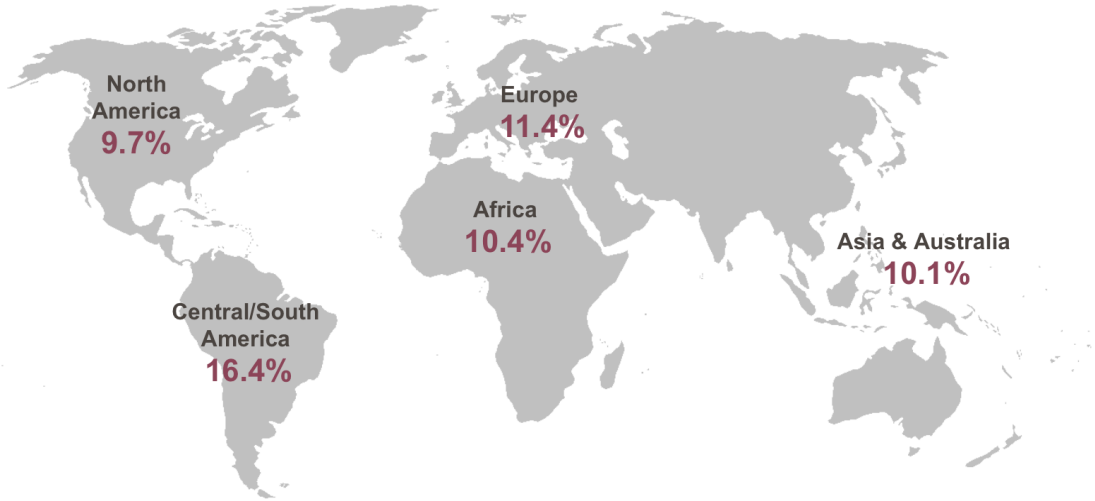

CONVEGNO REGIONALE SIN / SNO
Liguria - Piemonte e Valle d'Aosta
Ivrea, 6-7 dicembre 2019
Università infermieristica di Ivrea
TERZA SESSIONE
NEURO-NEWS: INNOVAZIONI DIAGNOSTICHE E TERAPEUTICHE IN NEUROLOGIA
LE NOVITÀ DELL'ULTIMO ANNO DA NON PERDERE
Moderatori: PAOLA CAVALLA, TIZIANA TASSINARI
Emicrania
MAURIZIO MAGGIO

IHS CLASSIFICATION ICHD-3

Primary headaches	**1.** Migraine, including: 1.1 Migraine without aura 1.2 Migraine with aura **2.** Tension-type headache, including: 2.1 Infrequent episodic tension-type headache 2.2 Frequent episodic tension-type headache 2.3 Chronic tension-type headache	**3.** Cluster headache and other trigeminal autonomic cephalalgias, including: 3.1 Cluster headache **4.** Other primary headaches
Secondary headaches	**5.** Headache attributed to head and/or neck trauma, including: 5.2 Chronic post-traumatic headache **6.** Headache attributed to cranial or cervical vascular disorder, including: 6.2.2 Headache attributed to subarachnoid haemorrhage 6.4.1 Headache attributed to giant cell arteritis **7.** Headache attributed to non-vascular intracranial disorder, including: 7.1.1 Headache attributed to idiopathic intracranial hypertension 7.4 Headache attributed to intracranial neoplasm **8.** Headache attributed to a substance or its withdrawal, including: 8.1.3 Carbon monoxide-induced headache 8.1.4 Alcohol-induced headache	**8.2** Medication-overuse headache 8.2.1 Ergotamine-overuse headache 8.2.2 Triptan-overuse headache 8.2.3 Analgesic-overuse headache **9.** Headache attributed to infection, including: 9.1 Headache attributed to intracranial infection **10.** Headache attributed to disorder of homoeostasis **11.** Headache or facial pain, attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures including: 11.2.1 Cervicogenic headache 11.3.1 Headache attributed to acute glaucoma **12.** Headache attributed to psychiatric disorder
Neuralgias and other headaches	**13.** Cranial neuralgias, central and primary facial pain and other headaches including: 13.1 Trigeminal neuralgia	**14.** Other headache, cranial neuralgia, central or primary facial pain

Globally >10% of population is estimated to suffer from migraine

Global prevalence of migraine[3]



Global prevalence:	Lifetime prevalence:	Migraine ranks among the
• Headache: 47%[1]	• Headache: 66%[1]	10 leading causes for
• Migraine: >10%[2,3]	• Migraine: 14%[9]	years lived with disability[2]

1 Stovner LJ, et al. Cephalalgia. 2007;27:193-210.
2. Vos T, et al. Lancet. 2016;388(10053):1545-1602.
3. Woldeamanuel YW, Cowan RP. J Neurol Sci. 2017;372:307-315.

Acute therapy- What we have: Triptans

- Introduced more than 25 years ago
- 5-HT 1B/1D receptor agonists
- Seven different Triptans
- Variety for route of delivery
  - Oral tablets or melts
  - Nasal spray
  - Subcutaneous injection

Issues with triptans

- Not effective in 30%
- Headache recurrence in up to 40% of patients
- Contraindications
  - High blood pressure, ischemic heart disease
  - Incidence of Heart attack or stroke in 1:1000000
- SE:
  - nausea, GI, ‘triptan chest’

Acute therapy: what is new

- Lasmiditan
  - Tablet
  - Migraine relief without vasoconstriction
  - 2 positive trials
    - Migraine freedom at 2 hours (32% Vs 15%)
  - Ongoing 3rd trial
  - Mild to moderate side effects

- CGRP antagonist

- Ubrogepant , remgepant : tablet

- Migraine relief without vasoconstriction

Preventive therapies: what we have!

- Tablets:
  - B-blockers
  - Topiramate
  - Amitriptyline
  - Candesartan
  - Pizotifen
  - Gabapentin
  - Valproate
  - Memantine

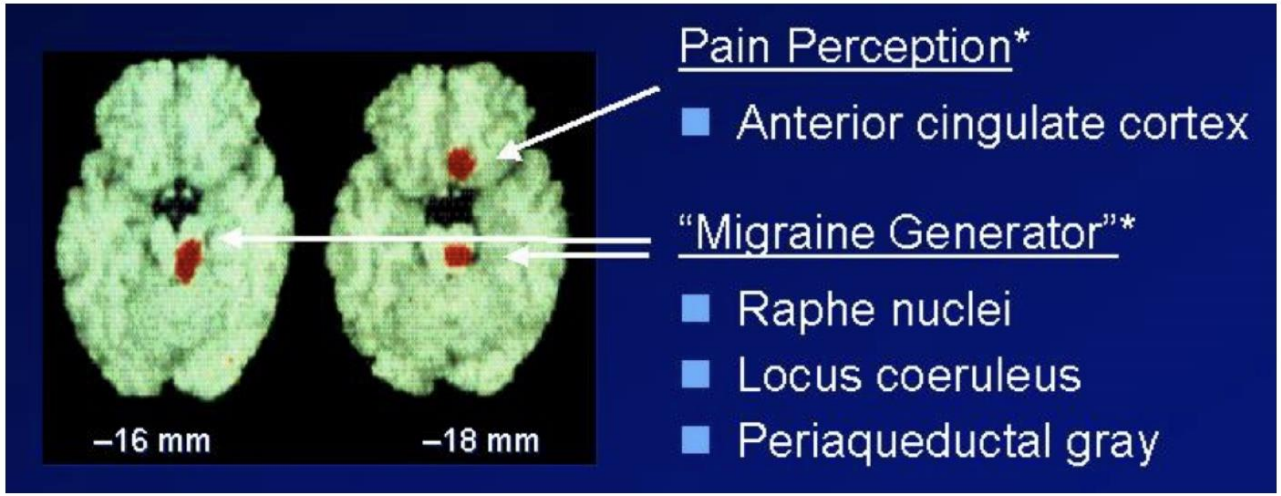
    Flunarizine
- Injections
  - Greater occipital nerve block
  - Botox

Starling AJ, et al. Cephalalgia. 2018;38:1038-

Migraine prevention: what is new!

- CGRP-mab
  - Erenumab
  - Galcanezumab
  - Fremenezumab
  - Eptinezumab
- CGRP antagonist
  - Gepants

Fisiopatologia dell'emicrania



- CNS activation dysfunction of brain stem pain and vascular control centers - the migraine generator in the pontine area will light up on PET scan

Fisiopatologia dell'emicrania

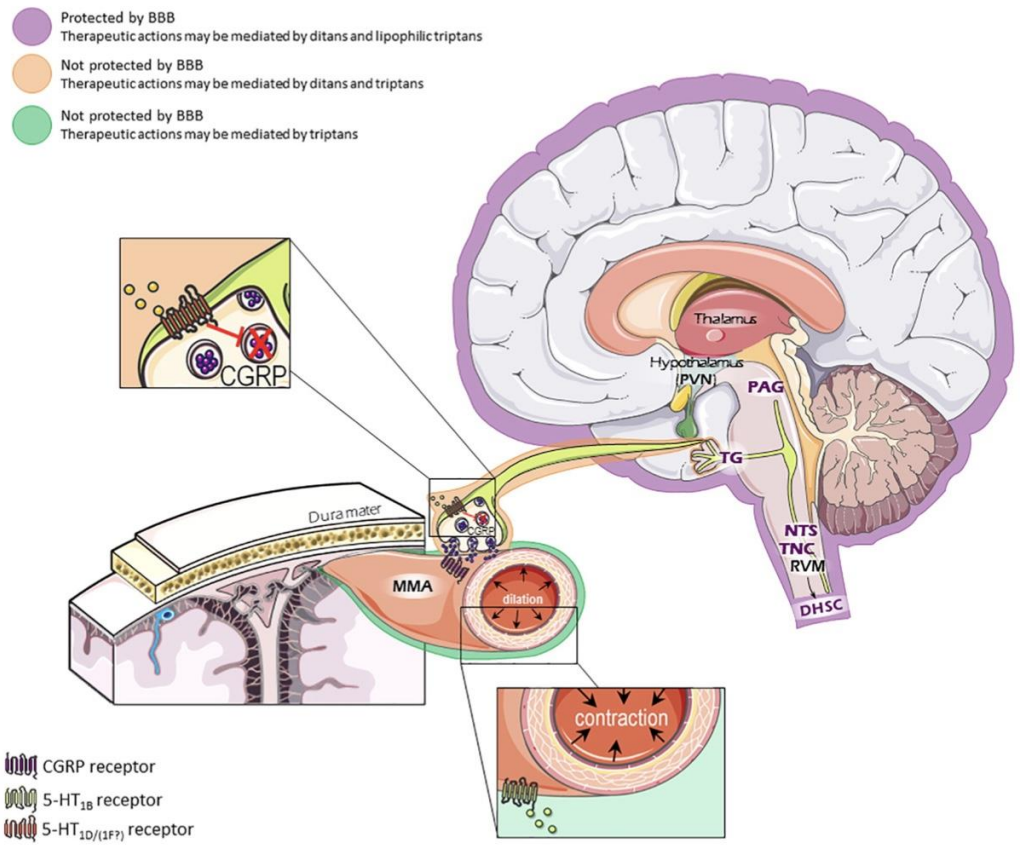
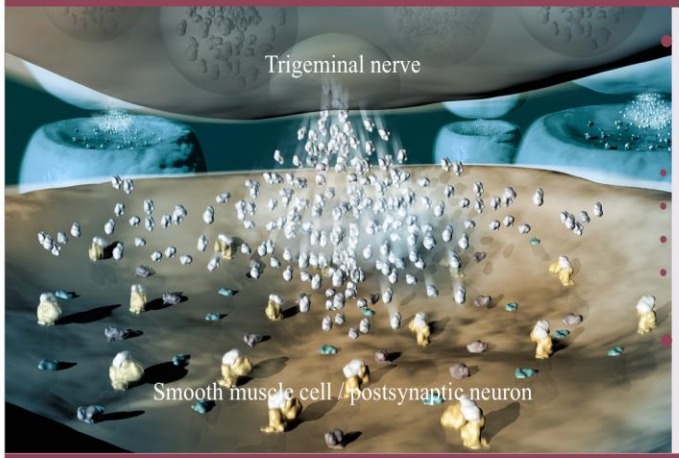


Fig. 3. Structures associated with migraine pathophysiology and/or treatment. The proposed therapeutic action of triptans is through the selective vasoconstriction of the MMA (green), as

Fisiopatologia dell'emicrania

Migraine pain starts with 'abnormal' activation of the TGVS

- The cause of migraine is unclear but involves abnormal activation of the TGVS1,2,3



TGVS activation causes release of various neuropeptides at the meninges:1,3

- Calcitonin
- CGRP
- Neurokinin A
- Substance P

These peptides can induce neurogenic inflammation2,4

- Inflammation and dysregulation contribute to a feed-forward loop, causing migraine5

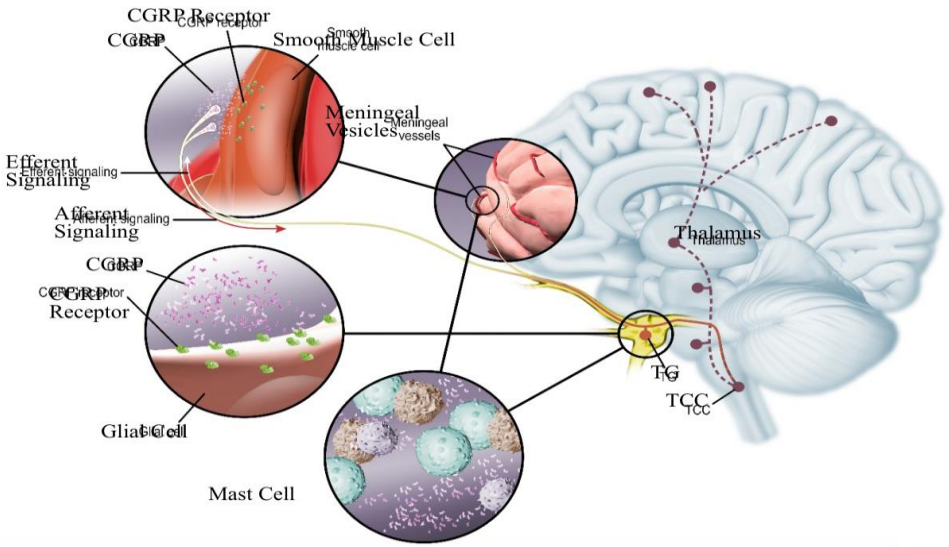
CGRP = calcitonin gene-related peptide; TGG = trigeminal ganglion; TGVS = trigeminovascular system.

1. Burgos-Vega C, et al. Prog Mol Biol Transl Sci. 2015;131:537-564.
2. Raddant AC, Russo AF. Expert Rev Mol Med. 2011;13:e36.
3. Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533-552.
4. Pietrobon D, Moskowitz MA. Annu Rev Physiol. 2013;75:365-391.
5. Demarquay G, Mauguière F. Headache. 2016;56:1418-1438.

Fisiopatologia dell'emicrania

CGRP Receptors in Sites That Are Important to Migraine Pathophysiology

- CGRP receptors are located both inside and outside of the blood–brain barrier1-3,a
- CGRP receptors are found in multiple areas2-5:
  - Trigeminal ganglion
  - Cerebral and meningeal vasculature
  - Brainstem (eg, TCC)
  - Brain (eg, thalamus)
- CGRP receptors are expressed on numerous cell types2-4,6:
  - Vascular smooth muscle cells
  - Neurons
  - Glial cells
  - Mast cells



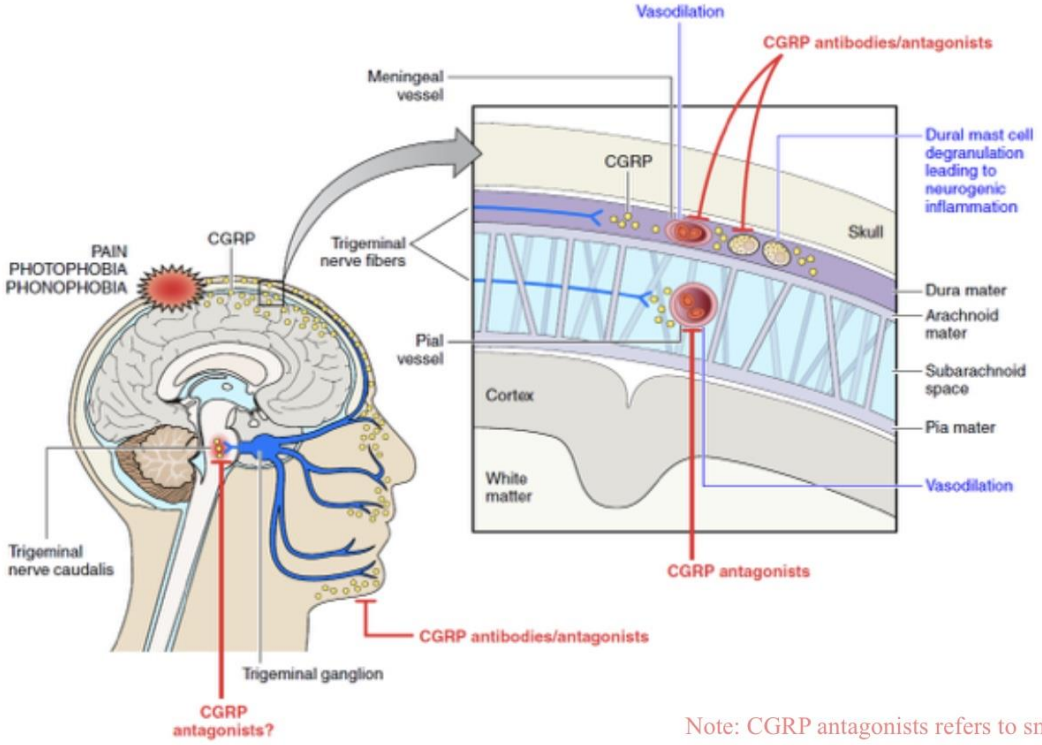
CGRP receptors are localized at several sites within the trigeminal pathway and brain regions involved in modulating trigeminal nociceptive signaling3,4

aCGRP receptor localization data are based on evidence of co-localization of the receptor components (RAMP1, CLR) and binding of CGRP receptor antagonists.2
CGRP may be expressed in additional brain regions in which CGRP receptor localization has not been established.7
CGRP = CGRP = calcitonin gene-related peptide; TCC = trigeminocervical complex; TG = trigeminal ganglion.

1. Russo. *Annu Rev Pharmacol Toxicol*. 2015;55:533-552.
2. Edvinsson. *Br J Clin Pharmacol*. 2015;80:193-199.
3. Eftekhari and Edvinsson. *Ther Adv Neurol Disord*. 2010;3:369-378.
4. Raddant and Russo. *Expert Rev Mol Med*. 2011;13:e36
5. Kerman and Goadsby. *Curr Neurol Neurosci Rep*. 2015;15:25

Fisiopatologia dell'emicrania

- CGRP plays a pivotal role in migraine



Note: CGRP antagonists refers to small molecule antagonis

Fisiopatologia dell'emicrania

Where does CGRP bind?

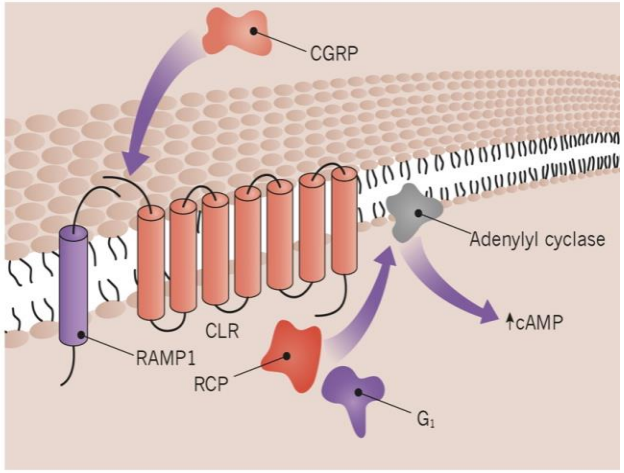
CGRP binds to **CGRP receptors**, which are found throughout the body.

The CGRP receptor is a heterotrimer comprised of:

- Calcitonin-like receptor (CLR), a seven transmembrane Gs protein coupled structure, and
- Receptor activity-modifying protein 1 (RAMP1).

When CLR is localized with RAMP2 or RAMP2, the receptor is activated by adrenomedullin.

The receptor component protein (RCP) is important for signaling. This links the receptor to the intracellular signalling pathway, which works through G proteins and adenylyl cyclase, causing raised cAMP levels.



CLR: Calcitonin receptor-like receptor
RAMP1: Receptor activity-modifying protein 1
RCP: Receptor component protein

Fisiopatologia dell'emicrania

What is Calcitonin Gene-Related Peptide (CGRP)?

CGRP is a 37-amino acid neuropeptide derived from the gene encoding calcitonin.
It is a potent vasodilator and also functions as a messenger in nerve cells.

Ala-Cys-Aap-Thr-Ala-Thr-Cys-Val-Thr-His-
Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-
Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-
Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2

CGRP exists in two forms in humans

α

α-CGRP is the predominant form

- Found in the peripheral and central nervous systems.
- Formed from alternative splicing of the calcitonin/CGRP gene on chromosome 11.

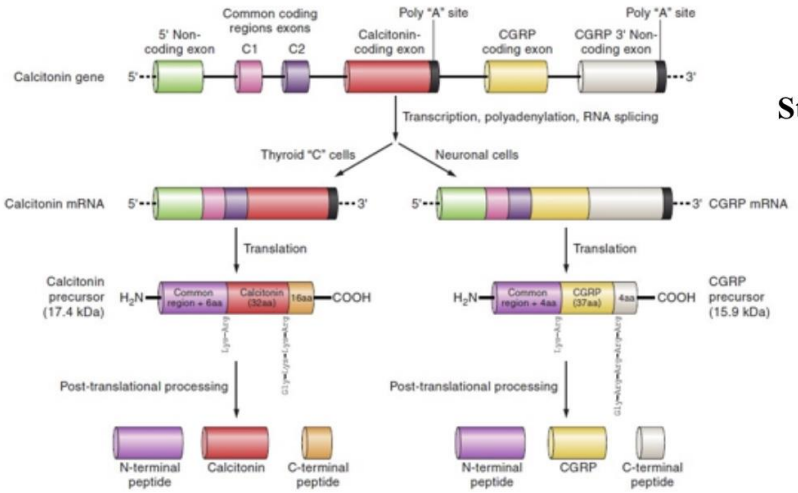
β

β-CGRP is found in the enteric nervous system. This differs in 3 amino acids.

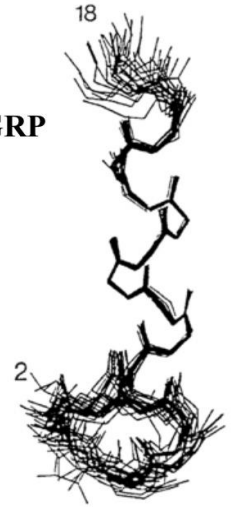
Fisiopatologia dell'emicrania

More about CGRP: Discovery and structure

CGRP was discovered in 1982-83 as an alternative transcript of the calcitonin gene



Structure of CGRP



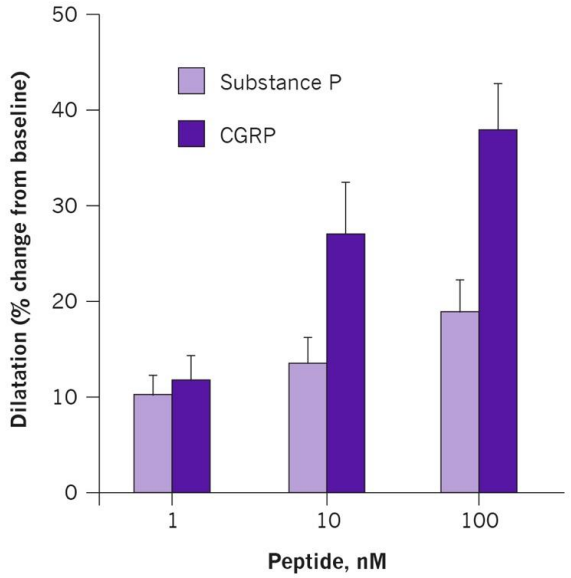
The processing of the calcitonin CALC I gene leads to either calcitonin in the thyroid or α-CGRP in sensory neurons.

Rosenfeld MG et al. Nature 1983;304:129.; Amara SG et al. Nature 1982;298:240

CGR

Fisiopatologia dell'emicrania

CGRP is a potent vasodilator of cerebral arteries

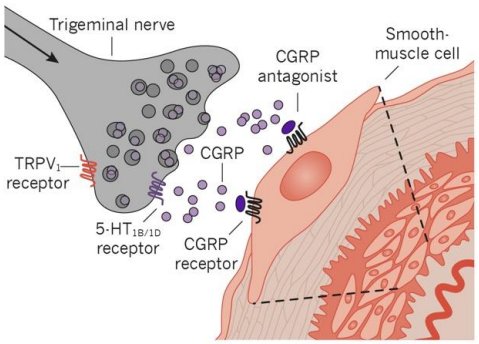


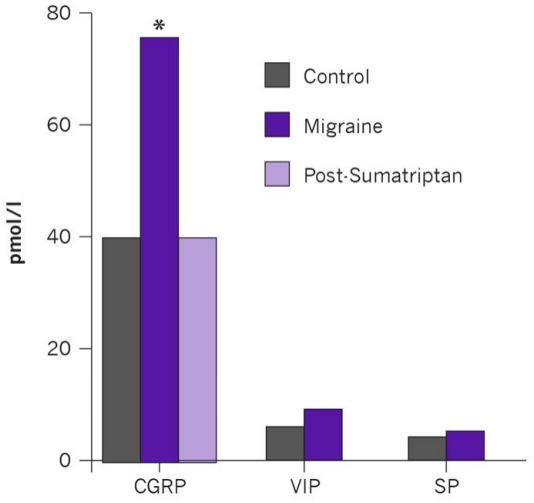
- CGRP was previously established as a potent dilator of blood vessels in peripheral vascular beds.
- In this *in vitro* study, CGRP was also significantly more potent than substance P as a vasodilator of cerebral vessels.

Fisiopatologia dell'emicrania

Triptans suppress CGRP release from trigeminal nerves

Sumatriptan acts via presynaptic 5-HT1B/D receptors to suppress CGRP release from trigeminal nerves



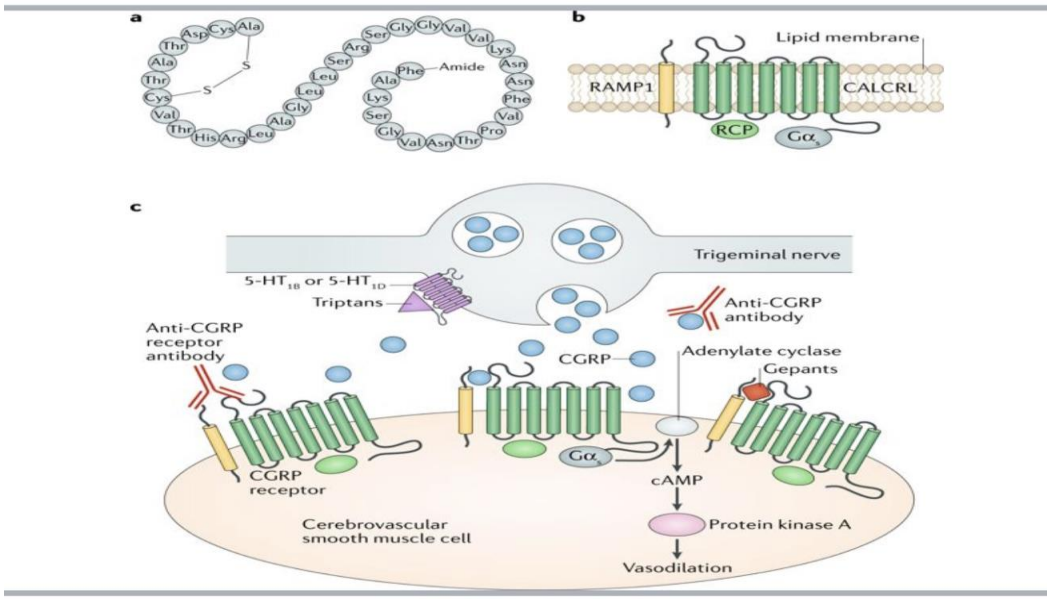


Treatment with sumatriptan normalized the increase in CGRP levels seen in acute migraine, with relief of headache pain

Fisiopatologia dell'emicrania

CGRP and its receptor: Key points

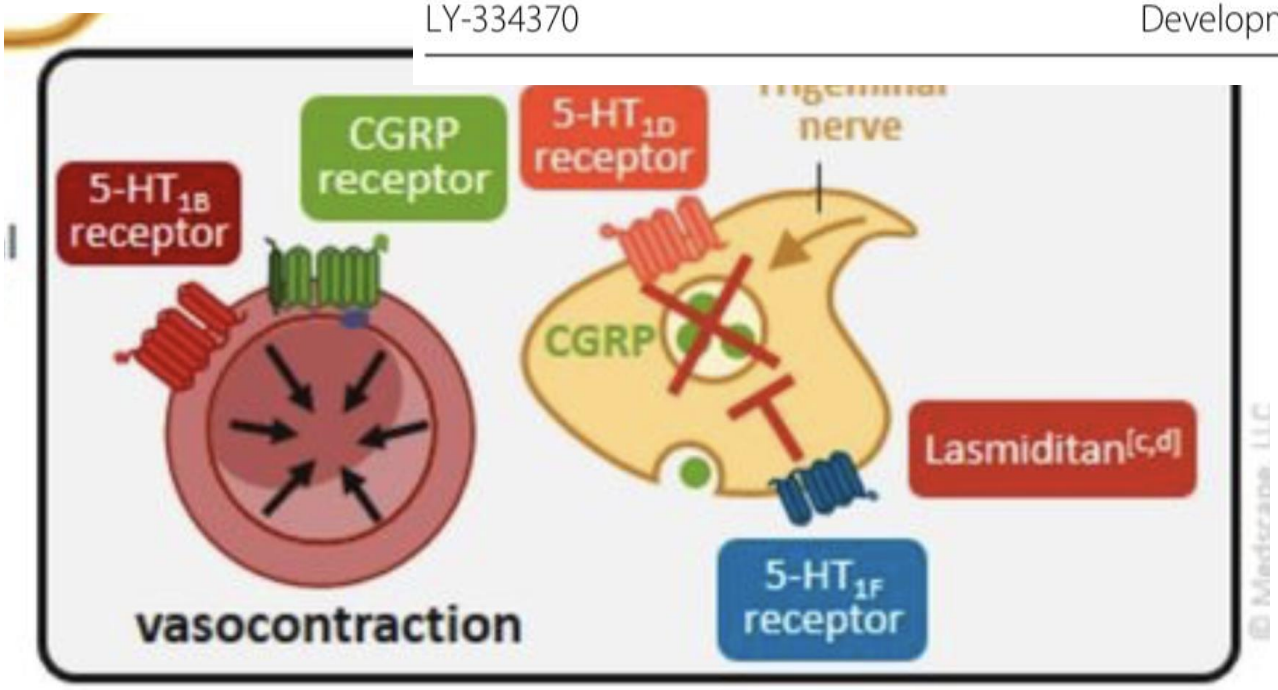
- **CGRP** is a potent vasodilator in the peripheral and central nervous systems. α-CGRP is the predominant form.
- **CGRP binds to CGRP receptors**, found throughout the body. CGRP receptor localization is consistent with a role in trigeminal sensitization and migraine pathology.
- Experimental and clinical studies support a **pivotal role for CGRP and its receptor in migraine**.
- Importantly, agents that target CGRP or its receptor **do not need to cross the blood brain barrier** or act centrally for efficacy.



Acute therapy: what is new

- Lasmiditan
  - Tablet

Drug	Status
Alniditan	Development terminated
Lasmiditan (COL-144)	Phase III clinical trials
LY-334370	Development terminated



Pueyo M. *Neurotherapeutics*. 2018; 15(2):291-303;

Acute therapy: what is new

- Lasmiditan
  - Tablet

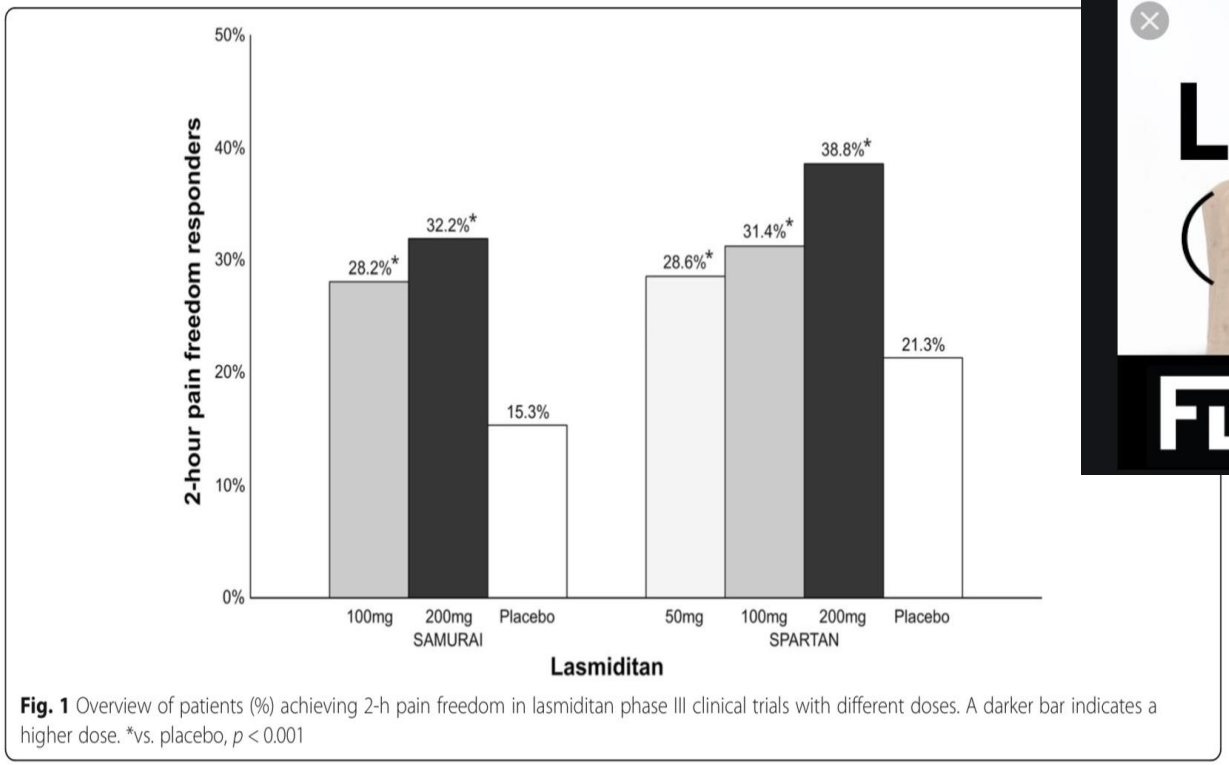
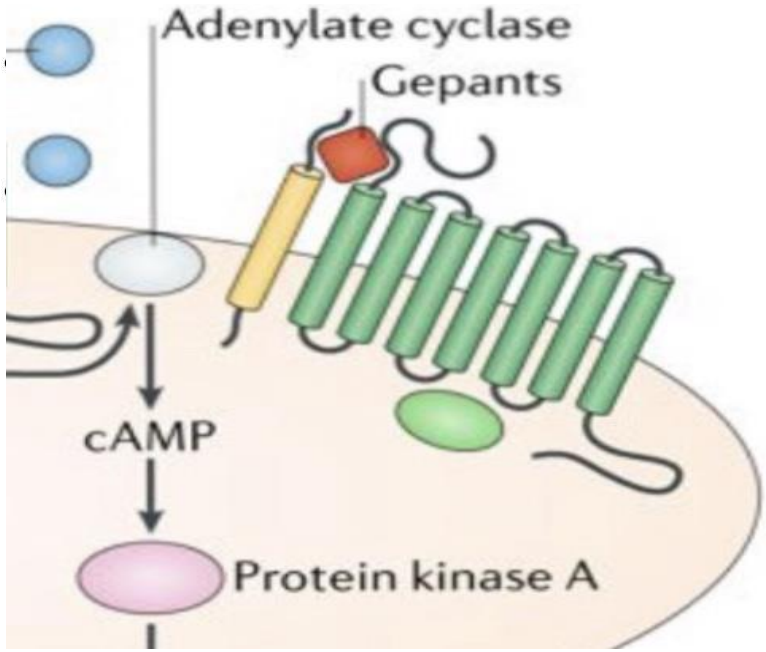


Fig. 1 Overview of patients (%) achieving 2-h pain freedom in lasmiditan phase III clinical trials with different doses. A darker bar indicates a higher dose. *vs. placebo, $p < 0.001$

Acute therapy: what is new

Drug	Status
Atogepant (AGN-241689, MK-8031)	Phase III clinical trials (prophylactic treatment)
BI 44370	Development terminated
MK-3207	Development terminated
Olcegepant (BIBN4096BS)	Development terminated
Rimegepant (BMS-927711, BHV3000)	Phase III clinical trials (acute treatment); phase II clinical trials (prophylactic treatment)
Telcagepant (MK-0974)	Development terminated
Ubrogepant (MK-1602)	Phase III clinical trials (acute treatment)



Acute therapy: what is new

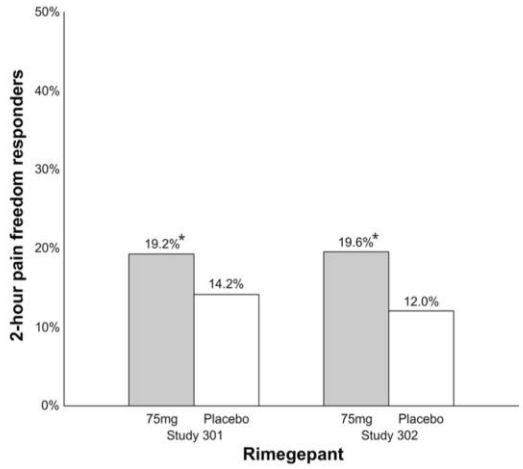


Fig. 4 Overview of patients (%) achieving 2-h pain freedom in rimegepant phase III clinical trials. *Study 301; vs. placebo, $p < 0.003$. St
placebo, $p < 0.001$

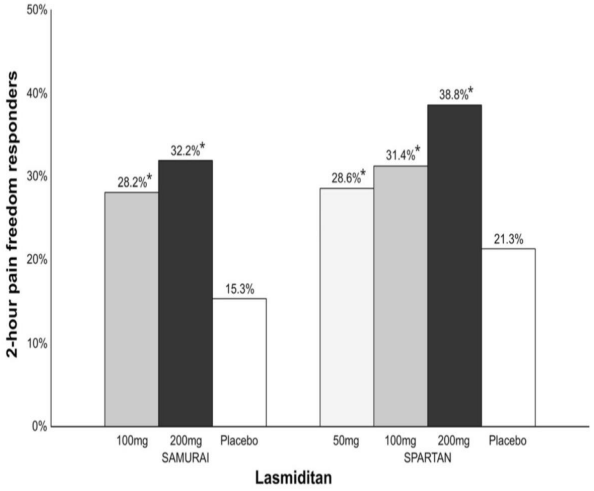


Fig. 1 Overview of patients (%) achieving 2-h pain freedom in lasmiditan phase III clinical trials with different doses. A darker bar indicates a higher dose. *vs. placebo, $p < 0.001$

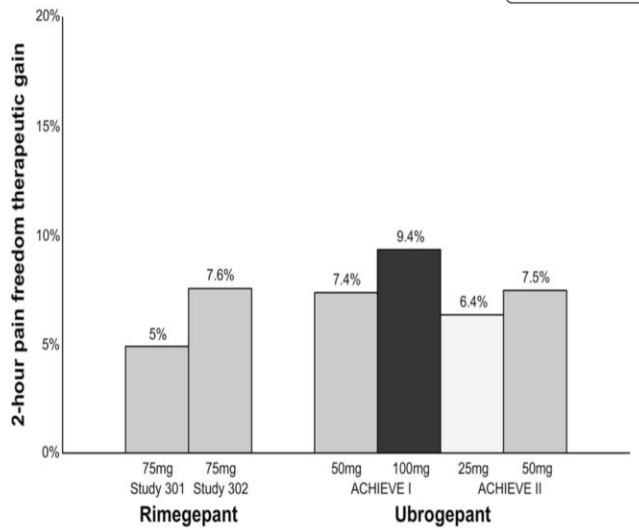


Fig. 6 Overview of the therapeutic gain* in 2-h pain freedom with gepants. A darker bar indicates a higher dose. *Therapeutic gain is defined as the difference between percentage of responders in active group compared to percentage of responders in placebo group

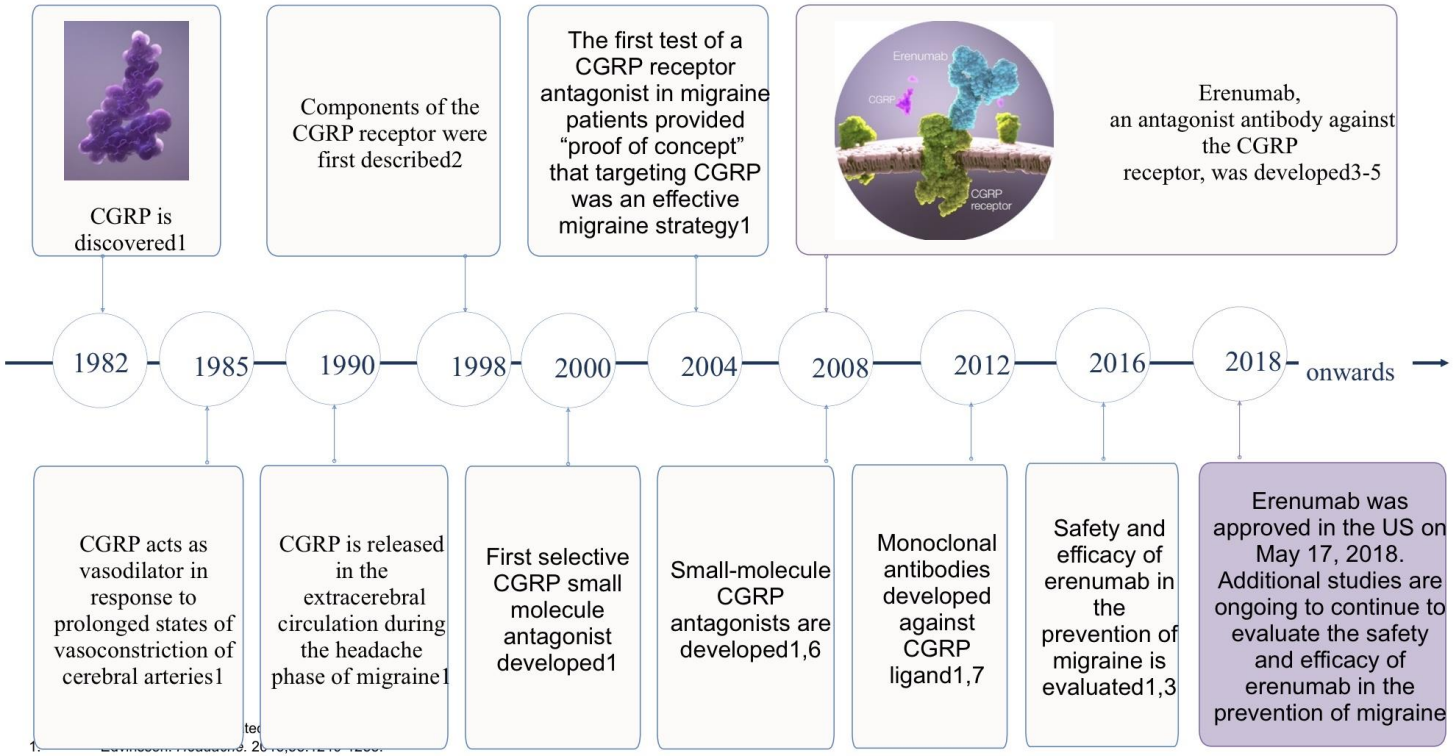
Starling AJ, et al. Cephalalgia. 2018;38:1038-

Migraine prevention: what is new!

Preliminary data from the phase II clinical trial on atogepant have been reported in press releases [46]. The trial included 834 patients and was designed as a placebo-controlled dose ranging study with doses ranging from atogepant 10 mg once a day to 60 mg twice a day. All doses showed a significant reduction in mean monthly migraine days compared to placebo. The trial raised no concerns regarding hepatic or cardiovascular

- CGRP antagonist
  - Gepants

Migraine prevention: what is new!



2. McLatchie, et al. *Nature*. 1998;393:333-339.
3. Shi, et al. *J Pharmacol Exp Ther*. 2016;356:223-231.
4. Tepper, et al. *Lancet Neurol*. 2017;16:425-434.
5. Boone, et al. inventors; Amgen Inc, assignee. Human CGRP Receptor Binding Proteins. US Patent 9,102,731 B2. August 11, 2015.
6. Ho, et al. *Neurology*. 2008;70:1304-1312.
7. Kovacevich, et al. inventors; Alderbio Holdings LLC, assignee. Anti-CGRP compositions and use thereof

Migraine prevention: what is new!

Table 3 Overview of anti-calcitonin-gene related (CGRP) (receptor) peptide monoclonal antibodies in order by target and alphabetical

Drug	Target	Administration	Interval between administrations	Status
Erenumab (AMG-334)	Receptor	Subcutaneous injection	4 weeks	FDA approved; phase III clinical trials
Eptinezumab (ALD403)	Ligand	Intravenous infusion	12 weeks	Phase III clinical trials
Fremanezumab (TEV-48125)	Ligand	Subcutaneous injection	4 or 12 weeks	FDA approved; phase III clinical trials
Galcanezumab (LY2951742)	Ligand	Subcutaneous injection	4 weeks	FDA approved; phase III clinical trials

*FDA: The US Food and Drug Administration

Migraine prevention: what is new!

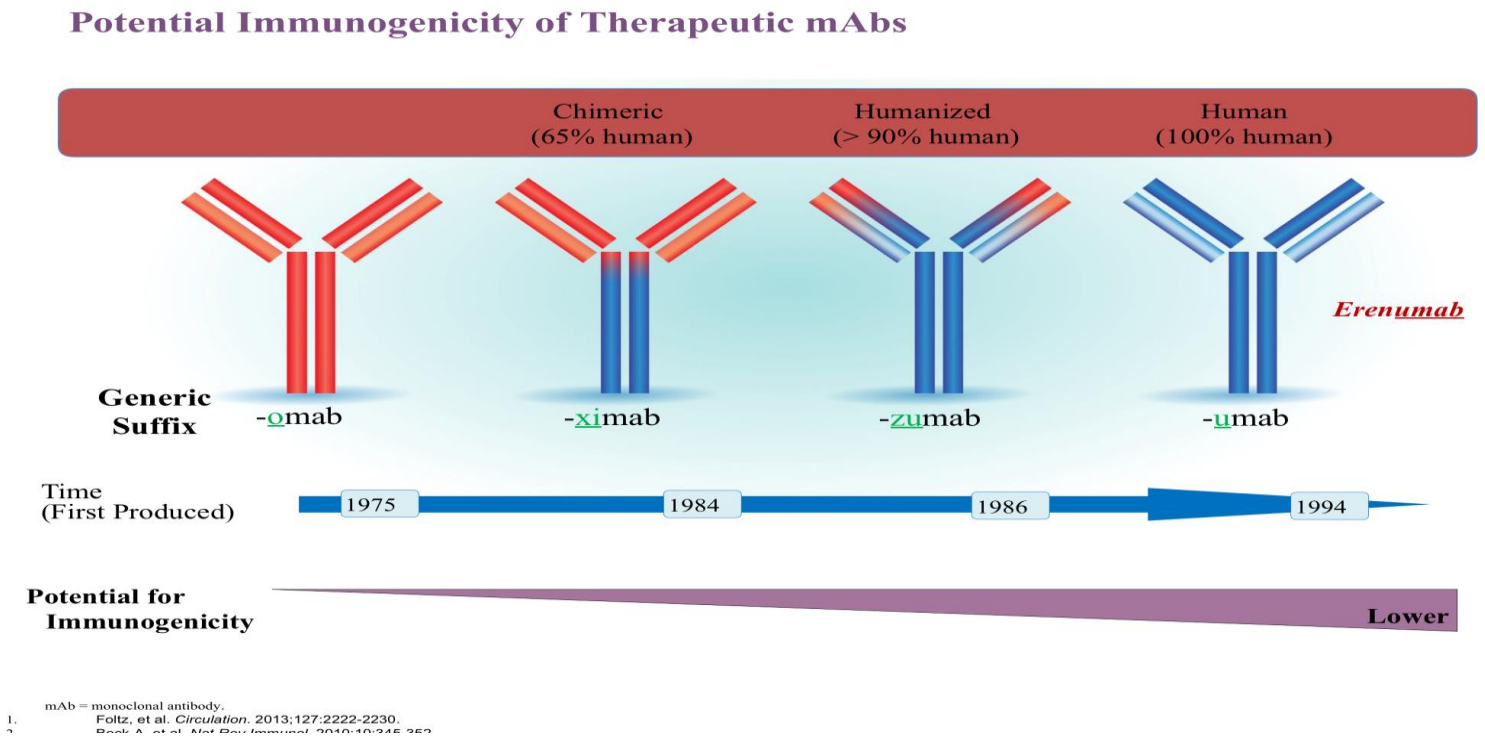
Table 1 Pharmacological characteristics of CGRP monoclonal antibodies

	Eptinezumab[a] [98]	Erenumab [27, 28, 97]	Fremanezumab [99, 100]	Galcanezumab [29, 30]
Antibody type	Humanised IgG_1	Human IgG_2	Humanised IgG_2	Humanised IgG_4
Antibody target	CGRP	CLR/RAMP1 receptor	CGRP	CGRP
IC_{50}	No data	2.3 nM	No data	0.35 nM
Route of administration	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous
Frequency of administration	3-Monthly	Monthly	Monthly or 3-monthly	Monthly
Production cell line	Yeast	Chinese hamster ovary	Chinese hamster ovary	Chinese hamster ovary
Bioavailability	Administered IV	Up to 74%	No data	No data
T_{max}	2.5–2.8 h	4–11 days	5–11 days	7–14 days
Clearance	0.146–0.1536 L/day	0.214 L/day	0.055–0.0625 L/day	0.452 L/day
$t_{½}$	23–33 days	~ 21 days	31–39 days	25–32 days

IC_{50} concentration of antibody by which CGRP-induced cAMP is reduced by 50%, *T_{max}* time to maximum concentration, *$t_{½}$* half-life, *IgG* immunoglobin G, *CGRP* calcitonin gene-related peptide, *CLR/RAMP1* calcitonin receptor-like receptor/receptor activity-modifying protein 1, *IV* intravenously, *cAMP* cyclic adenosine monophosphate

[a]Not currently available in clinical practice

Migraine prevention: what is new!

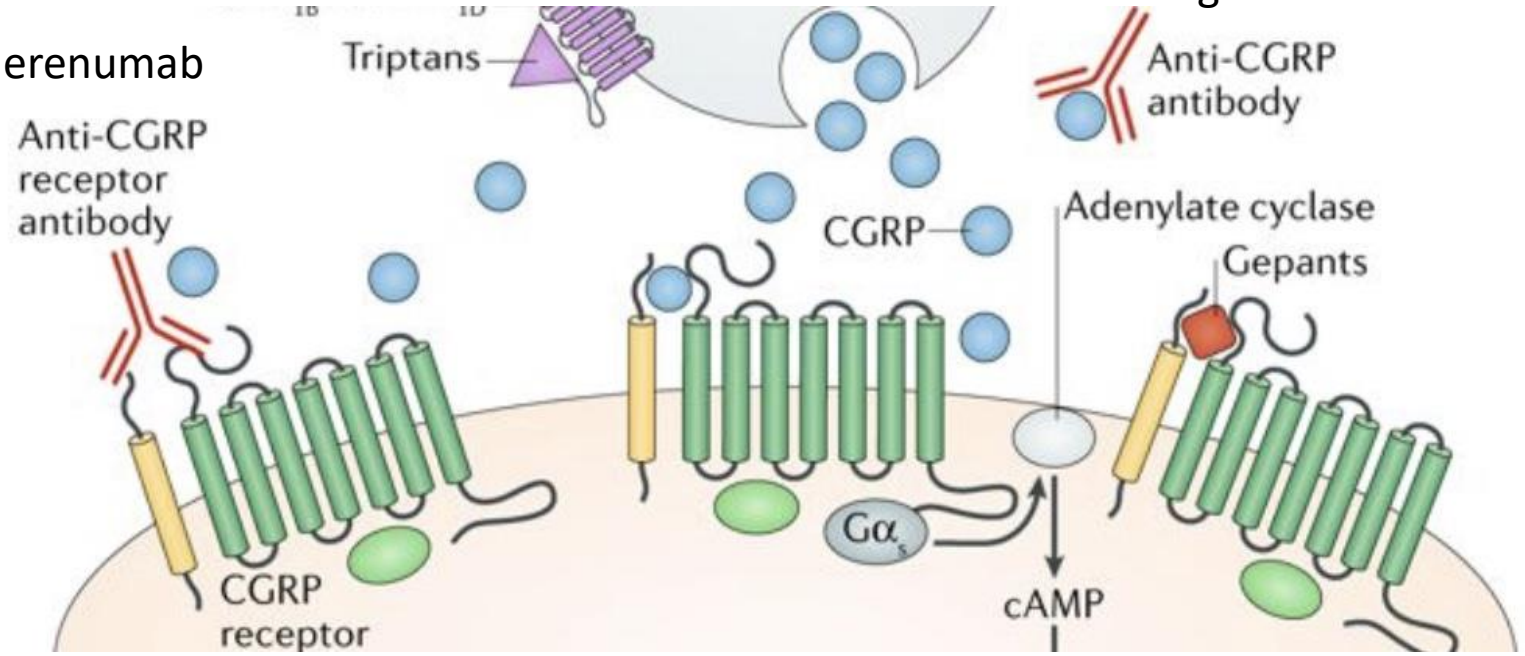


mAb = monoclonal antibody.

1. Foltz, et al. *Circulation*. 2013;127:2222-2230.

Migraine prevention: what is new!

Eptinezumab
Fremanezumab
galcanezumab



Migraine prevention: what is new!

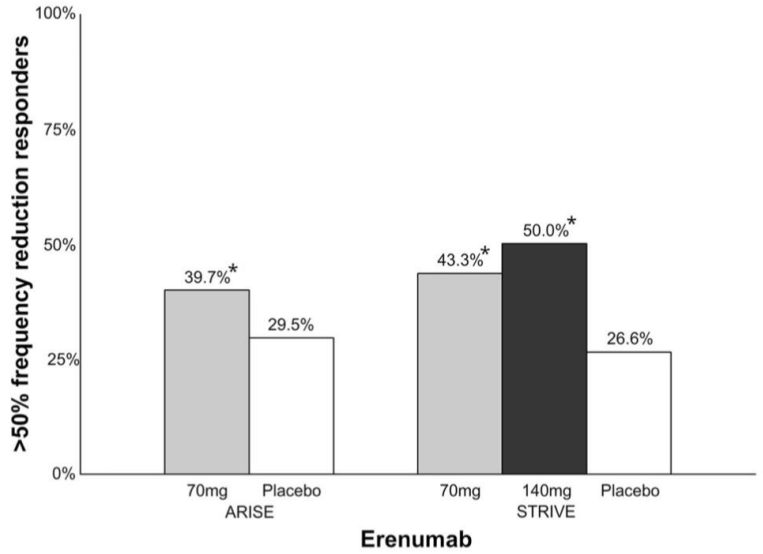


Fig. 7 Overview of patients (%) achieving > 50% reduction in migraine days in phase III clinical trials with erenumab. A darker bar indicates a higher dose. *ARISE; 70 mg vs. placebo, $p = 0.010$. STRIVE; 70 mg vs. placebo, $p < 0.001$; 140 mg vs. placebo, $p < 0.001$

Migraine prevention: what is new!

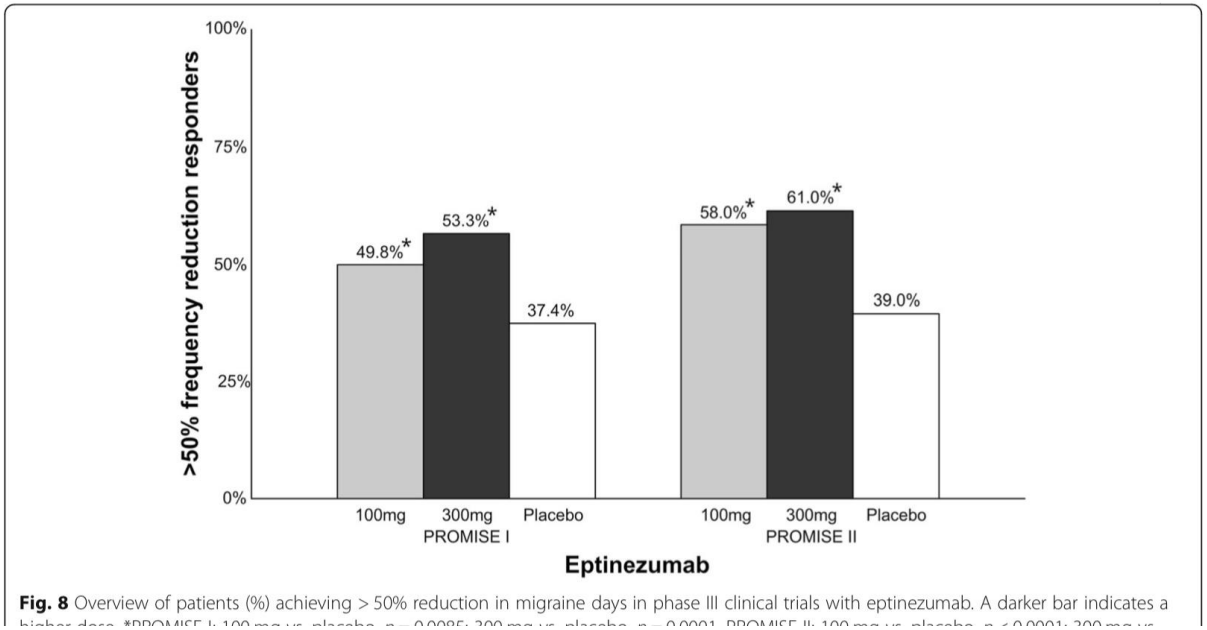


Fig. 8 Overview of patients (%) achieving > 50% reduction in migraine days in phase III clinical trials with eptinezumab. A darker bar indicates a higher dose. *PROMISE I: 100 mg vs. placebo, $p = 0.0085$; 300 mg vs. placebo, $p = 0.0001$. PROMISE II: 100 mg vs. placebo, $p < 0.0001$; 300 mg vs.

Migraine prevention: what is new!

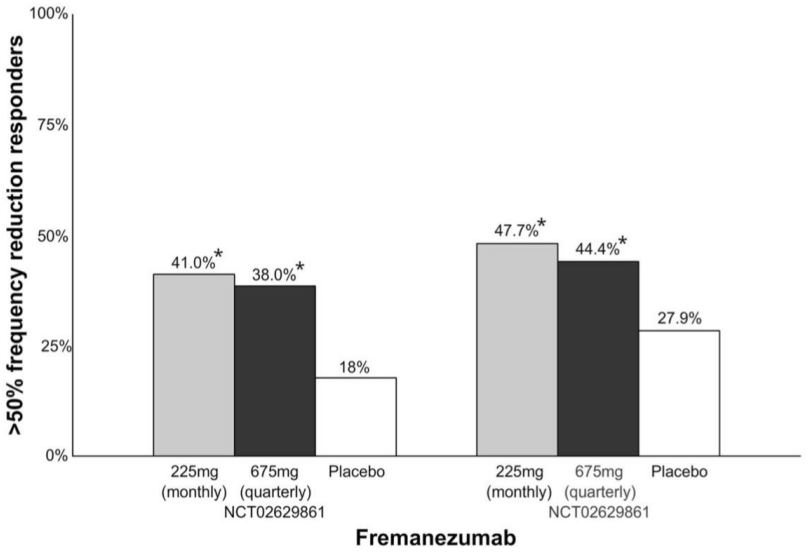


Fig. 9 Overview of patients (%) achieving > 50% reduction in migraine days in phase III clinical trials with fremanezumab. A darker bar indicates a higher dose. *NCT02629861 (left); 225 mg vs. placebo, $p < 0.001$; 675 mg vs. placebo, $p < 0.001$. NCT02629861 (right); 225 mg vs. placebo, $p < 0.001$; 675 mg vs. placebo, $p < 0.001$

Migraine prevention: what is new!

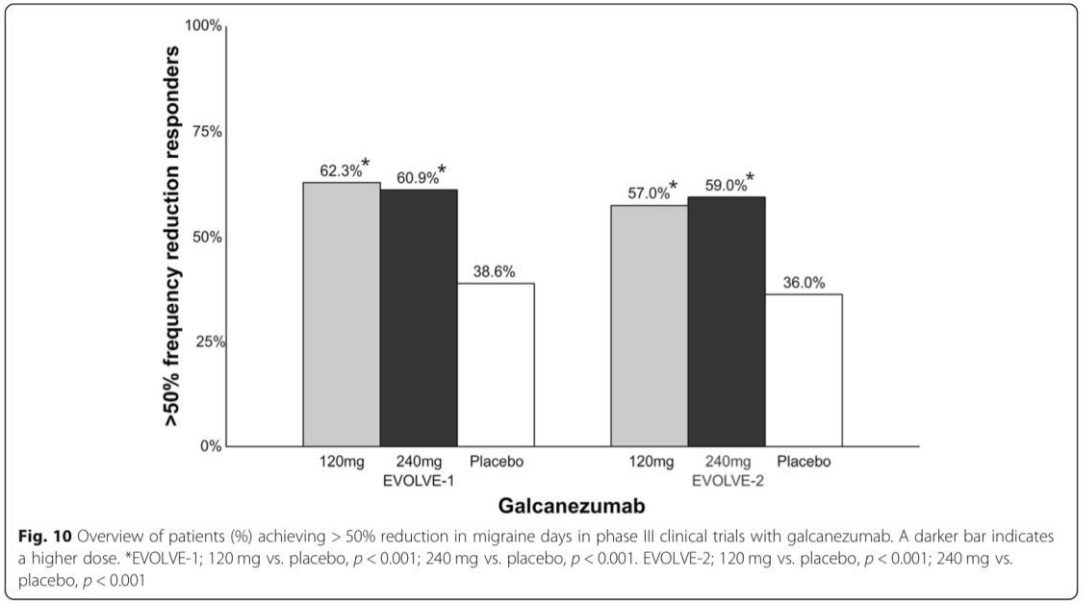


Fig. 10 Overview of patients (%) achieving > 50% reduction in migraine days in phase III clinical trials with galcanezumab. A darker bar indicates a higher dose. *EVOLVE-1; 120 mg vs. placebo, $p < 0.001$; 240 mg vs. placebo, $p < 0.001$. EVOLVE-2; 120 mg vs. placebo, $p < 0.001$; 240 mg vs. placebo, $p < 0.001$

Migraine prevention: what is new!

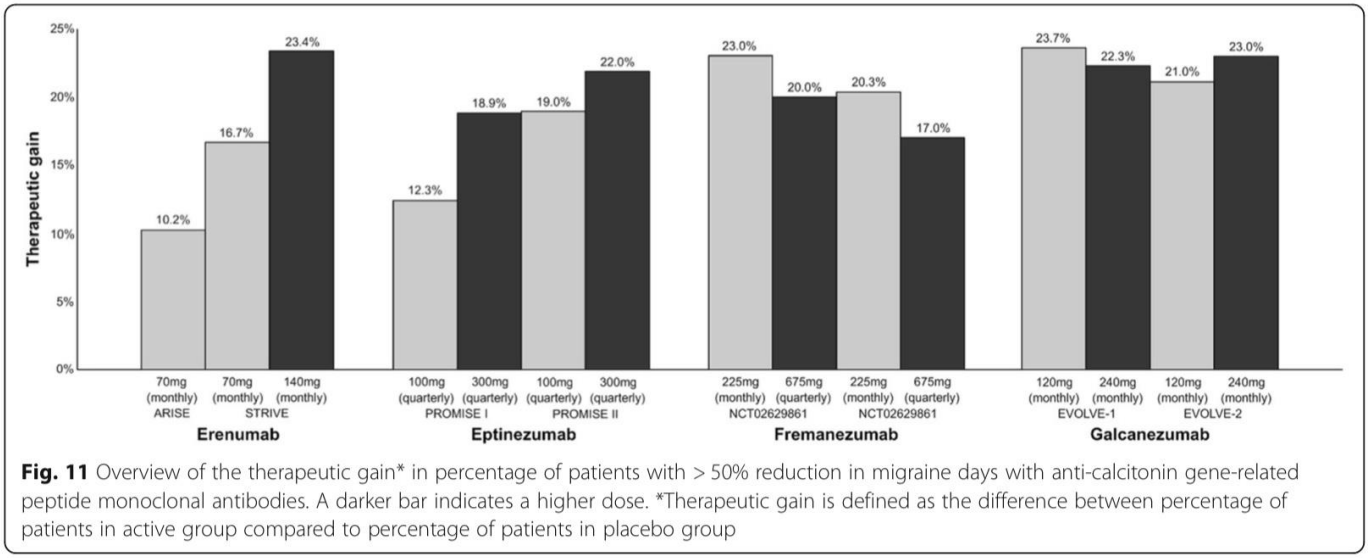


Fig. 11 Overview of the therapeutic gain* in percentage of patients with > 50% reduction in migraine days with anti-calcitonin gene-related peptide monoclonal antibodies. A darker bar indicates a higher dose. *Therapeutic gain is defined as the difference between percentage of patients in active group compared to percentage of patients in placebo group

Quando prescrivere gli antiCGRP mAbs

EMA Approved Indications for the Anti-CGRP mAbs

EMA indication for anti-CGRP mAbs, erenumab, fremanezumab, and galcanezumab:[a-c]

- To prevent migraine in adults who have migraines at least 4 days a month
  - Indications may differ outside the European Union

a. EMA website. Aimovig (erenumab) EPAR; b. EMA website. Emgality (galcanezumab) EPAR; c. EMA website. Ajovy (fremanezumab) EPAR.

Quando prescrivere gli antiCGRP mAbs

Criteria for Offering Preventive Migraine Treatment

American Headache Society Recommendations for Preventive Treatment

Prevention Should Be:	Headache Days/Month	Degree of Disability Required
Offered	≥ 6	None
	≥ 4	Some
	≥ 3	Severe
Considered	4 or 5	None
	3	Some
	2	Moderate

Preventive medication should be considered when:

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks (≥4 monthly headache days)
- Contraindication to, failure, intolerability to or overuse of acute treatments
- Patient preference

American Headache Society. *Headache.* 2019;59:1-18.

Quando prescrivere gli antiCGRP mAbs

Medication Overuse Headache: IHF Diagnostic Criteria

Headache occurring on ≥ 15 days/month in a patient with a pre-existing primary headache while using the following for > 3 months:

≥ 10 or more days per month
- Ergot derivatives
- Triptans
- Opioids
- Combination analgesics
- Combination of drugs from different classes that are not individually overused

≥ 15 or more days/month
Nonopioid analgesics
Paracetamol
NSAIDs

The headache usually, but not invariably, resolves after the overuse is stopped.

IHS. *Cephalalgia*. 2018;38:1-211.

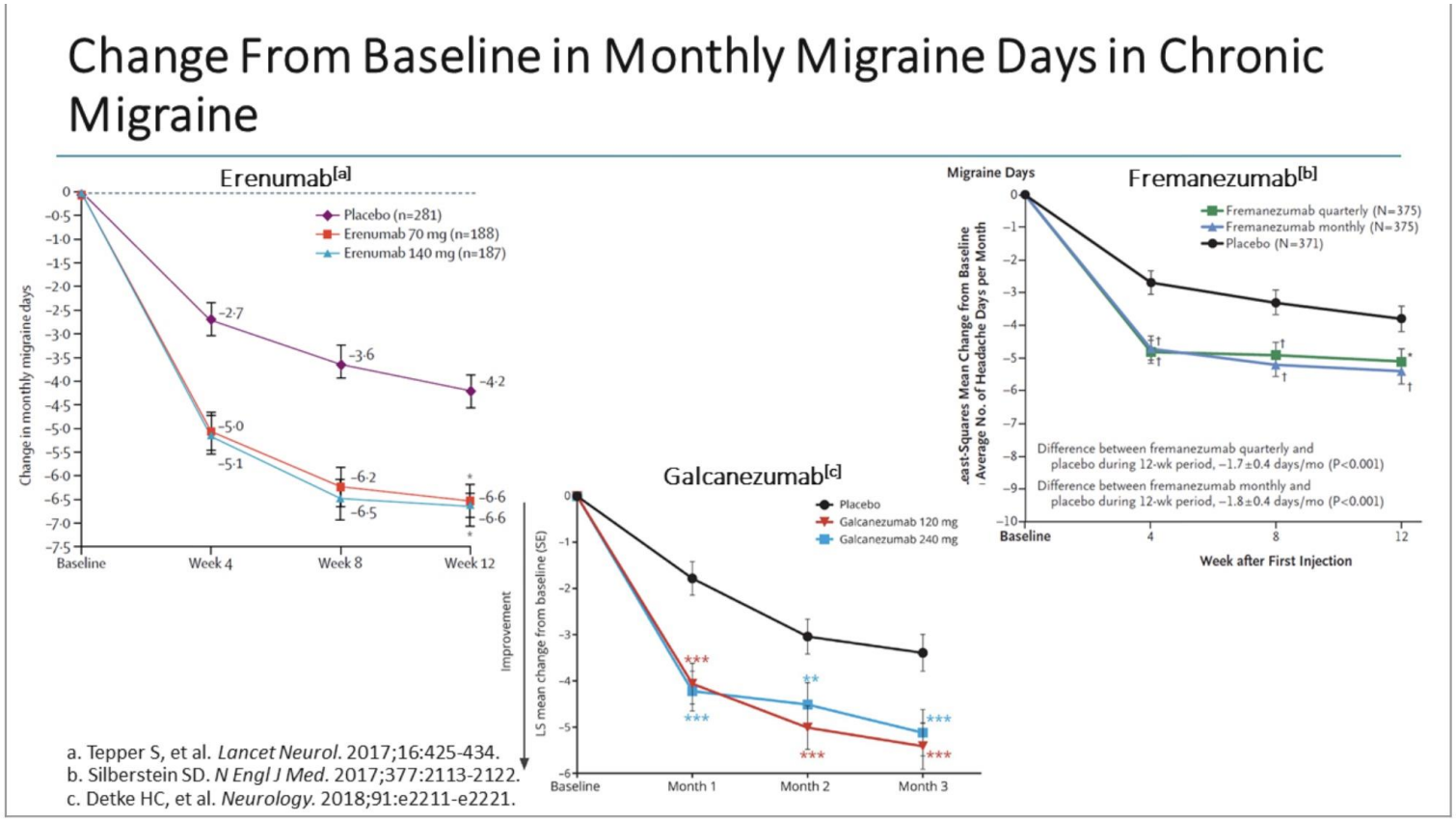
Quando prescrivere gli antiCGRP mAbs

ICHD-3 Criteria: Chronic Migraine

A. Headache on ≥ 15 days per month for > 3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had ≥ 5 attacks fulfilling criteria migraine without aura and/or criteria migraine with aura
C. On ≥ 8 days/month for > 3 months, fulfilling any of the following:
    1. Criteria migraine without aura
    2. Criteria for migraine with aura
    3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

IHS. *Cephalalgia.* 2018;38:1-211.

Quando prescrivere gli antiCGRP mAbs



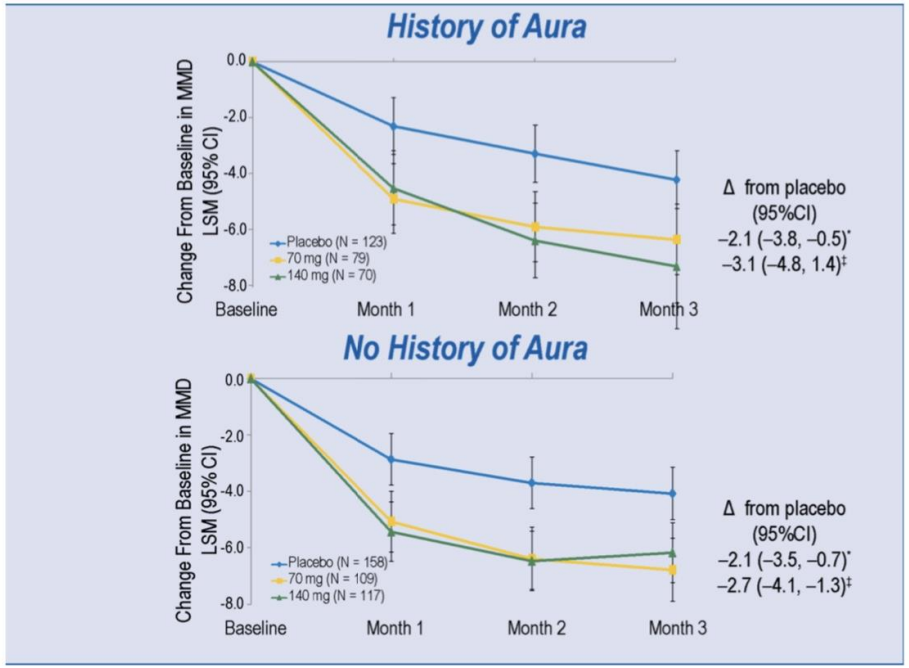
a. Tepper S, et al. *Lancet Neurol*. 2017;16:425-434.
b. Silberstein SD. *N Engl J Med*. 2017;377:2113-2122.
c. Detke HC, et al. *Neurology*. 2018;91:e2211-e2221.

Quando prescrivere gli antiCGRP mAbs

Efficacia di erenumab indipendente da aura

Patients **with history of AURA**: *N*=276
Placebo (N=124); erenumab 70 mg (N=81) ; erenumab 140 mg (N=71)
MMD at BSL: placebo: 18.1; erenumab 70 mg: 17.7; erenumab 140 mg; 17.7

Patients **without history of AURA**: N=391
Placebo (N=162); erenumab 70 mg (N=110); erenumab 140 mg (N=119)
MMD at BSL: placebo: 18.3; erenumab 70 mg: 17.9; erenumab 140 mg; 17.9



1. Ashina M, et al. Poster PO-01-014. IHC, Vancouver; September 7–10, 2017

Quando prescrivere gli antiCGRP mAbs

INDICAZIONE vs RIMBORSABILITÀ

Approvazione EMA

Erenumab è stato approvato da EMA per la profilassi dell'emicrania in adulti che hanno almeno 4 giorni di emicrania al mese.

La dose raccomandata è 70 mg ogni 4 settimane. Alcuni pazienti possono avere beneficio da una dose di 140 mg ogni 4 settimane.

POPOLAZIONE TARGET PER RIMBORSO

pazienti adulti (**18 – 65 aa**) con almeno **4 giorni di emicrania** al mese, con punteggio **scala MIDAS ≥11**, che abbiano mostrato una risposta insufficiente o che siano controindicate/intolleranza ad **almeno 3 altre classi** di farmaci per la profilassi dell'emicrania

Quando prescrivere gli antiCGRP mAbs

QUESTIONARIO MIDAS*

Che cos'è e come compilarlo?

Il MIDAS (Migraine Disability Assessment Score Questionnaire) è un questionario che offre un quadro della disabilità causato dagli attacchi emicranici nell'arco degli ultimi 3 mesi.
Si tratta di un questionario molto semplice, ma con dimostrata validità e affidabilità.
Dovrà rispondere a 5 domande che riflettono i giorni in cui le sue attività sono state impedite o nettamente limitate a causa dell'emicrania.

Come si calcola il punteggio al MIDAS?

Il punteggio totale si calcola dalla semplice somma dei punteggi ottenuti alle 5 domande.
Per cortesia, ora risponda alle seguenti domande su tutti i mal di testa che ha patito negli ultimi 3 mesi. Scriva le risposte nel quadratino accanto a ciascuna domanda. Scriva 0 (zero) se non ha avuto il disturbo negli ultimi 3 mesi.

Quando prescrivere gli antiCGRP mAbs

Negli ultimi 3 mesi quanti giorni non è potuto andare al lavoro o a scuola per il mal di testa?	Giorni:
Negli ultimi 3 mesi per quanti giorni ha dovuto ridurre almeno della metà la sua attività lavorativa per il mal di testa ? *(Non tenga conto degli eventuali giorni in cui non ha potuto andare al lavoro o a scuola che siano già stati riportati nella precedente risposta)*	Giorni:
Negli ultimi 3 mesi per quanti giorni non ha potuto svolgere, a causa del mal di testa, le attività che svolge abitualmente a casa ?	Giorni:
Negli ultimi 3 mesi per quanti giorni ha dovuto ridurre, a causa del mal di testa, di almeno la metà le attività che svolge abitualmente a casa ? *(Non includa gli eventuali giorni conteggiati nella risposta precedente nei quali non abbia potuto svolgere le abituali attività che svolge a casa)*	Giorni:
Negli ultimi 3 mesi per quanti giorni ha dovuto rinunciare ai contatti sociali o familiari a causa del mal di testa ?	Giorni:
	TOT:

Gradi di disabilità al MIDAS:

Se la somma delle domande da 1 a 5 è compresa tra:

0 - 5 = grado I, disabilità **minima o trascurabile**

6 - 10 = grado II, disabilità **lieve**

11 - 20 = grado III, disabilità **media**

21 o più = grado IV, disabilità **grave**.

VEDI D'Amico D. et al. Cephalalgia 2001; 21(10):947-952.

E per il futuro?

monoclonal antibodies

Drug	Target	Administration	Interval between administrations	Status
ALD1910	Ligand	N/A	N/A	Preclinical phase
AMG-301	Receptor	Subcutaneous injection	4 weeks	Phase II clinical tria

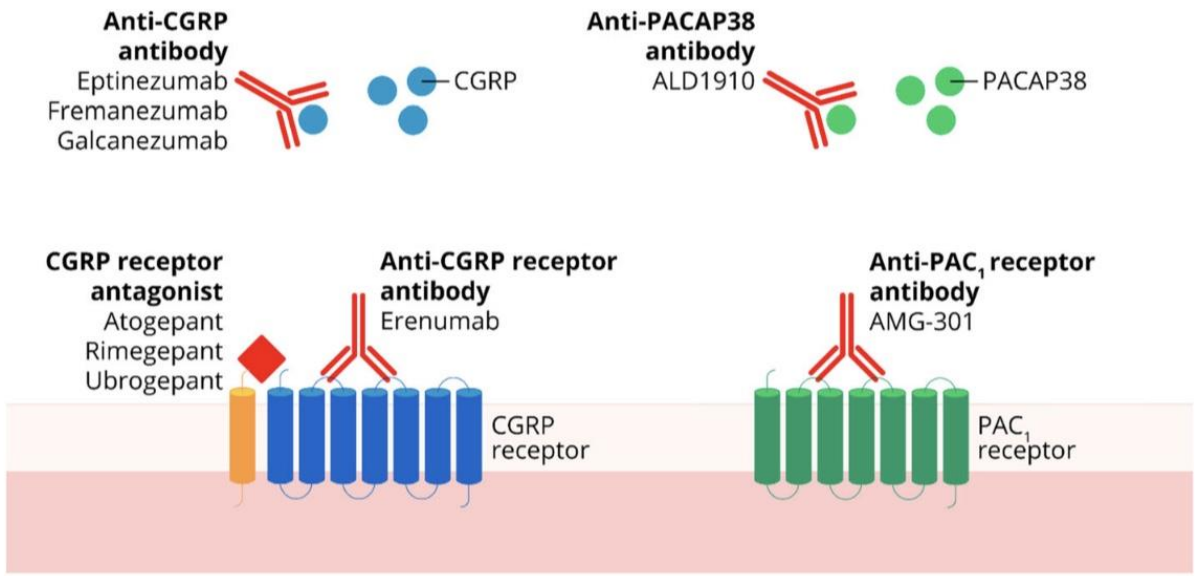


Fig. 3 Overview of the therapeutic novelties targeting the calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide/pituitary adenylate cyclase 1 (PACAP/PAC_1) pathways developed for migraine

Grazie per l'attenzione

GETTY IMAGES