Anti-CGRP monoclonal antibodies in migraine: current perspectives

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Running title: Anti-CGRP mAbs in migraine

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Manuscript "Anti-CGRP monoclonal antibodies in migraine: current perspectives" (re.no. IAEM-D-16-00051R1)

Response to reviewers' and editor's questions

We thank the reviewers and the Editor for their very constructive comments. We have revised the manuscript taking into account all their requests (changes in the manuscript are highlighted in yellow). A detailed account of the changes performed is provided below.

Q: Reviewer #1: The revised version of the ms is greatly ameliorated.
A: We thank the reviewer for these positive comments

Q: Reviewer #2: The manuscript is well organized and xcomplete. There are some minor concerns to be corrected as listet below.
A: We are grateful to the reviewer for the positive comments. All the minor concerns raised have been taken into account, as below specified.
The issues raised from page 5 onwards, however, appear to relate to the first version-submission of our manuscript (the indicated pages and lines correspond to this version and not to the revised one), therefore several requests here listed had already been taken care of in our previous revision. Those which had not yet been considered have now been addressed, as detailed below.

Q: PAGE 2
Line 4: "whose" be replace with "which"
Line 6: "classically" be placed after "are", in the subsequent line
A: Both correction have been performed

Q: PAGE 3
Line 4: "in spite of" be replace with "notwithstanding"
Line 21: "effective" be replace with "efficacy"; a "," be placed after "trials"
A: Correction on both lines have been performed

Q: PAGE 4
Line 13: Remove "in"
Line 36: "aimed at" be replaced with "aimed to"
Line 40: "aimed at" be replaced with "aimed to"

A: All corrections on this page have been performed

PAGE 5

Q: Line 13: Add "Topiramate and Valproic Acid" as preventative measure of proven efficacy in chronic migraine (Bagnato F, Good J.The Use of Antiepileptics in Migraine Prophylaxis. Headache 2016 Mar; 56(3): 603-15).

A: We added topiramate and Valproic Acid and quoted the relative ref., as requested

Q: Line 32: Remove "of activation"

A: This expression, present in our first version of the paper, had already been eliminated in our revised version

Q: Line 36: "among which" be replace with "including"

A: Correction performed, as requested

Q: Line 40: Remove "made"

A: Correction performed, as requested

PAGE 7

Q: Line 19: Remove "not"

A: This had already been removed in our revised version of the manuscript

Q: Line 21: Remove "small molecules such as" and "antibodies against CGRP" be replace with "CGRP receptor antagonists"

A: Correction performed, as requested

Q: PAGE 8

Line 2: Remove "that by"

Line 11: Remove "engagement"

Line 19: Remove "that assisted"

A: All the requested changes on page 8 are relative to our first version of the manuscript. The relative text where these requested changes should be performed is no longer present in the revised version of the manuscript.

PAGE 9

Q: Line 2: "(n.1109" be replace with "(n.110)"

A: This correction had already been performed in our revised version

Q: Line 13: Remove "with"
A: Correction performed, as requested

Q: Line 45: "indeed" be replace with "has"
A: This sentence had already been changed in the revised version

Q: Line 47: "while" be replace with "moreover"
A: Correction performed, as requested

Q: Line 58: "December" be replace with "June"
A: Correction already performed in the revised version

Q: PAGE 10
Line 30: "phase 2 trial" be replace with "exploratory phase 2 trial" Line 30: Remove "carried out in 2013"
Line 34: "design" be replace with "study"
Lines 34-36: Remove "Of 174 patients randomly assigned to 26 centers in the US,"
Lines 40-42: Remove "(randomization via an interactive web response system)"
A: All corrections in this page have been performed, as requested

PAGE 11
Q: Line 11: "testifying" be replace with "justifying"
A: Correction performed, as requested

Q: Line 15: Remove "at least"
A: Correction performed, as requested

Q: Line 19: Add "an effective" before "treatment"
A: Correction performed, as requested

Q: Line 25: "July" be replace with "November"
A: This correction had already been performed in the revised version

Q: Line 32: Add "more than" before "600"
A: Correction performed, as requested

Q: Lines 38-45: Rewrite this lines in "(a) safety, assessed via laboratory variables, ECG and AEs; (b) peak plasma concentration of the compound (Cmax); (c) time to achieve peak plasma concentration (Tmax); (d) area under the plasma concentration

(AUC) vs time curve of the compound."
A: Correction performed, as requested

Line 53: Add "randomized" before "placebo-controlled"
A: Correction performed, as requested

PAGE 12
Q: Line 1: "April" be replace with "June"
A: This correction had already been performed in the revised version

Q: Line 40: "being advance" be replace with "in advanced stage"
A: Correction performed, as requested

Q: Line 53: "for which" be replace with "studied in"
A: Correction performed, as requested

Q: Lines 55-57: Remove "(a single dedicated cardiovascular safety study and a repeat-dose, chronic study, respectively), were"
A: Correction performed, as requested

Q: Line 57: "cytomolgus" be replace with "cynomolgus"
A: This correction had already been performed in the revised version

Q: PAGE 13
Line 4: Add "high" before "importance"
Line 11: "delivered to volunteers" be replace with "administered to healthy volunteers"
Line 15: Remove "(day 1)"
Line 17: Remove "(day 1 and day 14)"
A: All corrections on this page have been performed, as requested

Q: PAGE 14
Line 8: Remove "its"
Line 10: "in contrast" be replace with "compared"
Lines 51-58: Rewrite the last four lines in "LSM differences in the decrease of headache-days were -2.63 days among the placebo group and 225 mg dose group ($p < 0.0001$) and -2,58 days among the placebo groups and the 675 mg dose group ($p < 0.0001$). Adverse events occurred in 56% of patients in placebo group, in 46% of patients in 225 mg group and in 59% of 675 mg group's patients. They were moderate-severe in 27%, 25% and 27% of cases, respectively".
A: All corrections on this page have been performed, as requested

Q: PAGE 15
Line 4: "data" be replace with "thus"
Line 32: Remove "all"
A: Both corrections on this page have been performed, as requested

PAGE 16
Q: Lines 53-55: The named phase 1 study is a phase 2 study, please recollocate the description of the study in the phase 2 study list (Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Lenz R. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016 Apr; 15(4): 382-90).
A: This correction had already been performed in our revised version of the manuscript

PAGE 17
Q: Lines 1-2: The named phase 1 study is a phase 2 study, please recollocate the description of the study in the phase 2 study list (Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Lenz R. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016 Apr; 15(4): 382-90).
A: This correction had already been performed in our revised version of the manuscript

Q:Lines 36-38: "aimed at" be replace with "aimed to"
A: Correction performed, as requested

Q: Lines 40-42: ", planning to recruit approximately 651" be replace with "study which enrolled 667"
A: Correction performed, as requested

Q: Line 47: Remove "a"
A: Correction performed, as requested

Q:Line 55: Remove "the"
A: Correction performed, as requested

PAGE 18
Q: Line 2: "May" be replace with "April" and remove "though"
A: This correction had already been performed in the revised version

Q:Line 4: "is estimated to be" be replace with "was in"
A: This part had already been removed in the revised version

Q:Line 6: "aimed at" be replace with "aimed to"
A: correction performed, as requested

Q:Line 23: "7mg" be replace with "70 mg"
A: Correction already performed in the revised version

Q: Line 25: "2.28 reduction" be replace with "2.28 reduction of migraine's days"
A: Correction performed, as requested

Q:Line 30: Add "of the drugs." after "tolerability"
A: Correction performed, as requested

Q: Lines 30-34: Remove ": exploratory endpoints were the change in monthly headache days and in monthly acute migraine-specific medication use days."
A: Correction performed, as requested

Q: Line 43: Remove "that of"
A: Correction performed, as requested

Q: Line 58: Add ")." after "months" and remove "- completion of open"
A: Correction performed, as requested

PAGE 19
Q: Line 1: Remove "label treatment)."
A: Correction performed, as requested

Q:Line 4: Remove "change in monthly migraine attacks from baseline" and add "change in monthly acute migraine-specific medication treatment days from baseline; d) change in monthly cumulative hours of headache from baseline." after "c)"
A: Correction performed, as requested

Q: Line 6: "July" be replace with "March" and "490" be replace with "612"

A: This correction had already performed in the revised version

Q: Line 13: Remove "of the AMG334 NCT02066415 parent study"
A: Correction performed, as requested

Q: Lines 26-28: "at evaluating" be replace with "to evaluate"
A: Correction performed, as requested

Q:Line 45: Remove "thus"
A: Correction performed, as requested

Q: Line 47: "time frame:" be replace with "considering"
A: Correction performed, as requested

Q: PAGE 20
Line 8: "February 2018" be replace with "June 2017"
Line 13: "It plans to recruit 852" be replace with "There was recruited 955"
Line 40: "vasodilator" be replace with "vasodilating"
A: All corrections on this page have been performed, as requested

PAGE 21
Line 2: "toxicity" be replace with "impairment"
Line 8: "although" be replace with "where"
Line 10: Add "Nevertheless, " after "responders."
Line 13: Remove "for istance"
A: All corrections on this page have been performed, as requested

Comment of the editor-in-chief
Please also try to quote all relevant material published in IEM in the recent years
A: Relevant papers recently published in IEM have been added

Abstract

Migraine is a highly disabling neurological pain disorder which management is frequently problematic. Most abortive and preventative treatments employed are classically non-specific, and their efficacy and safety/tolerability are often unsatisfactory. Mechanism-based therapies are therefore needed. Calcitonin-Gene-Related-Peptide (CGRP) is recognized as crucial in the pathophysiology of migraine and new compounds that target the peptide have been increasingly explored in recent years. First tested were CGRP receptor antagonists; they proved effective in acute migraine treatment in several trials, but were discontinued due to liver toxicity in long-term administration. Monoclonal antibodies against CGRP (LY2951742, ALD-403 and LBR-101/TEV-48125) or its receptor (AMG334) were subsequently developed. As reviewed in this article, numerous phase 1 and 2 trials and preliminary results of phase 3 trials have shown a good safety/tolerability profile and efficacy in migraine prevention, especially in high frequent episodic and chronic forms. Being macromolecules, these mAbs are not suitable for oral administration; however their intravenous or subcutaneous delivery can be performed at relatively low frequency - every month or even quarterly - which enhances patients' compliance. Although not all migraineurs respond to this treatment, and longer administration periods will be needed to assess long-term effects, the results so far obtained are extraordinarily promising. The future introduction of mAbs on the market will probably represent a turning point for prevention similar to that represented by triptans for abortive treatment in migraine.

Key words: migraine, CGRP, monoclonal antibodies against CGRP, migraine prophylaxis.

Introduction

Migraine is a common neurological disorder of intense, recurrent/chronic pain, representing a cause of extreme disability for the affected subjects [1-3]. Notwithstanding considerable progress made in recent decades, its management often remains problematic, being still dependent on drugs that, to a large extent, are not primarily designed for the condition [4,5]. New treatment regimens, more pathophysiologically-based, are therefore imperatively needed [6]. In this framework, the research of the last decade has focused on the crucial role played by Calcitonin-Gene-Related-Peptide (CGRP) in the triggering of the attacks and, as a consequence, new drugs antagonizing the effects of this peptide have been tested [7-16]. CGRP antagonists showed efficacy in several clinical trials, but their severe side effects/adverse events with long-term administration discouraged further research, their production was thus interrupted. The recently developed monoclonal antibodies against CGRP or its receptor (anti-CGRP mAbs) have triggered much interest in the headache community and a number of clinical trials have been carried out, are underway or have been planned in migraine prevention [17-23]. After a necessary premise on migraine characteristics and current treatment options, as well as notes on pathophysiological mechanisms, particularly in relation to CGRP, the present review will thus focus on the results of the studies on anti-CGRP mAbs, critically discussing the future implications for their systematic employment in migraine management.

Migraine: a therapeutic challenge

Migraine has a high epidemiological and socioeconomic impact. With a prevalence ranging from 15 to 18% in the general population (female/male ratio = 3:1), it is the 6th cause of disability worldwide when considered alone, and the 3rd when also Medication Overuse Headache (MOH) is included in the disability estimate [1,3]. The characteristics of the condition fully account for its disabling nature: repeated attacks of moderate-severe pain, most often unilateral and pulsating in nature, aggravated by

physical activity, accompanied by nausea and/or vomiting, and by phono- and photophobia. The patient is usually completely unable to carry out any activity during the pain, most often lying in bed [24]. In the form of "migraine with aura", which occurs in about one third of the cases, whereby aura is a complex of reversible focal neurological symptoms usually preceding the pain, the disability is even worse. Patients are also deeply affected between the attacks, mostly due to the fear of the "next attack" if they feel they are not able to prevent it [4]. Chronic migraine (CM), affecting over 4% of the population, is the extreme form of the condition, where a minimum of 15 days/month of headache pain occurs (at least 8 of which have migraine characteristics)[25,26]. CM most often coexists with the above-mentioned MOH, which further complicates the clinical picture and the therapeutic approach. MOH, in fact, involves an excessive consumption of acute headache medications producing a vicious circle of increased headache frequency and reduced efficacy of treatments. It develops in about 50% of CM, but virtually any patient with a primary episodic headache may be at risk of the condition, with a world prevalence ranging from 0.5 to 7.2% (F:M ratio = 4:1) [27-29].

Migraine treatment is both symptomatic and preventative. The former aims to interrupt the attack and is the only measure applied for low frequency episodic forms (up to 2-4 monthly attacks), while the latter aims to reduce attack number/intensity by at least 50% and necessarily needs to be additionally carried out in high frequency episodic and chronic forms. As already reported in the Introduction, antimigraine drugs are largely aspecific. Apart from triptans, in fact, most of the employed drugs have not been primarily conceived for the condition, e.g., from Non-Steroidal Antiinflammatory Drugs (NSAIDs) and simple and combination analgesics as symptomatics, to beta-blockers, calcium-channel blockers, tricyclic antidepressants and anti-epileptics as preventative drugs [8,30-32]. An insufficient response to these classic therapies is unfortunately found in a substantial percentage of patients. In addition, safety is frequently a problem, due to side effects and contraindications but

also drug-drug interactions in the case of comorbidities, very frequent in migraine, such as psychiatric and cardiovascular diseases, various forms of visceral pain, fibromyalgia or myofascial pain syndromes [33-44]. Alternative treatments are therefore necessary, particularly in the field of prophylaxis of high frequency episodic and chronic migraine. Especially in CM, whether or not associated with MOH, in fact, very limited therapeutic options exist to date, the only preventative measures of proven efficacy being Topiramate, Valproic Acid and OnabotulinumtoxinA [4,5,45]. The need is specifically for more mechanism-based therapies.

Migraine pathophysiology: the role of CGRP

Migraine pathophysiology is complex and multifactorial. While vascular mechanisms were given great emphasis in the past [46,47], current knowledge point to central nervous system dysfunction as the primary factor behind the condition, in brainstem centers important in regulating vascular tone and pain sensation, with a number of messenger molecules implicated in pain generation, including 5 hydroxytryptamine (5-HT), nitric oxide (NO), substance P and CGRP [24,48-50]. In genetically predisposed individuals, migraine-specific triggers would cause primary brain dysfunction with consequent dilation of cranial blood vessels innervated by sensory fibers of the trigeminal nerve. The dilation would mechanically activate these perivascular fibers with a pain message then conveyed to the brainstem and higher brain centers and release of vasoactive peptides, such as substance P (SP) and CGRP from trigeminal fibers. SP is a potent mediator of increased microvascular permeability and CGRP is an extremely potent vasodilator. These peptides are responsible for neurogenic inflammation, with increased blood flow, edema formation, and recruitment of inflammatory cells to the local area, with degranulation of mast cells and release of proinflammatory and inflammatory molecules [51-53]. The process can activate meningeal nociceptors [49] with further increase in the level

of activation of the sensory trigeminal fibers, perpetuating the release of vasoactive peptides, including CGRP. As migraine progresses, sensitization occurs in spinal cord and brainstem centers that are the first to receive the nociceptive impulses from the trigeminal afferents. As a consequence, migraine pain increases and hypersensitivity develops to environmental and other stimuli. In the sequence of the described processes, CGRP thus appears to play a fundamental role [24,46,50,54].

CGRP was discovered 30 years ago [55], as a neuropeptide of 37 amino acids, produced from alternative RNA processing of the calcitonin gene. It has two major forms in humans: α-CGRP, the form primarily involved in migraine, prevalently expressed in primary sensory neurons of the dorsal root ganglia, throughout the trigeminal system (located on Adelta-fibers and Cfibers) and in vagal ganglia, and β-CGRP found mainly in intrinsic enteric neurons gray [11,56-59]. CGRP belongs to a group of peptides all acting on an unusual receptor family. These receptors consist of calcitonin receptor-like receptor (CLR) linked to an essential receptor activity modifying protein 1 (RAMP1), a relatively small, single, transmembrane-spanning protein, which is essential for full functionality [60]. RAMP1 is, in fact, able to act as a pharmacological switch and chaperon, and it can regulate signalling and/or trafficking in a receptor-dependent manner. It has two main roles: it facilitates the cell-surface expression of CLR and is also essential for the binding of CGRP to the receptor. It seems likely that amongst other residues, Y66, F93, H97 and F101 form a binding site for CLR. These cluster together on the same face of the extracellular portion of RAMP1, probably close to where it enters the plasma membrane. Residues at the other end of RAMP1 are most likely to be involved in CGRP recognition, although it is currently unclear exactly how they do this [61]. The RAMP family of proteins is comprised of three members: RAMP1, RAMP2, and RAMP3, each with <30% sequence homology but sharing a similar structure. While the true receptor for CGRP is considered to be formed by the CLR/RAMP1 complex, dimerization of the CLR and RAMP2 creates a receptor that is highly responsive to the related peptide

adrenomedullin (AM1 receptor). The RAMP3 receptor confers a second adrenomedullin receptor (AM2 receptor) that also has some selectivity for CGRP [60]. As already mentioned, CGRP has potent vasodilator capacity. It is responsible for both protective actions (at cardiovascular level, in processes of wound healing) and pain signalling (e.g., it enhances the release of substance P from primary afferent terminals, favouring the transmission of nociceptive messages, and modulates the synaptic transmission of glutamate) [60,62-64]. Its role in migraine is well established and has been increasingly recognized in recent decades [65]. Its levels are, in fact, elevated during migraine pain in patients, with normalization after administration of the anti-migraine agents, the triptans (5-$HT_{1B/1D}$ agonists) and concurrent resolution of the headache component [66-70]. Intravenous infusion of CGRP can induce migraine-like attacks in migraine patients, i.e., a delayed headache about 2 – 4 h after injection with some headaches meeting criteria for migraine [71-74]. During the migraine-like attack, Asghar et al (2011) showed a CGRP-induced dilation of both the middle meningeal artery and the middle cerebral artery; sumatriptan administration effectively reversed the CGRP-induced migraine [71]. In contrast, CGRP infusion in non-migraine sufferers produces only an initial mild headache, with none meeting criteria for experimentally induced migraine [72,75].

In chronic migraine, a recent study in patients showed high levels of CGRP in the peripheral blood (measured by ELISA) also in the pain-free interval when compared with healthy controls [76], suggesting that CGRP measure could be a biomarker of CM.

Initially, CGRP role in migraine was ascribed mainly to its vasodilator capacity. It subsequently became clear, however, that a fundamental action resides in its ability to modulate neuronal excitability, with triggering and maintenance of peripheral and central sensitization, crucial phenomena in migraine [16,50,77]. As suggested by animal data, CGRP is probably also involved in the generation of light intolerance, typical of the condition [78].

It is not surprising, on this basis, that the peptide has generated increasing interest as a primary target for promising novel treatments for migraine pain [9,10,16].
First developed were CGRP receptor antagonists, which compete with endogenous CGRP at the receptor binding sites. These are small molecules, as such suitable for absorption after oral administration, whose ability as both abortive and preventative treatments was tested in numerous previous studies [4,79]. Though several compounds of this class proved effective in the control of migraine pain (without causing vasoconstriction, which is a main concern with triptans), serious safety problems - liver toxicity - occurred with their employment for prolonged periods [9,10]. Their clinical development was therefore suspended.

More recently, monoclonal antibodies against CGRP and its receptor have been developed.

Monoclonal antibodies against CGRP in migraine prevention

Anti-CGRP mAbs are macromolecules made of proteins that either directly target the ligand (CGRP), i.e., they bind to and neutralize the excessive CGRP released at perivascular trigeminal sensory nerve fibers, or target the CGRP receptor [16,17]. These target specific macromolecules do not have the off-target toxicities common to the previously tested CGRP receptor antagonists. Due to large particle size, mAbs also have minimum possibility to pass the blood-brain barrier (only 0.1-0.5%). Their primary site of action is therefore peripheral, in structures involved in migraine pathophysiology, including trigeminal ganglia [9,10]. Target specificity, prolonged half-lives that generally allow for monthly or even quarterly dosing, and limited potential for hepatotoxicity and drug-drug interactions render anti-CGRP mAbs the ideal candidates for preventive treatment of migraine [18,23].
Three anti-CGRP mAbs, which target the ligand, are currently under clinical development, namely: *LY2951742* [developed by Arteaus Therapeutics (USA), with

rights subsequently acquired by Eli Lilly and Co.], *ALD-403* [Alder Biopharmaceuticals (USA)] and *LBR-101, now TEV-48125* [developed by Labrys Biologics—Pfizer (USA), then acquired by Teva Pharmaceuticals]. Only one mAb targets the CGRP receptor: *AMG334* [Amgen, Inc. (USA)].

Experimental pre-clinical studies conducted with mAbs helped to plan their subsequent employment in patients [80,81]. Numerous trials have been/are being carried out with anti-CGRP mAbs for the prevention of both episodic and chronic migraine [23], a detailed report of which is provided below, separately for each molecule.

LY2951742 (Table 1)

This fully humanized mAb, which potently and selectively binds to CGRP, has proven well-tolerated in *phase 1* trials at single and multiple doses (NCT02576951; NCT02104765) [22].

In a *phase 2a* clinical trial (NCT01625988) it was delivered subcutaneously (s.c.) at a dose of 150 mg in episodic migraine (4-14 migraine days/month), showing significantly higher results than placebo in migraine prevention, with a good tolerability profile [82]. More in detail, this was a randomized, double-blind, placebo-controlled study involving 35 different centers in the US which was conducted between July 2012 and September 2013. The 218 enrolled patients (aged 18-65 years) were randomly assigned (1:1) to LY2951742 150 mg (n. 108, but one patient withdrew before starting the treatment) or placebo (n. 110) s.c. once every 2 weeks for 12 weeks. Parameters evaluated were: the mean change in the number of headache days over a period of 28 days, assessed at 9-12 weeks, and safety, assessed over 24 weeks (12 weeks of treatment and subsequent 12 weeks post-treatment). At week 12 vs baseline, a significantly higher decrease in migraine days occurred in the active group vs placebo (-4.2 ± 3.1 SD vs -3 ± 3, respectively, $p<0.004$). Serious adverse events attributable to treatment did not occur, although side effects, such as

pain and/or erythema at injection site, abdominal pain, infections of the respiratory tract, were more frequent with LY2951742 than placebo.

A second *phase 2b* study (NCT02163993) in episodic migraine was recently completed (Summer 2015). Already in June 2015, Eli Lilly announced in a press release (https://investor.lilly.com/releasedetail.cfm?ReleaseID=918405) that the primary endpoint of this study had been met and the data were then presented at the 57th Annual American Headache Society meeting in June in Washington D.C. In this randomized, double-blind, placebo-controlled study, efficacy and safety were evaluated of four different doses of LY2951742 (5mg, 50mg, 120mg, 300mg) delivered subcutaneously once-monthly during a 12-week treatment period in a sample of over 400 patients. The primary objective was to assess if at least one dose of this mAb was superior to placebo in preventing migraine attacks (mean change from baseline in the number of migraine headache days in the last 28-day period of the 12-week treatment phase). The 120mg dose of LY2951742 reduced, in a statistically significant manner ($p<0.005$), the number of migraine days as compared with placebo, moreover showing a good safety and tolerability profile, in line with the results of the previous phase 2a study.

At the moment of this writing, three *phase 3* trials are underway: 1) NCT02614196, a randomized, double-blind, placebo-controlled efficacy study with s.c. LY2951742 once a month every 6 months in episodic migraine, to be completed in June 2017 (EVOLVE-2 Study, 825 patients); 2) NCT02614261, a randomized, double-blind, placebo-controlled efficacy study with s.c. LY2951742 once a month for 3 months in chronic migraine (REGAIN Study, 825 patients) to be completed in April 2018; and 3) NCT02614287, a long-term, open-label safety study with s.c. LY2951742 once a month for up to 12 months in episodic or chronic migraine with or without aura (250 patients, to be completed in September 2017).

ALD403 (Table 2)

This anti-CGRP mAb was first evaluated in a *phase 1* trial (NCT01579383), completed in April 2013, on 104 healthy subjects of both sexes, 18-65 years old. This single dose, placebo-controlled, ascending dose study on ALD403 administered by intravenous infusion and subcutaneous injection showed a satisfactory profile of safety, tolerability and pharmacokinetics of the compound [16].

In an *exploratory phase 2* trial (NCT01772524) completed in February 2014, intravenous ALD403 was tested as preventative treatment of frequent episodic migraine for efficacy, safety and tolerability in a randomized, double-blind, placebo-controlled, exploratory study. One hundred and sixty-three patients (18 -55 years), complaining of 5-14 migraine days over a 28-day period received either a single intravenous dose of ALD403 1000 mg (n=81) or placebo (n=82). Safety was assessed at 12 weeks (primary objective), efficacy was evaluated as change in frequency of migraine days from baseline to weeks 5—8 (primary efficacy endpoint). For exploratory safety and efficacy analyses (done by intention-to-treat), patients were followed-up for 24 weeks. Adverse events occurred in 57% of ALD493 patients vs 52% of the placebo patients, the most frequent of which were, in decreasing order, infection of the upper respiratory tract and urinary tract, fatigue, back pain, joint pain, nausea and vomiting. Serious adverse events occurred in only three patients (2 in the active group, 1 in the placebo group), all judged unrelated to the treatment. Laboratory safety data did not differ between the two treatment groups [83]. The mean change in migraine days was -5.6 ± 3.0 (SD) for ALD403 vs -4.6 ± 3.6 for placebo (significant difference, $p < 0.04$). Of particular note is that the single dose of 1000mg proved efficacious in completely annulling pain attacks in 26% of the patients during the first month after treatment, justifying the rapidity of action of the compound, with 16% of patients reporting no migraines for the full 12 weeks ($p<0.001$) vs 0% for placebo [84]. These results confirm that, for a subgroup of

migraine patients, CGRP is the main protagonist of the development of the attacks; its inhibition is thus fundamental for an effective treatment.

A *phase 2b*, quarterly infusion formulation trial, with ALD403 in the prevention of chronic migraine, is ongoing (NCT02275117). Started in October 2014, it should be completed in November 2016, though the final data collection for the primary outcome measure should be available soon. This is a parallel group, double-blind, placebo-controlled, dose-ranging study to assess efficacy, safety and pharmacokinetics of the product administered intravenously to more than 600 chronic migraineurs of both sexes (aged 18-55 years). The primary outcome measure is the change in the number of migraine days at week 12 vs baseline. A number of parameters are evaluated as secondary outcome measures in the time frame of 49 weeks: (a) safety, assessed via laboratory variables, ECG and AEs; (b) peak plasma concentration of the compound (Cmax); (c) time to achieve peak plasma concentration (Tmax); (d) area under the plasma concentration (AUC) vs time curve of the compound.

Also ongoing is a *phase 3* trial (NCT02559895) (PROMISE1: PRevention Of Migraine via Intravenous ALD403 Safety and Efficacy 1), in the prevention of frequent episodic migraine. This is a randomized, parallel-group, double-blind, placebo-controlled, dose ranging (three dose levels) clinical trial for evaluation of efficacy and safety of intravenous ALD403 administered quarterly. Started in September 2015, it should be completed in June 2017, enrolling 600 patients of both sexes (18-75 years), with 150 patients per group (3 doses and placebo). The primary outcome measure is the responder rate in the time frame of 12 weeks. Secondary outcome measures are: (a) change in frequency of migraine days (12 weeks) and (b) laboratory variables, ECG and adverse events (32 weeks)

In 2016, a second *pivotal trial*, PROMISE2, will be initiated to evaluate efficacy and safety of ALD403 in chronic migraine. This is a 450-patient double-blind, randomized, placebo-controlled, multi-dose trial where two dose levels of ALD403

and placebo will be administered quarterly, i.v., with 150 patients per group. As for PROMISE1, the primary endpoint will be the change in migraine days between ALD403 and placebo, determined calculating the difference in responder rates over 12 weeks.

If supported by the data, the results of PROMISE1 and 2 will be used to support a Biologics License Application submission to the US Food and Drug Administration (FDA) for the infusion formulation of ALD403 [http://www.alderbio.com/wp-content/uploads/2015/10/Alder-ALD403-FEM-Pivotal-trial-initiation-finalupdated.pdf].

Interestingly, the clinical development of a formulation of ALD403 for quarterly *self-administration* is currently in advanced stage by Alder, and a phase 1 study in healthy volunteers has been initiated. Subsequent to completion of this study a dose-ranging phase 2b study will be started in 2016 with this formulation in patients with episodic migraine.

LBR-101 / TEV-48125 (Table 3)

This is a genetically engineered humanized mAb studied in two independent preclinical studies carried out in cynomolgus monkeys. These showed that the long-term inhibition of CGRP by the LBR-101 does not affect cardiovascular and hemodynamic parameters, and the compound is well tolerated, a result of high importance in view of the clinical applicability [85].

LBR-101 successfully completed *phase 1* trials with active drug being intravenously administered to healthy volunteers. In 2013 Bigal et al [86] published the pooled results of the phase 1 program, where LBR-101 was given to 94 subjects and placebo to 45 subjects with doses ranging from 0.2mg to 2000mg given once (single i.v. infusion) or up to 300mg given twice. Although the study did not identify a maximally tolerated dose, it showed no significant safety problems: averaged adverse

events were 1.3 with placebo, 1.4 with any dose of LBR-101 and 1.6 with 1000mg or a higher dose of LBR-101. AEs related to treatment occurred in 17.7% of placebo subjects vs 21.1% of LBR-101 subjects. A thoracic aortic aneurysm found in a subject was later correlated to an unreported history of Ehlers-Danlos syndrome and thus did not have any relationship with the treatment. Subjects receiving active treatment did not show significant changes in ECG, vital signs and laboratory findings.

The excellent safety profile of LBR-101 was also confirmed by a subsequent double-blind, placebo-controlled study by the same authors [87]. Cardiovascular and hemodynamic parameters (blood pressure, heart rate and ECGs) were evaluated in 31 healthy women of over 40 years of age - thus a population at increased risk of cardiovascular events - who were administered LBR-101 at doses up to 2000mg. They were confined for 7 days and followed for 168 days; no relevant changes were observed in any of the evaluated parameters at any time point during the observation period.

A further *phase 1* trial (NCT01991509) was completed in early 2015. This randomized, placebo-controlled, double-blind, parallel group study assessed safety, tolerability and pharmacokinetics (blood levels) of two different doses of LBR-101 given intravenously and subcutaneously to 36 healthy volunteers (primary outcome measure was: relative bioavailability of i.v. vs s.c. administration of LBR-101).

The results of the six phase 1 studies performed so far with the compound (in addition to the clinical trials) were summarized by Walter and Bigal [88] in a recent review where the authors underline the safety profile, along with its efficacy in the prevention of migraine pain, compared to CGRP antagonists.

Two *phase 2* clinical trials were completed in March 2015 on episodic and chronic migraine, respectively. The first (NCT02025556) was a multicenter (62 sites in the USA), randomized, double-blind, placebo-controlled, parallel-group study comparing

efficacy and safety of two doses of monthly subcutaneous administration of TEV-48125 with placebo for the preventative treatment of high frequency episodic migraine (8-14 days per month). A total of 297 patients (both sexes, 18-65 years), enrolled between January and October 2014, were treated with s.c. placebo (n. 104) or TEV-48125 225mg (n. 96) or TEV-48125 675mg (n. 97) (randomly assigned to these three groups, stratified by sex and use of concomitant preventive drugs) every 28 days for 12 weeks, thus three cycles, after a 28 day run-in period. Headache parameters were evaluated by patients using an electronic diary compiled on a daily basis. The primary efficacy endpoint was the reduction of the number of migraine/days during weeks 9-12 with respect to baseline. Other primary endpoints were safety and tolerability assessed by the change from baseline in frequency and severity of adverse events in the same time frame. At 9-12 weeks vs baseline, while in the placebo group there was a least square mean (LSM) change in number of migraine-days of -3.46 ± 5.40, the change was -6.27 ± 5.38 for TEV-48125 at 225mg and -6.09 ± 5.22 for TEV-48125 at 675mg. LSM differences in the decrease in headache-days were -2.63 days between the placebo group and 225mg dose group ($p<0.0001$) and -2.58 days between the placebo group and the 675mg dose group ($p<0.0001$). Adverse events occurred in 56% of patients in the placebo group, in 46% of patients in the 225mg group and in 59% of the 675mg group patients. They were moderate-severe in 27%, 25% and 27% of the cases, respectively. The authors conclude that both doses of TEV-48125 are effective and safe in migraine prevention when delivered at the regimen of 3 administrations over a 12-week period, thus supporting the plan to perform phase 3 clinical trials in this field [89].

The second *phase 2b* trial (NCT02021773) was a multicenter (62 sites in the USA), randomized, double-blind, double-dummy, placebo-controlled, parallel group, multi-

dose study to assess if monthly subcutaneous administration of TEV-48125 vs placebo is a safe and effective prevention in chronic migraine.

A total of 264 patients (both sexes, 18-65 years) were randomly assigned to 3 groups (1:1:1, stratified by sex and use of concomitant preventive drugs): placebo (n. 89) or two different regimens of TEV-48125 administration, subcutaneously, every 28 days for 12 weeks (three times). The first TEV-48125 regimen was the 675/225 mg (n. 88): patients were treated with 675mg the first time and 225mg the second and third times. The second TEV-48125 regimen was the 900mg (n. 87): patients received this dose three times during the 12-week treatment. Patients compiled an electronic diary on a daily basis. The primary efficacy endpoint was the change in the number of headache hours in weeks 9-12 of treatment vs baseline. Additional primary endpoints were safety and tolerability of treatment, measured as AEs over the same period. The secondary efficacy endpoint was the change in the number of moderate-severe headache days in weeks 9-12 relative to baseline.

At weeks 9-12 compared to baseline, while in the placebo group the mean change in the number of headache hours was -37.10 ± 79.44, in the 675/225mg group it was -59.84 ± 80.38 and in the 900mg group it was -67.51 ± 79.37. The LSM difference in the reduction of headache-hours between placebo and active treatment groups was -22.74 hours for the 675/225mg dose and -30.41 hours for the 900mg dose ($p<0.04$ and $p<0.006$, respectively).

AEs occurred in 40% of the placebo patients vs 53% and 47% of the 675/225mg and 900mg TEV-48125 groups, respectively. Adverse events judged as treatment-related were 17% in placebo, 29% in 675/225mg and 32% in the 900mg active groups, respectively; in most cases these were mild injection-site pain and pruritus. No serious treatment-related AEs occurred; blood pressure or other vital signs did not undergo significant modifications. The reduction of the number of moderate-severe headache days from baseline (secondary endpoint) was 4.7 ± 6.0 for placebo, 6.6 ± 6.0 for 675/225 and 6.5 ± 5.6 for 900mg active regimens. A post-hoc analysis showed

that 34% of the patients receiving the low TEV-48125 dose and 31% of those receiving the high dose presented over 75% reduction of migraine days throughout the study period [90]. Here again the authors concluded that subcutaneous injection of TEV-48125 every 28 days is effective and well tolerated.

All these positive results on both safety and efficacy with the compound prompted the development of *phase 3* studies. A phase 3 trial (NCT02621931) is already underway: a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing efficacy and safety of 2 dose regimens of subcutaneous TEV-48125 vs placebo for preventative treatment of chronic migraine which plans to recruit 1020 patients (both sexes, 18-70 years), to be completed in October 2017.

AMG334 (Table 4)

This mAb, developed by Amgen (now in partnership with Novartis, as announced in September 2015) is targeted against the CGRP receptor rather than the free peptide, in contrast to the previously described antibodies. It is the mAb in the earliest phases of development, but the trials performed so far are showing promising results.

A *phase 1* study was completed in July 2014 (NCT01723514). This was a randomized, double-blind, placebo-controlled, ascending multiple-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG334 in healthy subjects and in migraine patients (48 subjects recruited, 18-55 years).

A further *phase 1* study (NCT02542605) has recently been started (November 2015) and should be completed in October 2016. This is a randomized, parallel-group, double-blind, placebo-controlled, single dose study to evaluate the blockade of CGRP receptor by AMG334 in preventing PACAP-38 induced migraine-like attacks in migraine patients (with ≥ 1 and ≤ 5 migraine days per month). It plans to recruit 42 patients of both sexes (18-45 years).

The molecule is also currently being tested in *phase 2* studies for episodic and chronic migraine [http://www.prnewswire.com/news-releases/amgen-presents-first-phase-2-data-for-amg-334-in-the-prevention-of-episodic-migraine-300084005.html]. In particular, two phase 2 trials are underway.

The first trial (NCT01952574)(https://clinicaltrials.gov/ct2/show/NCT01952574), designed to evaluate efficacy and safety of AMG334 in migraine prevention in patients with episodic migraine (4-14 monthly migraine days), is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study of 12 weeks, which will be followed by an open-label extension phase of up to 256 weeks, planned to be completed in March 2020, to assess the long-term safety of the antibody. It has been primarily designed to assess the effects of AMG334 vs placebo on the change from baseline in monthly migraine days. The first results of this study were presented at the 17th congress of the International Headache Society in Valencia, Spain, May 2015. From Aug 6, 2013, to June 30, 2014, the study involved 483 patients (both sexes, 18-60 years) recruited at 59 headache and clinical research centres in North America and Europe. They were randomized to receive subcutaneous monthly placebo (n. 160) or AMG334 (7mg, 21mg or 70mg)(n. 108, n.108, n.107) in a 3:2:2:2 ratio. The change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase represented the primary endpoint of the study. At baseline, mean monthly migraine days were 8.7. Patients receiving the 70mg dose had a reduction of 3.4 days of migraine vs the 2.28 reduction of migraine days observed with placebo; the difference was significant. Secondary endpoints were: a 50% responder rate, monthly migraine attacks, safety and tolerability of the drugs (adverse events, clinical laboratory values, vital signs, and anti-AMG 334 antibodies were safety endpoints). AMG334 vs placebo showed a statistically significant increase in the 50% responder rate (47% vs 30%). In patients taking the 70mg dose as compared to placebo, a statistically significant reduction was also observed of monthly headache days (-3.54 vs -2.39) and monthly migraine-specific medication

use days (-1.64 vs -0.69). The decrease in monthly migraine days with the 7mg and the 21mg doses did not differ significantly from that observed with placebo. Tolerability of AMG334 was similar to placebo for all doses. Adverse events occurred in 82 (54%) patients of the placebo group, 54 (50%) patients in the AMG334 7mg group, 54 (51%) patients in the AMG334 21mg group, and 57 (54%) patients in the AMG334 70mg group. Frequently observed adverse events were nasopharyngitis, fatigue, influenza, joint and back pain. One patient in the AMG334 7mg group reported a ruptured ovarian cyst and one patient in the AMG334 70mg group had migraine and vertigo; in both cases the events were judged to be unrelated to AMG334 treatment. Neutralising antibodies were found in nine (3%) of 317 patients, but no evident association could be found between patients with positive anti-AMG 334 antibodies and adverse events [91,92].

The second trial (NCT02066415), designed to evaluate efficacy and safety of AMG334 in chronic migraine prevention, is multicenter, randomized, double-blind, placebo-controlled, which enrolled 667 patients of both sexes (18-65 yrs) randomized to receive either placebo, or one of two AMG334 subcutaneous doses every month for the duration of 12-week double-blind treatment phase. A safety follow-up visit will also be performed.

The primary outcome measure is the change in monthly migraine days from baseline in the last 4 weeks of the 12-week double-blind treatment phase. Secondary outcomes measures are: (a) proportion of patients experiencing at least a 50% reduction from baseline of monthly migraine days; (b) change in monthly acute migraine-specific medication treatment days; (c) change in monthly cumulative hours of headache. The study should be completed in April 2016.

A further *phase 2* study (NCT02174861) is being carried out to assess the long-term safety and efficacy of AMG334 in chronic migraine prevention. This is a multicenter

open-label extension study (OLE) with primary outcome measure represented by subject incidence of adverse events (time frame of 13 months*). Secondary outcome measures are: (a) change in monthly migraine days from baseline (*); (b) at least 50% reduction from baseline in monthly migraine days (*); (c) change in monthly acute migraine-specific medication treatment days from baseline; d) change in monthly cumulative hours of headache from baseline (*). Initiated in June 2014, it should be completed in May 2017, enrolling n. 612 adult patients of both sexes (18-66 years). All patients will receive AMG334 periodically for 13 months followed by a safety follow-up visit. Patients who complete the 12-week double-blind treatment phase and meet all the present study eligibility criteria will be included, with enrolment occurring within 14 days after the week 12 visit of the parent study.

Phase 3 trials are also underway, with first data expected in 2017.

A first *phase 3* trial (NCT02483585) is the ARISE, a randomized, double-blind, placebo-controlled study of 12 weeks followed by a 28-week open-label treatment phase. It aims to evaluate the effect of AMG334 vs placebo on the change from baseline in monthly migraine days, in episodic migraine. Currently recruiting participants, it started in June 2015 and should be completed in March 2017. The study plans to enroll 540 patients of both sexes (18-65 years) with a history of episodic migraine (≥ 4 to < 15 migraine days per month) with or without aura for $\geq$ 12 months. They will be randomized 1:1 to AMG334 or placebo, which will be administered double-blind over 12 weeks, while open-label AMG 334 will be given during 28 weeks. AMG334 doses are fixed and will not be adjusted individually in the course of the study.

The primary outcome measure is the change from baseline in mean monthly migraine days (considering completion of the double-blind treatment phase at month 3*). Secondary outcome measures are: (a) proportion of patients with at least a 50% reduction from baseline of monthly migraine days (*); (b) change from baseline in

monthly acute migraine-specific medication treatment days (*); (c) change from baseline in physical impairment, as evaluated through Migraine Physical Function Impact Diary (MPFID) (*); (d) change from baseline in impact on everyday activities, as evaluated through MPFID (*).

Another ongoing *phase 3* trial (NCT02456740) is STRIVE, evaluating efficacy and safety of AMG334 in migraine prevention (July 2015-June 2017). The effect of AMG334 vs placebo will be evaluated on the change from baseline in monthly migraine days in 955 recruited patients of both sexes. It is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study followed by active-treatment phase. Adults with one-year history of episodic migraine and not receiving migraine prophylactic medication will be randomized to one of two AMG334 treatment groups or a placebo treatment group during the double-blind treatment phase.

Critical considerations and Conclusions

The numerous studies so far conducted with the available anti-CGRP monoclonal antibodies have shown satisfactory safety and efficacy outcomes in migraine prevention.

Regarding safety, a major worry with compounds that antagonize CGRP effects is linked to the block of the vasodilating action of the peptide, with possible consequences at cardiovascular level, such as inhibition of cardio-protective mechanisms during ischemia or the occurrence of medication-induced hypertension [16]. As already reported, however, pre-clinical studies in monkeys and rats demonstrated that anti-CGRP mAbs, administered in a way to determine a long-term inhibition of CGRP, do not cause significant electrocardiogram or hemodynamic changes [12,85,87,93] and their administration in humans – both healthy subjects and

patients – at wide ranges of dosage does not produce relevant cardiovascular side effects or laboratory abnormalities [86]. No other off-target impairment, such as the liver toxicity observed with GCRP antagonists, has furthermore been recorded.

Regarding efficacy, the global outcome response in migraine prevention is undoubtedly significant in the treated patients, even in the challenging forms of high frequency episodic and chronic migraine, where it has to be acknowledged that not all patients are responders. Nevertheless, in a recently published article, Pasqual [94] underlines how, in the trials with TEV-48125, 45% of patients who received high doses and 47% of those receiving low doses did not meet the main goal of a 50% reduction of moderate or severe headache-days, normally regarded as the basic positive outcome of a preventative regimen [89,90]. Among the reasons for the apparent lack of satisfactory effects of CGRP antibodies in some patients, the author considers the multifactorial nature of migraine pathophysiology, with other molecules in addition to CGRP (e.g., vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, glutamate) involved in pain generation [95]. Simply acting upon CGRP – in spite of the crucial role played by this peptide - might thus not be sufficient to provide a clinically significant relief in certain patients.

For efficacy but also safety assessment, the importance of longer periods of prophylaxis with anti-CGRP mAbs in further trials also needs to be stressed. Efficacy could be challenged by the development of autoantibodies against these CGRP antibodies; the fully humanized characteristics of the employed mAbs fortunately minimize the immunologic liability, however this possibility cannot be excluded with prolonged treatment regimens [86]. Central and systemic adverse events could also manifest in the long run. Although it is true, in fact, that these large molecules do not cross the blood-brain barrier in normal conditions, this crossing could potentially take place if the barrier is no longer intact, as could happen during the headache attack, an issue currently under discussion [96]. The occurrence of adverse side effects due to

chronically depleting systemic levels of CGRP should also be ruled out in long-term treatment regimens.

Despite these critical considerations, the overall profile of anti-CGRP mAbs so far shown can be regarded as highly favourable. Even the potential disadvantage, for patients' compliance, of their parenteral administration, is compensated by the low frequency of delivery (once a month-quarterly vs daily oral intake of most other preventative drugs) [17]. In addition, the new parenteral formulations for self-administration currently being developed will hopefully facilitate a future larger scale application.

With further studies addressing/ruling out most of the described concerns, in the forthcoming years anti-CGRP mAbs will probably equal, in preventative treatment, the revolution introduced by triptans in acute treatment of migraine. More than 30 years after the genial intuition and the first studies published by the man who can be considered the father of CGRP on headache, Lars Edvinsson, the path he traced then is today a highway that could revolutionize the life of almost one billion migraine patients [9,97].

References

1.Global Burden of Disease Study 2013 Collaborators (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (published online June 8, 2015 at http://dx.doi.org/10.1016/S0140- 6736(15)60692-4)

2. Pieroni A, Caso V, Cittadini E, Hamam M, Paciaroni M (2012) A case of typical headache with an atypical diagnosis. Intern Emerg Med 7 Suppl 2:S121-123

3. Steiner TJ, Birbeck GL, Jensen RH, Katsarava Z, Stovner LJ, Martelletti P (2015) Headache disorders are third cause of disability worldwide. J Headache Pain 16:58

4. Giamberardino MA, Martelletti P (2015) Emerging drugs for migraine treatment. Expert Opin Emerg Drugs 20:137-147

5. Martelletti P (2015) The therapeutic armamentarium in migraine is quite elderly. Expert Opin Drug Metab Toxicol 11:175-177

6. Curto M, Lionetto L, Fazio F, Mitsikostas DD, Martelletti P 2015 Fathoming the kynurenine pathway in migraine: why understanding the enzymatic cascades is still critically important. Intern Emerg Med 10(4):413-421

7. Bigal ME, Walter S, Rapoport AM (2013) Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. Headache 53(8):1230-1244

8. Diener HC, Charles A, Goadsby PJ, Holle D (2015) New therapeutic approaches for the prevention and treatment of migraine. Lancet Neurol 14:1010-1022

9. Edvinsson L (2015) The Journey to Establish CGRP as a Migraine Target: A Retrospective View. Headache 55:1249-1255

10. Edvinsson L (2015) CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. Br J Clin Pharmacol 80:193-199

11. Karsan N, Goadsby PJ (2015) Calcitonin gene-related peptide and migraine. Curr Opin Neurol 28:250-254

12. Mitsikostas DD, Rapoport AM (2015) New players in the preventive treatment of migraine. MC Med 13:279

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

14. Sabato D, Lionetto L, Martelletti P (2015) The therapeutic potential of novel anti-migraine acute therapies. Expert Opin Investig Drugs 24:141-144

15. Schuster NM, Vollbracht S, Rapoport AM (2015) Emerging treatments for the primary headache disorders. Neurol Sci 36:109-113

16. Wrobel Goldberg S, Silberstein SD (2015) Targeting CGRP: A New Era for Migraine Treatment. CNS Drugs 29:443-452

17. Bigal ME, Walter S, Rapoport AM (2015) Therapeutic antibodies against CGRP or its receptor. Br J Clin Pharmacol 79:886-895

18. Bigal ME, Walter S (2014) Monoclonal antibodies for migraine: preventing calcitonin gene-related peptide activity. CNS Drugs 28:389-399

19. Edvinsson L, Warfvinge K (2013) CGRP receptor antagonism and migraine therapy. Curr Protein Pept Sci 14(5):386-392

20.Negro A, Lionetto L, Simmaco M, Martelletti P (2012) CGRP receptor antagonists: an expanding drug class for acute migraine? Expert Opin Investig Drugs 21:807-818

21.Silberstein SD (2013) Emerging target-based paradigms to prevent and treat migraine. Clin Pharmacol Ther 93:78-85

22.Silberstein SD (2015) Therapeutic monoclonal antibodies for migraine. US Neurol US Neurology 11(1):64–65

23.Silberstein S, Lenz R, Xu C (2015) Therapeutic Monoclonal Antibodies: What Headache Specialists Need to Know. Headache 55:1171-1182

24.Headache Classification of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:627-808

25.Manzoni GC, Torelli P (2010) Epidemiological classification and social impact of chronic headache. Intern Emerg Med 5(Suppl 1):S1-S5

26.Negro A, D'Alonzo L, Martelletti P (2010) Chronic migraine: comorbidities, risk factors, and rehabilitation. Intern Emerg Med 5 (Suppl 1):S13-S19

27.Farinelli I, Dionisi I, Martelletti P (2011) Rehabilitating chronic migraine complicated by medication overuse headaches: how can we prevent migraine relapse? Intern Emerg Med 6(1):23-28.

28.Geppetti P, De Cesaris F, Nicoletti P, Benemei S (2010) Chronic headaches and medication overuse. Intern Emerg Med 5 (Suppl 1):S7-S11

29.Giamberardino MA, Mitsikostas DD, Martelletti P (2015) Update on Medication-Overuse Headache and Its Treatment. Curr Treat Options Neurol 17:368

30.Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, Savi L, Pini LA, Sances G, Santoro P, Zanchin G, Omboni S, Ferrari MD, Brighina F, Fierro B (2011) A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. J Headache Pain 12:361-8

31. Loder E (2010) Triptan therapy in migraine. N Engl J Med 363:63–70

32. Ungprasert P (2016) NSAIDs and cardiovascular disease: time to say no to diclofenac. Intern Emerg Med 11(1):1-2

33. Affaitati G, Costantini R, Fabrizio A, Lapenna D, Tafuri E, Giamberardino MA (2011) Effects of treatment of peripheral pain generators in fibromyalgia patients. Eur J Pain 15(1):61-69

34. Affaitati G, Fabrizio A, Savini A, Lerza R, Tafuri E, Costantini R, Lapenna D, Giamberardino MA (2009) A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: evaluation of pain and somatic pain thresholds. Clin Ther 31(4):705-720

35.Giamberardino MA, Affaitati G, Costantini R (2006) Chapter 24 Referred pain from internal organs. Handb Clin Neurol 81:343-361

36.Giamberardino MA, Affaitati G, Costantini R (2010) Visceral referred pain. J Musculoske Pain 18:403-410

37.Giamberardino MA, Affaitati G, Fabrizio A, Costantini R (2011) Myofascial pain syndromes and their evaluation. Best Pract Res Clin Rheumatol 25:185-198

38.Giamberardino MA, Affaitati G, Fabrizio A, Costantini R (2011) Effects of treatment of myofascial trigger points on the pain of fibromyalgia. Curr Pain Headache Rep 15:393-399

39.Giamberardino MA, Affaitati G, Martelletti P, Tana C, Negro A, Lapenna D, Curto M, Schiavone C, Stellin L, Cipollone F, Costantini R (2016) Impact of migraine on fibromyalgia symptoms. J Headache Pain doi: 10.1186/s10194-016-0619-8. Epub 2016 Mar 22

40.Giamberardino MA, Costantini R, Affaitati G, Fabrizio A, Lapenna D, Tafuri E, Mezzetti A (2010) Viscero-visceral hyperalgesia: characterization in different clinical models. Pain 151(2):307-322

41.Giamberardino MA, Tafuri E, Savini A, Fabrizio A, Affaitati G, Lerza R, Di Ianni L, Lapenna D, Mezzetti A (2007) Contribution of myofascial trigger points to migraine symptoms. J Pain 8:869-878

42.Giamberardino MA, Tana C, Costantini R (2014) Pain thresholds in women with chronic pelvic pain. Curr Opin Obstet Gynecol 26:253-259

43.Tana C, Santilli F, Martelletti P, di Vincenzo A, Cipollone F, Davì G, Giamberardino MA (2015) Correlation between Migraine Severity and Cholesterol Levels. Pain Pract 15:662-670

44.Tana C, Tafuri E, Tana M, Martelletti P, Negro A, Affaitati G, Fabrizio A, Costantini R, Mezzetti A, Giamberardino MA (2013) New insights into the cardiovascular risk of migraine and the role of white matter hyperintensities: is gold all that glitters? J Headache Pain 1;14:9

45. Bagnato F, Good J (2016) The Use of Antiepileptics in Migraine Prophylaxis. Headache 56(3): 603-615

46.Goadsby PJ (2009) The vascular theory of migraine -- a great story wrecked by the facts. Brain 132:6-7

47.Silberstein SD (2004) Migraine pathophysiology and its clinical implications. Cephalalgia 24 (Suppl 2):2-7

48.Durham PL, Calcitonin Gene-Related Peptide (CGRP) and Migraine (2006) Headache 46 (Suppl 1): S3–S8

49.Messlinger K (2009) Migraine: Where and how does the pain originate? Exp Brain Res. 196:179–193

50.Goadsby PJ (2007) Recent advances in understanding migraine mechanisms, molecules and therapeutics. Trends Mol Med 13:39-44

51.Cao T, Pinter E, Al Rashed S, Gerard N, Hoult JR, Brain SD (2000) Neurokinin-1 receptor agonists are involved in mediating neutrophil accumulation in the inflamed,

but not normal, cutaneous microvasculature: an in vivo study using neurokinin-1 receptor knockout mice. J Immunol 164: 5424–5429

52.Markowitz S, Saito K, Moskowitz MA (1987) Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. J Neurosci 7:4129–4136

53.Raddant AC, Russo AF (2011). Calcitonin gene-related peptide in migraine: Intersection of peripheral inflammation and central modulation. Expert Reviews Molec Med 13:e36

54.Akerman S, Holland PR, Goadsby PJ (2011) Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 12:570-84

55.Rosenfeld MG, Mermod JJ, Amara SG, Swanson LW, Sawchenko PE, Rivier J, Vale WW, Evans RM (1983) Production of a novel neuropeptide encoded by the calcitonin gene via tissue specific RNA processing. Nature 304:129–135

56.Eftekhari S, Salvatore CA, Johansson S, Chen TB, Zeng Z, Edvinsson L (2015) Localization of CGRP, CGRP receptor, PACAP and glutamate in trigeminal ganglion. Relation to the bloodbrain barrier. Brain Res 1600:93–109

57.Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L (2013) Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J Pain 14:1289–1303

58.Mulderry PK, Ghatei MA, Bishop AE, Allen YS, Polak JM, Bloom SR (1985) Distribution and chromatographic characterisation of CGRP-like immunoreactivity in the brain and gut of the rat. Regul Pept 12: 133–143

59.Wimalawansa SJ, Morris HR, Etienne A, Blench I, Panico M, MacIntyre I (1990) Isolation, purification and characterization of beta-hCGRP from human spinal cord. Biochem Biophys Res Commun 167: 993–1000

60.Russell FA, King R, Smillie S-J, Kodji X (2014) Calcitonin Gene-Related Peptide: Physiology and Pathophysiology. Brain Physiological Reviews 94:1099-1142

61.Barwell J, Wootten D, Simms J, Hay DL, Poyner DR (2012) RAMPs and CGRP receptors. Adv Exp Med Biol 744:13-24.

62.Marvizón JC, Pérez OA, Song B, Chen W, Bunnett NW, Grady EF, Todd AJ (2007) Calcitonin receptor-like receptor and receptor activity modifying protein 1 in

the rat dorsal horn: localization in glutamatergic presynaptic terminals containing opioids and adrenergic alpha2C receptors. Neuroscience 148:250–265

63.Oku R, Satoh M, Fujii N, Otaka A, Yajima H, Takagi H (1987) Calcitonin gene-related peptide promotes mechanical nociception by potentiating release of substance P from the spinal dorsal horn in rats. Brain Res 403:350–354

64.Seybold VS (2009) The role of peptides in central sensitization. Handb Exp Pharmacol 194:451–491

65.Walker CS, Hay DL (2013) CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amylin receptors? Br J Pharmacol 170(7):1293-1307.

66.Gallai V, Sarchielli P, Floridi A, Franceschini M, Codini M, Glioti G, Trequattrini A, Palumbo R (1995) Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally. Cephalalgia 15: 384–390

67.Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33: 48–56

68.Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28: 183–187

69.Juhasz G, Zsombok T, Jakab B, Nemeth J, Szolcsanyi J, Bagdy G (2005) Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. Cephalalgia 25:179–183

70.Sarchielli P, Alberti A, Codini M, Floridi A, Gallai V (2000) Nitric oxide metabolites, prostaglandins and trigeminal vasoactive peptides in internal jugular vein blood during spontaneous migraine attacks. Cephalalgia 20: 907–918

71.Asghar MS, Hansen AE, Amin FM, van der Geest RJ, Koning P, Larsson HB, Olesen J, Ashina M (2011) Evidence for a vascular factor in migraine. Ann Neurol 4:635–645

72.Hansen JM, Hauge AW, Olesen J, Ashina M (2010) Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 30:1179–1186

73.Lassen L, Haderslev P, Jacobsen V, Iversen H, Sperling B, Olesen J (2002) CGRP may play a causative role in migraine. Cephalalgia 2:54–61

74.Lassen LH, Jacobsen VB, Haderslev PA, Sperling B, Iversen HK, Olesen J, Tfelt-Hansen P (2008) Involvement of calcitonin gene-related peptide in migraine: regional cerebral blood flow and blood flow velocity in migraine patients. J Headache Pain 9: 151–157

75.Petersen KA, Lassen LH, Birk S, Lesko L, Olesen J (2005) BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. Clin Pharmacol Ther 3:202–213

76.Cernuda-Morollón E, Larrosa D, Ramón C, Vega J, Martínez-Camblor P, Pascual J (2013) Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology 81:1191–1196

77.Strassman AM, Raymond SA, Burstein R (1996) Sensitization of meningeal sensory neurons and the origin of headaches. Nature 384:560–564

78.Recober A, Kuburas A, Zhang Z, Wemmie JA, Anderson MG, Russo AF (2009) Role of calcitonin gene-related peptide in light-aversive behavior: implications for migraine. J Neurosci 29:8798–8804

79.Hougaard A, Tfelt-Hansen P (2015) Review of dose-response curves for acute antimigraine drugs: triptans, 5-HT1F agonists and CGRP antagonists. Expert Opin Drug Metab Toxicol 11:1409-1418

80.Neal F, Arnold J, Rossant CJ, Podichetty S, Lowne D, Dobson C, Wilkinson T, Colley C, Howes R, Vaughan TJ (2016) Isolation of Potent CGRP Neutralizing Antibodies Using Four Simple Assays. J Biomol Screen 21(1):24-34

81.Vermeersch S, Benschop RJ, Van Hecken A, Monteith D, Wroblewski VJ, Grayzel D, de Hoon J, Collins EC (2015) Translational Pharmacodynamics of Calcitonin Gene-Related Peptide Monoclonal Antibody LY2951742 in a Capsaicin-Induced Dermal Blood Flow Model. J Pharmacol Exp Ther 354:350-357

82.Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS (2014b) Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin

gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 13:885-892

83.Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J (2014) ALD403 study investigators. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 13:1100-1107

84.Goadsby PJ, Dodick DW, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J (2015) Randomized, double-blind, placebo-controlled trial of ALD403, an anti-CGRP antibody in the prevention of frequent episodic migraine. In: 17th Congress of the International Headache Society, Valencia, 2015.

85.Walter S, Alibhoy A, Escandon R, Bigal ME (2014) Evaluation of cardiovascular parameters in cynomolgus monkeys following IV administration of LBR-101, a monoclonal antibody against calcitonin gene-related peptide. MAbs 6:871–878

86.Bigal ME, Escandon R, Bronson M, Walter S, Sudworth M, Huggins JP, Garzone P (2013) Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: Results of the Phase 1 program. Cephalalgia 34:483-492

87.Bigal ME, Walter S, Bronson M, Alibhoy A, Escandon R (2014) Cardiovascular and hemodynamic parameters in women following prolonged CGRP inhibition using LBR-101, a monoclonal antibody against CGRP. Cephalalgia 34:968–976

88.Walter S, Bigal ME (2015) TEV-48125: a review of a monoclonal CGRP antibody in development for the preventive treatment of migraine. Curr Pain Headache Rep 19:6.

89.Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, Loupe PS, Burstein R, Newman LC, Lipton RB (2015a) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14:1081-1090

90.Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, Burstein R, Loupe PS, Ma Y, Yang R, Silberstein SD (2015b) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a

multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14:1091-1100

91.Lenz R, Silberstein S, Dodick D, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Sun H (2015) Results of a randomized, double-blind, placebo-controlled, phase 2 study to evaluate the efficacy and safety of AMG 334 for the prevention of episodic migraine. In: 17th Congress of the International Headache Society, Valencia, 2015.

92.Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Lenz R (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 15(4):382-390.

93.Zeller J, Poulsen KT, Sutton JE, Abdiche YN, Collier S, Chopra R, Garcia CA, Pons J, Rosenthal A, Shelton DL (2008) CGRP function-blocking antibodies inhibit neurogenic vasodilatation without affecting heart rate or arterial blood pressure in the rat. Br J Pharmacol 155:1093–1103

94.Pascual J (2015) CGRP antibodies: the Holy Grail for migraine prevention? Lancet Neurol 14:1066-1067

95.Gazerani P, Cairns BE (2013) New insight in migraine pathogenesis: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) in the circulation after sumatriptan. Scandinavian Journal of Pain 4: 208–210

96.Tfelt-Hansen P (2015) Site of effect of LY2951742 for migraine prophylaxis. Lancet Neurol 14:31–32

97.Edvinsson L, Ekman R, Uddman R, Kingman TA, McCulloch J (1984) Calcitonin gene related peptide (CGRP)-containing perivascular fibres in brain vessels: Localization and its effects in vitro and in situ. Presented at INSERM Symposium no.25: Regulatory Peptides in Digestive, Nervous and Endocrine Systems. Paris: CNRS; 1984

Conflict of interest statement

In the past 3 years:
Maria Adele Giamberardino received research funding from Epitech Group, honoraria for participation in Advisory Board Meeting from Bayer, and participation in conferences from IBSA Institute Biochimique and Helsinn Healthcare, and Royalties from IASP Press.

Giannapia Affaitati received honoraria for participation in conferences from Helsinn Healthcare and IBSA Institute Biochimique.

Raffaele Costantini declares no conflict of interest.

Martina Curto declares no conflict of interest.

Andrea Negro received travel grants and participated to the Advisory Boards of Allergan, Electrocore and Medtronic.

Paolo Martelletti received travel grants, onoraria consultancy and participated to the Advisory Boards of Allergan, Bayer, Medtronic, Mylan and Teva.

Authors' contribution

MAG and PM participated in the search of the background literature, conception and writing of the paper.

GA, MC, RC and AN participated in the search of the background literature and writing of the paper.

All Authors approved

Table 1: Completed and ongoing clinical trials with LY2951742 (target: CGRP)

Study Protocol and Completion date	Treated condition	Population size active vs placebo	Modality of administration	Primary efficacy outcome	Adverse Events (AEs)
NCT01625988 phase 2a randomized double- blind placebo-controlled *September 2013*	Episodic migraine 4-14 days/month	218 (108 vs 110)	150mg sc once every 2 weeks for 12 weeks	week 12 vs basis decrease in migraine days: active vs placebo ($p<0.004$)	Erythema, abdominal pain, respiratory infection: more frequent in active vs placebo
NCT02163993 phase 2b randomized double- blind placebo-controlled dose-ranging *August 2015*	Episodic migraine 4-14 days/month	410 (273 vs 137)	5,50,120,300mg sc once every 28 days for 12 weeks	week 12 vs basis decrease in migraine days: 120mg vs placebo ($p<0.005$)	Injection site pain, nasopharyngitis, respiratory infection, nausea, dysmenorrhea: more frequent in active vs placebo
NCT02614196 phase 3 randomized double- blind placebo-controlled efficacy study *June 2017*	Episodic migraine	825	2 active doses sc once a month for 6 months	month 6 vs basis: change in number of monthly migraine days	----------
NCT02614287 phase 3 long-term open-label safety study *September 2017*	Episodic migraine Chronic migraine	250	2 active doses sc once a month for 12 months	percentage of participants who discontinue	_____
NCT02614261 phase 3 randomized double-blind placebo-controlled efficacy study *April 2018*	Chronic migraine	825	2 active doses sc once a month for 3 months	month 3 vs basis: change in number of monthly migraine days	_____

Table 2: Completed and ongoing clinical trials with ALD403 (target: CGRP)

Study Protocol and Completion date	Treated condition	Population size active vs placebo	Modality of administration	Primary efficacy outcome	Adverse Events (AEs)
NCT01772524 phase 2 randomized double- blind placebo-controlled *February 2014*	Frequent episodic migraine (5-14 days/month)	163 (81 vs 82)	1000mg iv once	5-8 weeks vs basis decrease in migraine days: active vs placebo ($p<0.04$)	Respiratory and urinary infection, fatigue, back pain, joint pain, nausea, vomiting
NCT02275117 phase 2b randomized double- blind placebo-controlled dose-ranging efficacy, safety and pharmacokinetics *November 2016*	Chronic migraine	600	4 active doses iv once	week 12 vs basis decrease in migraine days:	Evaluated in 49 weeks
NCT02559895 phase 3 randomized double- blind placebo-controlled dose-ranging efficacy and safety study *June 2017*	Frequent episodic migraine	600	3 active doses iv once	responder rate in 12 weeks	Evaluated in 32 weeks

Table 3: Completed and ongoing clinical trials with LBR-101 / TEV-48125 (target: CGRP)

Study Protocol and Completion date	Treated condition	Population size active vs placebo	Modality of administration	Primary efficacy outcome	Adverse Events (AEs)
NCT02025556 phase 2 randomized double- blind placebo-controlled *March 2015*	Frequent episodic migraine 8-14 days/month	297 (96,97 vs 104)	225, 675mg sc once every 28 days for 12 weeks	weeks 9-12 vs basis decrease in migraine days: active vs placebo ($p<0.0001$) (both doses)	Dizziness, tooth abscess, dry mouth, ECG changes
NCT02021773 phase 2b randomized double- blind double-dummy placebo-controlled multi-dose *March 2015*	Chronic migraine	264 (175 vs 89)	675/225mg and 900mg sc once every 28 days for 12 weeks	weeks 9-12 vs basis decrease in migraine hours: 65/225mg vs placebo ($p<0.04$) 900mg vs placebo ($p<0.006$)	Injection site pain, pruritus: more frequent in active vs placebo
NCT02621931 phase 3 randomized double- blind placebo-controlled efficacy and safety study *October 2017*	Chronic migraine	1020	2 active doses sc	week 12 vs basis: change in number of monthly migraine days	% of patients with AES in 12 weeks

Table 4: Completed and ongoing clinical trials with AMG334 (target: CGRP receptor)

Study Protocol and Completion date	Treated condition	Population size active vs placebo	Modality of administration	Primary efficacy outcome	Adverse Events (AEs)
NCT01952574 phase 2 randomized double- blind placebo-controlled *June 2014*	Episodic migraine 4-14 days/month	483 (108,108,107 vs 160)	7,21,70mg sc once every month for 12 weeks	week 9-12 vs basis decrease in migraine days: 70mg vs placebo ($p<0.03$)	Nasopharyngitis, fatigue, influenza, joint pain, back pain
NCT02066415 phase 2 randomized double-blind placebo-controlled *April 2016*	Chronic migraine	667	2 active doses sc one every month for 12 weeks	weeks 9-12 vs basis decrease in migraine days active vs placebo	_____
NCT02174861 phase 2 open-label extension study of NCT02066415 *May 2017*	Chronic migraine	612	Dose 2 of NCT02066415 sc periodically for 13 months	Primary outcome measure: subject incidence of adverse events	
NCT02483585 phase 3 randomized double-blind placebo-controlled *March 2017*	Episodic migraine 4-14 days/month	540	1 active dose sc periodically for 12 weeks	weeks 9-12 vs basis change in migraine days active vs placebo	_____
NCT02456740 phase 3 randomized double-blind placebo-controlled *February 2018*	Episodic migraine 4-14 days/month	852	2 active doses sc periodically for 24 weeks	24 weeks vs basis: change in number of monthly migraine days	_____