recorded. It was proven, that administration of the drug influenced the improvement of functioning of the patients, as measrured in the MPFiD-eA, and MPFiD-Pi scales.
Dodick et al. 2018 [55]	Multicenter, randomized, double-blind, placebo-controlled study (ARISE)	Erenumab 70 mg (n = 286), placebo (n = 291) – *sc* once a month for 12 weeks	577 patients with episodes of migraine	A statistically significant difference from baseline to weeks 9–12 of treatment was demonstrated between the trial groups in monthly migraine days (2.9 *vs* 1.8 days; ($p < 0.001$) and the number of monthly days of use of migraine-specific medication (1.2 *vs.* 0.6). The administration of the drug also improved the daily functioning of the patients. The most frequent adverse effects included: upper respiratory tract infection, injection site pain, and nasopharyngitis.
Lipton et al. 2018 [56]	Markov health state transition model	Erenumab 140 mg, *sc* every 28 days ; supportive care	Migraine patients	Erenumab in connection with supportive care brought about a reduction in migraine day frequency, which was connected with an increase in the total discounted QALYs per person of 0.18 over the 10-year perspective. Erenumab decreased the secondary and primary costs of migraine treatment.
de Hoon et al. 2018 [57]	One-way crossover, double-blind, placebo-controlled, randomized study	Group A (n = 12): placebo *iv* + sumatriptan *iv* (12 mg – 2 days wash-out period; Group B (n = 22): Erenumab 140 mg *iv* + Sumatriptan 12 mg *iv*–2 days wash-out period	Healthy volunteers	Combined administration of sumatriptan and erenumab did not influence arterial blood pressure and the pharmacokinetic parameters of sumatripan.
Ashina et al. 2018 [58]	Randomized, double-blind, placebo-controlled study	Erenumab *sc* monthly: 70 mg (n = 138), 140 mg (n = 136); placebo (n = 218)	667 adult patients with chronic migraine (73.8% received prior prophylactic treatment)	After 3 months of therapy both doses of erenumab casued a reduction in monthly migraine days (erenumab 70 mg *vs.* placebo, 2.7 [4.2,1.2], $p<0.001$; erenumab 140 mg *vs.* placebo, 4.3 [5.8, 2.8], $p<0.001$]. Reduction of monthly migraine days was observed both in the group of patients who did not receive prior prophylactic treatment, and in the sub-groups who received prior, standardized prophylactic treatment, but with no effect. Erenumab therapy also caused a reduction in monthly acute migraine-specific medication days. Higher efficacy was observed in case of those patients treated with erenumab, who noted no

Table 7 (*Continued*)

Author date of publication	Study	Dosage	Patients	Results
				improvement after prior prophylactic therapy, as compared to those, who earlier did not receive prophylactic treatment.

Table 8
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of anti-CGRP monoclonal antibodies – eptinezumab.

Author date of publication	Study	Dosage	Patients	Results
Dodick et al. 2014a [59]	Randomised, double-blind, placebo-controlled trial	ALD403 1000 mg (n = 81) or placebo (n = 82); *iv* single dose	163 patients with episodes of migraine	After 5-8 weeks of treatment there was a reduction in the mean change in migraine days (5.6 ± 3·0 days for the ALD403 group *vs.* 4.6 ± 3.6 for the placebo, $p = 0.03$). The most frequent adverse events were upper respiratory tract infection, urinary tract infection, fatigue, back pain, arthralgia, nausea and vomiting.
Dodick et al. 2017 [60]	Double-blind, randomized, placebo-controlled, parallel group	ALD403: 10 mg (n = 123), 30 mg (n = 117), 100 mg (n = 118), 300 mg (n = 114) or placebo (n = 116); *iv* single dose	616 patients with chronic migraine	75% reduction in migraine days from baseline to week 12 was observed in all patients participating in the trial (eptinezumab: 300 mg-33%, 100 mg - 31%, placebo -21% patients). Eptinezumab also reduced acute headaches (21% for 300 mg, 16% for 100 mg, 18% for 30 mg, 16% for 10 mg, and 10% for placebo). The most common adverse effects included: upper respiratory tract infections, dizziness, and nausea.

eliminated by proteolytic degradation to amino-acids by reticulo-endothelial cells in the skin, muscle, liver, and gut. Due to the large size of the IgG molecule, its poor ability to penetrate cell walls, and its instability in the gastrointestinal tract, monoclonal antibodies are administered parenterally. However, they cannot pass through a healthy blood-brain barrier. Interestingly, intravenously injected IgG shows poor tissue distribution; only about 10–15% of its serum concentration is found in skin, lungs, kidneys, liver, spleen, and heart; only 0.35% is found in the brain parenchyma; and less than 0.1% is found in the cerebrospinal fluid. These findings suggest that CGRP receptor antibodies are active outside the blood-brain barrier; for example, in the meninges, circumventricular regions, neural ganglia, and trigeminal vasculature [47,48].

Four types of monoclonal antibodies have been tested to date. Of these, only erenumab is a human antibody; the other three, eptinezumab, galcanezumab, fremanezumab, are humanized antibodies. Erenumab is also the only antibody directed against the CGRP receptor; the other three are directed against the CGRP ligand. Eptinezumab is administered intravenously, and the other antibodies are injected subcutaneously.

Patients that receive antibodies may produce neutralizing antibodies, which raises the risk of reduced therapy efficacy. Antibodies have relatively long biological half-lives; thus, there are long periods between dose administrations. This long duration of the drug in tissues might increase the risk of adverse effects.

To date, clinical trials have indicated that, when monoclonal antibodies directed against CGRP receptors were used preventively, they reduced the number of days with migraine headache and the number of migraine attacks. The evidence has suggested that treatment with these drugs can improve the quality of life (Tables 7–10). For example, a meta-analysis by Hou et al. [75] that included 1001 patients with migraines showed that anti-CGRP antibodies lowered the number of migraine headache days (1st-4th week by 0.49 days, 5th-8th week by 0.43 days, and 9th-12th week by 0.37 days). There were no significant differences in the total number of adverse effects or the main adverse effects; i.e., nasopharyngitis, nausea, injection-site pain, and back pain. Compared to placebo, the only significant adverse effect associated with monoclonal antibodies was an increase in vertigo.

Another update meta-analysis carried out in 3166 patients showed that CGRP mAb led to improvement in 50% of responder rate (37.4% in CGRP mAb group *vs.* 19.1% in placebo group, $I^2 = 0\%$, $p < 0.00001$), 75% responder rate (12.7% in CGRP mAb group *vs.* 6.1% in placebo group, $I^2 = 0\%$, $p = 0.001$), migraine-days from baseline to weeks 9–12 ($I^2 = 0\%$, $p < 0.00001$), days using acute drugs from baseline to week 9–12 ($I^2 = 0\%$, $p < 0.00001$) and headache-hours after CGRP mAb administrated ($I^2 = 0\%$, $p < 0.00001$) [76].

Recent studies have investigated the relationship between individual efficacy of anti-CGRP treatment and susceptibility to migraine induced by CGRP administration. It has been demonstrated that migraine patients who responded to erenumab therapy were highly susceptible to induction of migraine with use of CGRP. The thus authors suggest that the CGRP-associated migraine model could form a marker for assessment of the efficacy of anti-CGRP monoclonal antibody treatment and would give clinicians the ability to appropriately select the pharmacotherapy for migraine patients [77]. Nevertheless, Lee et al. [78] believe that the concentration of CGRP in serum cannot form a feasible biomarker in patients with chronic migraine. The CGRP concentration does not correlate with the severity of the disease and does not differ in patients with aura and without aura. Further research should be carried out to validate CGRP, before possibly entering its concentration assay in clinical practice.

In 2018, both the FDA and the EMA approved the use of erenumab in adults for the prophylaxis of episodic and chronic migraines. In September 2018, the FDA also approved fremenezumab and galcenezumab for use in migraine prophylaxis. Currently, ongoing clinical trials aim to confirm the efficacy and safety of the other monoclonal antibody treatments, for both adult and juvenile patients.

It is considered that prophylactic treatment should be given to people with severe and frequent migraine attacks, impaired functioning and non-responsive or poorly tolerated emergency medications. It is recommended that the benefits of using anti-CGRP mAbs should be evaluated after 3 months when using the

Table 9
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of anti-CGRP monoclonal antibodies - galcanezumab (LY2951742).

Author date of publication	Study	Dosage	Patients	Results
Dodick et al. 2014b [61]	Randomised, double-blind, placebo-controlled study	LY2951742 (150 mg, n = 108) or placebo (n = 110) – *sc* once every 2 weeks for 12 weeks	218 patients with episodes of migraine	After 12 weeks of therapy the group receiving treatment demonstrated a statistically significant reduction of the number of migraine headache days *vs*. placebo (4.2 ± 3.1 *vs.* 3.0 ± 3.0; $p = 0{\cdot}003$). Galcanezumab caused a significant reduction in headache days (4.9 ± 4.1 *vs.* 3.7 ± 4.2, $p = 0.012$), and migraine attacks (3.1 ± 2.4 *vs*.2.3 ± 2.5, $p = 0.0051$). Patients receiving galcanezumab had better quality of life, as evaluated with use of the MSQL questionnaire and HIT-6. The most common adverse effects of drug administration included: injection site pain, erythema, upper respiratory tract infections, and abdominal pain.
Monteith et al. 2017 [62]	Double-blind, randomized, placebo-controlled study	Galcanezumab *sc* single dose-1, 5, 25, 75, 200, and 600 mg (n = 7/ dose) or placebo (n = 2/dose), multiple (4) doses every 2 weeks–150 mg (n = 7) or placebo (n = 2).	Healthy male volunteers	After administration of a single dose of medication T_{max} varied from 7 to 14 days, and $T_{1/2}$ was -25-30 days. After multiple doses the T_{max} was 3 days and $T_{1/2}$ - 31.9 days. Galcanezumab permanently and dose-dependent inhabited the capsaicin-dependant dermal blood flow. The drug was well tolerated and there were no statistically significant differences in frequency of adverse effects between the groups participating in the trial.
Skljarevski et al. 2018a [63]	Double-blind, randomized, placebo-controlled study	Galcanezumab : 5 mg (n = 68), 50 mg (n = 68), 120 mg (n = 70), or 300 mg (n = 67) or placebo (n = 137) – *sc* once monthly for 3 months	410 patients with episodes of migraine	The overall change from baseline to month 3 was the statistically significant reduction in the number of migraine headache days versus placebo (120 mg – 4.3 *vs.* 3.4; 300 mg – 4.3 *vs.* 3.4). Galcanezumab, 120 mg, was also superior to placebo at month 3 for all secondary outcomes (migraine plus probable MHDs – 5.9 *vs.* 4.0, migraine attacks -3.5 *vs* 2.7, 50% response rate–47/62, 75.8%, and 100% response rate–78/126, 61.9%), except probable MHD (0.9 *vs*. 0.5). The most frequent adverse effects of galcanezumab included: injection-site pain, upper respiratory tract infection, nasopharyngitis, dysmenorrhea, and nausea.
Oakes et al. 2018 [64]	Multicenter, double-blind, randomized study	Galcanezumab: 5 mg (n = 68), 50 mg (n = 68), 120 mg (n = 70) or 300 mg (n = 67) or placebo (n = 137) – *sc* once every 4 weeks for 12 weeks	410 patients with episodic migrene	The most frequent adverse effects of galcanezumab administration included: injection-site reaction, upper respiratory tract infection, nasopharyngitis. In the group treated with galcanezumab 4.6% of patients demonstrated production of antibodies against this drug. The presence of antibodies did not influence the pharmacodynamic and pharmacokinetic properties of the drug or its safety.
Stauffer et al. 2018 [65]	Double-blind, randomized, placebo-controlled trial (EVOLVE-1)	Galcanezumab: 120 mg (n = 213) and 240 mg (n = 212) or placebo (n = 433) – *sc*, once monthly.	858 patients with episodes of migraine	After administration of the drug a statistically significant reduction in the number of migraine headache days (120 mg *vs.* placebo–4.7 *vs.* 2.8; 240 mg *vs.* placebo–4.6 *vs.* 2.8) and the mean monthly headache hours (120 mg *vs.* placebo–29.7 *vs.* 15.7; 240 mg *vs.* placebo–29.3 *vs.* 15.7) were observed.
Skljarevski et al. 2018b [66]	Global, double-blind, 6-month study (EVOLVE-2)	Galcanezumab 120 mg (n = 231) or 240 mg (n = 223) or placebo (n = 461) – *sc* once monthly	915 patients with episodes of migraine	Both doses of galcanezumab statistically significantly reduced the number of migraine headache days (120 mg *vs*. placebo–4.3 *vs.* 2.3 days, 240 mg *vs*. placebo–4.2 *vs.* 2.3 days). Galcanezumab resulted in significant reductions in MHDs with acute migraine medication use compared to the placebo group (120 mg - 3.67 days, 240 mg-3.63 days, placebo-1.85 days). The most frequent adverse effects of drug administration included: injection site pain, injection site reaction, injection site erythema, injection site pruritus, and injection site swelling.

medicine once a month and after 6 months when drug is using every quarter. Treatment can only be continued if the benefits of the treatment can be documented as follows: reduction in mean monthly headache days (≥50% relative to the pretreatment baseline) and clinical improvements in validated migraine-specific scales: MIDAS - *Migraine Disability Assessment* (reduction of ≥5 points when baseline score is 11–20 or reduction of ≥30% when baseline scores >20), MPFID - *Migraine Physical Function Impact Diary* (reduction of ≥5 points), HIT-6 - *Headache Impact Test* (reduction of ≥5 points) [79].

Summary

The high prevalence of migraine, especially in patients at the age of their apex productivity, makes this disease relevant for the whole society and it also has significant socio-economic impact. Improvement in quality of life, reduction of activity limitations and improvement of daily functioning of patients are the main goals of migraine treatment. Phase II and Phase III trials demonstrated that the anti-CGRP antibodies were markedly more efficient in migraine management, than placebo. The low rate of patients'

Table 10
Completed and published clinical tests for evaluation of efficacy, safety, pharmacological properties, and pharmacodynamics of anti-CGRP monoclonal antibodies - fremanezumab (TEV48125).

Author date of publication	Study	Dosage	Patients	Results
Bigal et al. 2014 [67]	Double-blind, placebo-controlled trial	LBR-101 (n=94): single dose *iv* – 0.2, 1, 3, 10, 30, 100, 300, 1000, 1500, 2000 mg; twice–300 mg; placebo (n=45)	139 healthy volunteers	LBR-101 was not found to influence arterial blood pressure, heart rhythm, temperature or blood laboratory test results. The most frequent adverse effects included: headache, nasopharyngitis, gastroenteritis, and back pain.
Bigal et al. 2015 [68]	Multicentre, randomised, double-blind, placebo-controlled, study	TEV-48125: 225 (n=96), 675 mg (n=97), placebo (n=104) – *sc* once every 28 days for 3 months	297 patients with episodes of migraine	Administration of the drug reduces the number of migraine-days from baseline both after phase 1 (weeks 1-4: 225 mg by 4.27 days, 675 mg by 4.57 days, placebo by 2.14 days), phase 2 (weeks 4-8; 225 mg by 5.38 days, 675 mg by 5.32 days, placebo by 2.89 days), and in the third phase of therapy (weeks 9-12: 225 mg by 6.14 days, 675 mg by 5.26 days, placebo by 3.52 days). TEV-48125 decreased mean number of days of acute drug consumption (weeks 9-12: 225 mg by 4.86 days, 675 mg by 4.8 days, placebo by 3.1 days). 50% reduction in the number of migraine-days was recorded in 53%, 59% and 28% patients in 225 mg, 675 mg or placebo groups respectively; 75% reduction in the number of migraine-days was recorded in 34%, 31% and 11% of the patients from the 225 mg, 675 mg or placebo groups, respectively. Most frequent adverse effects of treatment included: injection-site pain or erythema.
Bigal et al. 2016 [69]	Randomized placebo-controlled study	TEV-48125 675/225 mg (n=88), 900 mg (n=87) or placebo (n=89) – *sc* once-monthly	261 patients with chronic migraine	Reduction of the mean number of headache hours after 1 week of therapy (675/225 mg by 9.08 hours, 900 mg by 11.37 hours, placebo by 2.85 hours) recorded, this beneficial effect extended to subsequent weeks of therapy. After 3 weeks of therapy a 50% reduction in the number of migraine-days was recorded in case of 33% patients in the 675/225 group, 40.3% in the 900 mg group and 27% in the placebo group.
Cohen et al. 2017 [70]	Two randomized placebo-controlled studies	EM Study- 12 weeks: fremanezumab 225 mg (n=32), placebo (n=28), *sc* once-monthly CM Study – 12 weeks: fremanezumab 657/225 mg (n=35), placebo (n=66) sc once-monthly	133 patients with chronic migraine	The number monthly of headache decreased by 4.16 days after administration of fremanezumab and by 2.47 after placebo. Fremanezumab also significantly decreased the mean number of days using acute medication relative to placebo (3.88 ±0.58 *vs.* 2.52±0.63). The most frequent adverse effects included: injection-site pain, nasopharyngitis.
Silberstein et al. 2017 [71]	Randomized, double-blind, placebo-controlled, parallel-group trial	Fremanezumab quarterly 675 mg (n=376), fremanezumab monthly 675 mg (n=379), placebo (n=375) – 12 weeks	1130 patients with chronic migraine	The mean (±SE) number of headache days per month was subject to significant reduction (fremanezumab-quarterly group by 4.3±0.3 days; fremanezumab-monthly group by 4.6±0.3 days; placebo by 2.5±0.3 days). At least 50% reduction in the average number of headache days per month was also recorded (fremanezumab-quarterly group 38%; fremanezumab-monthly group – 41%; placebo–18%). The average number of days per month in which acute headache medication was also reduced in the group receiving fremanezumab (fremanezumab-quarterly group by 3.7±0.3 days; fremanezumab-monthly group by 4.2±0.3 days; placebo by 1.9±0.3 days). The most frequent adverse effects of fremanezumab administration included: injection-site induration and erythema.
Cohen-Barak et al. 2018 [72]	Randomized, double-blind, placebo-controlled study	Four cohorts of four treatments: 225, 675, or 900 mg fremanezumab, or placebo (n=4 for each group in the respective cohort) – *sc* for 36-week	123 healthy subjects of Japanese and Caucasian origin	The tested pharmacokinetic parameters did not differ for the Japanese and Caucasians. T_{max} was recorded after 5-7 days, and C_{max} was 0.91 μg/mL for the 225 mg dose, 1.04 μg/mL for 675 mg and 1.14 μg/mL for 900 mg. Mean $t_{1/2}$ values ranged between 31.36 and 38.58 days. The most frequent adverse effects of treatment included: injection site erythema, injection site induration, injection site pain, and injection site hemorrhage.
Halker Singh et al. 2018 [73]	Multicenter, two randomized, double-blinded, placebo-controlled 12-week phase	HFEM study: fremanezumab – 225 mg (n=96), 675 mg (n=97) or placebo (n=104); CM study: fremanezumab – 675/225 mg (n=88), 900 mg (n=86) – *sc* monthly	560 patients with high-frequency episodic migraine (HFEM) and chronic migraine (CM)	The sustained results achieved in the HFEM study were: 50% reduction in migraine days–39%, 35% and 10% for the 225 mg, 675 mg and placebo doses, respectively; moderate-to-severe (M/S) headache days (36% for 225 mg, 38% for 675 mg and 16% for placebo) and acute medication use days (36% for

Table 10 (*Continued*)

Author date of publication	Study	Dosage	Patients	Results
Dodick et al. 2018 [74]	Randomized, double-blind, placebo-controlled, parallel-group study	Fremanezumab: 225 mg, n=290; three times), 675 mg (n=291; 675 mg at baseline; placebo at weeks 4 and 8); placebo (n=294; three times); *sc* 12 weeks	875 patients with episodes of migraine	225 mg, 27% for 675 mg and 8% for placebo) and were statistically significantly reduced in the treated patients. In the CM study: 50% (32% for 675/225 mg, 40% for 900 mg and 15% for placebo) and 75% (10% for 675/225 mg, 13% for 900 mg and 3% for placebo) sustained reduction in M/S headache days and days of acute medication use (26% for 675/225 mg, 22% for 900 mg and 11% for placebo), these were significantly higher in the group of patients who received treatment. The most frequent adverse effects included: pain, erythema and/or pruritus. No anti-drug antibodies were found. After 12 weeks of therapy there was a statistically significant reduction in the treated groups (by 1.5 days in the group treated with the 225 mg dose, and by 1.3 days in the group treated with the higher dose, and by 0.72 days in the placebo group). At least a 50% reduction in mean number of monthly migraine days was 47.7% in the 225 mg dose group, 44.4% in the group receiving the higher dose and 27.9% in the placebo group. The most frequent adverse effects of treatment were injection site reactions: pain, induration, erythema.

resignations from treatment indicates good tolerance and safety of the aforesaid drugs [80]. Even if the effects of long-term blocking of CGRP receptors, and the cardio- and cerebrovascular risks in particular, remain unknown, these drugs are believed to have a favorable benefit/risk ratio [81]. The results concerning urogepant and rilmegepant also appear promising. Most likely the CGRP-active drugs will prove to be an effective therapeutic option in patients with migraine, although the price of medication and lack of its availability for all patients requiring the treatment may form a significant limitation [82].

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