Efficacia, sicurezza e tollerabilità dei MAbs

MAbs anti CGRP nel trattamento dell'emicrania

Prof. Filippo Baldacci, UO Neurologia AOUP

DISCLOSURES

	Expenses	Consultant	Funded research
Abbvie	x	x	x
Ely Lilly	x	x	
Teva	x		

OBJECTIVEs

- *STRUCTURAL CHARACTERISTICS OF ANTI-CGRP MONOCLONAL ANTIBODIES*
- *CGRP GENE AND CLASSIFICATION OF CGRP RECEPTORS*
- *CGRP IN THE PATHOPHYSIOLOGY OF MIGRAINE*
- *DIFFERENCES IN MECHANISMS OF ACTION AND RESISTENCE AMONG THE ANTI-CGRP MONOCLONAL ANTIBODIES*
- *EFFICACY AND EFFECTIVENESS*
- *DISEASES AND CONDITIONS POTENTIALLY RELATED TO CGRP BLOCK*
- *CONCLUSIONS AND OPEN QUESTIONS*

NOVEL TARGET THERAPY IN MIGRAINE

PREVENTIVE TREATMENT

Two classes of CGRP inhibitors — monoclonal antibodies and small molecule antagonists (gepants)

- Four monoclonal antibodies (Eptinezumab, Erenumab, Fremanezumab, Galcanezumab) largerly used in episodic and chronic migraine, with long post-trial follow-up and real life experience
- Two gepants (atogepant and rimegepant)

ACUTE TREATMENT

One class of CGRP inhibitors (gepants) and one class of selective 5HT1F agonist (Ditans)

- Three gepants (ubrogepant, rimegepant and zavegepant)
- One Ditan (Lasmiditan)

CGRP Inhibition – *Anticorpi anti CGRP*

Monoclonal antibodies	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
Target	CGRP receptor	CGRP ligand	CGRP ligand	CGRP ligand
IgG type	IgG2, human	IgG4, humanized	IgG2a, humanized	IgG1, humanized
Administration	Monthly SC	Monthly SC	Monthly or quarterly SC	Quarterly IV
Doses approved for migraine prevention (EM, CM)	70 mg or 140 mg	120 mg (240 mg loading dose)	225 mg monthly or 675 mg quarterly	100 mg or 300 mg
Other headache disorders (approved or under investigation)	cCH, PTH	eCH (approved 300 mg monthly), cCH (no primary endpoint met)	eCH and cCH (primary endpoint unlikely to be met), PTH	eCH, cCH

Abbreviations: *cCH* Chronic cluster headache, *eCH* Episodic cluster headache, *IV* Intravenous, *SC* Subcutaneous injection, *PTH* Acute post-traumatic headache

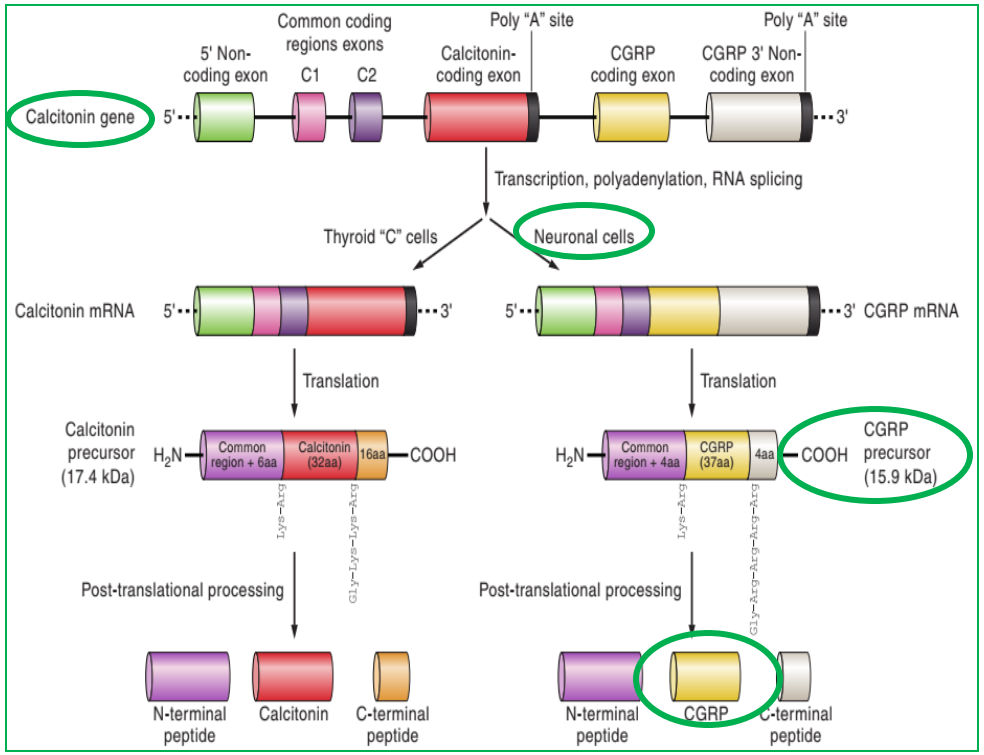
Generic drug name	Indication	Dosage and administration	T_{max}	$t_{1/2}$
mAb targeting the CGRP receptor				
Erenumab	• Preventive treatment of migraine in adults	70 or 140 mg monthly single dose s.c. injection	4–6 days[a]	28 days
mAbs targeting the CGRP ligand				
Eptinezumab	• Preventive treatment of migraine in adults	100 or 300 mg i.v. infusion over 30 min every 3 months	End of infusion	~27 days
Fremanezumab	• Preventive treatment of migraine in adults	225 mg monthly, or 675 mg every 3 months s.c. injection	5–7 days[a]	~31 days
Galcanezumab	• Preventive treatment of migraine, and • Treatment of episodic cluster headache	240 mg s.c. injection loading dose, followed by monthly doses of 120 mg	5 days[a]	27 days

	Gepants	Anti-CGRP monoclonal antibodies
Target	CGRP receptor	CGRP receptor or ligand
Clearance	Liver, kidney	Reticuloendothelial system
Half-life	5–11 h	3–7 weeks
Size	0.5–0.6 kDa	143–146 kDa
Ability to cross blood–brain barrier	Low (1.4% CSF/plasma ratio)	No
Administration	Oral, intranasal	Parenteral
Immunogenicity	No	Yes

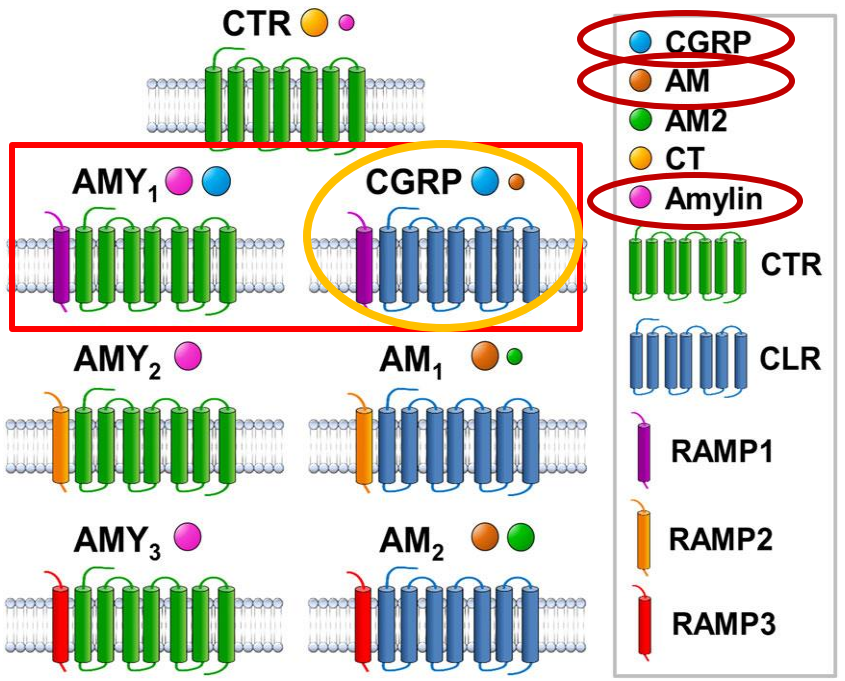
Boinpally R Clin Transl Sci 2024

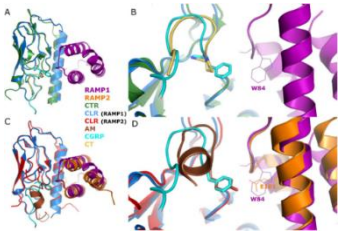
Linda Al-Hassany Lancet Neurol 2022

CGRP GENE AND CLASSIFICATION FOR THE HUMAN CT RECEPTOR FAMILY



*CGRP is a peptide of 37 amino acids in 2 isoforms (**α-CGRP** e β-CGRP) that differ for 3 aminoacids and are trascripted from 2 genes - **CALC1 (CALCA)** and CALC2 (CALCB), both on chromosome 11*



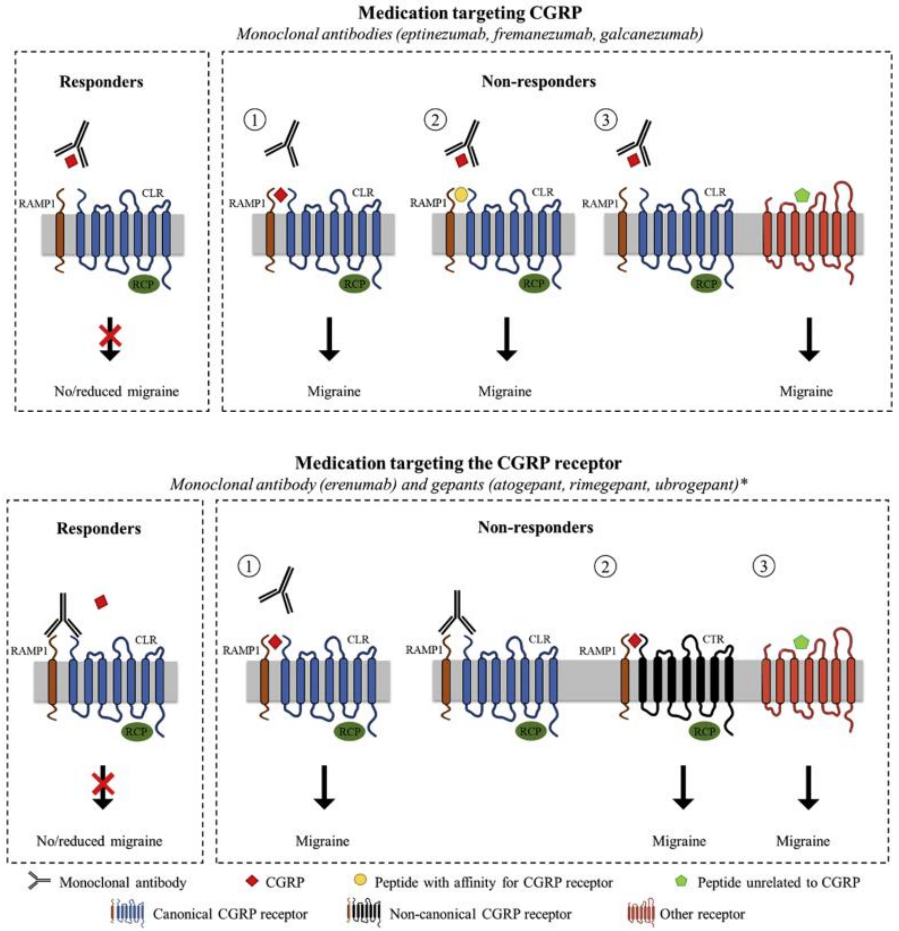


AM, adrenomedullin; AMY, amylin receptor; CLR, calcitonin receptor-like receptor; CT, calcitonin; CTR, calcitonin receptor; RAMP, receptor activity-modifying protein;

Agents that **block both CLR/RAMP1 and CTR/RAMP1** can <u>fully antagonize</u> the effects of CGRP in vivo

Edvinsson Nat Rev Neurol 2018
Hay British Journal of Pharmacology 2018
Russell Physiol Rev 2014
Walker British Journal of Pharmacology 2013
Ray JNNP 2021

RESPONDERS AND NON TO ANTIBODIES TARGETING CGRP OR ITS RECEPTOR



In responders to <u>medications targeting CGRP</u> (eptinezumab, fremanezumab and galcanezumab), CGRP is sufficiently blocked, leading to a reduction in migraine.

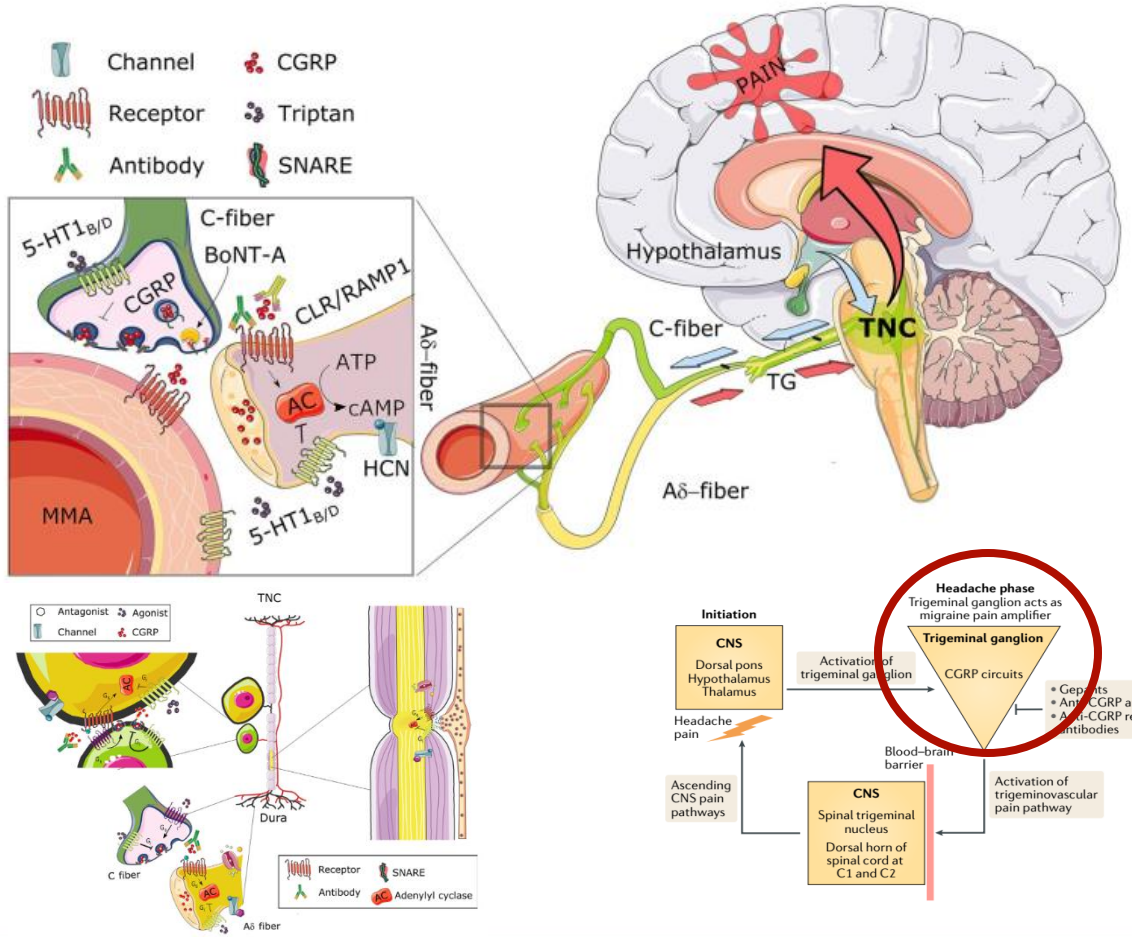
In non-responders, multiple situations are possible 1) **Blocking of CGRP is insufficient**. 2) Blocking of CGRP is sufficient, but **other peptides** (e.g. adrenomedullin) **can activate the CGRP receptor**. 3) Blocking of CGRP is sufficient, but migraine is induced **via a different pathway**.

In responders to <u>medications targeting the CGRP receptor</u> (erenumab *or the gepants; atogepant, rimegepant, ubrogepant, zavegepant*), the receptor is sufficiently blocked. In non-responders. 1) **Blocking of the CGRP receptor is insufficient**. 2) Blocking of the CGRP receptor is sufficient but **CGRP can activate related receptors** (e.g. AMY1 receptor). 3) Migraine is induced **via a different pathway**

De Vries T Pharmacology & Therapeutics 2020

MIGRAINE PATHOPHYSIOLOGY AND POTENTIAL MECHANISMS OF SPECIFIC TREATMENTS

- The migraine attack is initiated with premonitory symptoms and activation of the hypothalamus.
- The trigeminus nucleus caudalis (TNC) is activated. This leads to **activation of the trigeminal ganglion** (TG), and **CGRP release (C-fibers)**.
- The CGRP release at the middle meningeal artery (MMA), leads to vasodilation. CGRP **activates CLR/RAMP1 (CGRP receptor) on the Aδ-fiber**.
- The CGRP receptor activates adenylate cyclase (AC), increasing intracellular cyclic adenosine monophosphate (**cAMP**). This leads to a hyper-excitability and a hypothesized activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels.
- cAMP **increases the open-probability giving an action potential from the Aδ-fiber**, **which travels back to the TNC** and is further sensed as pain. Sensitization of Aδ-fibers might, in addition, lead to normal stimuli, such as touch, being sensed as pain.



Edvinsson Nature Rev Neurol 2018

Edvinsson Trends In Pharmacological Sciences 2021

PHASE 3 RANDOMISED CONTROLLED CLINICAL TRIALS

		Inclusion criteria	Randomised patients	Treatments	MMD reduction	Fifty-percent responders	1° endpoint follow-up
Erenumab (Ere)	STRIVE	Episodic migraine	955	Ere 70mg, Ere 140mg, Placebo	−3.2 −3.7 −1.8	43.3% 50.0% 26.6%	3 months
	LIBERTY	Episodic migraine, (2–4 failed prophylaxes)	246	Ere 140mg, Placebo	−1.8 −0.2	30% 17%	3 months
	ARISE	Episodic migraine	577	Ere 70mg, Placebo	−2.9 −1.8	39.7% 29.5%	3 months
Galcanezumab (Gal.)	EVOLVE-1	Episodic migraine	862	Gal 120mg, Gal 140mg, Placebo	−4.7 −4.6 −2.8	62.3% 60.9% 38.6%	6 months
	EVOLVE-2	Episodic migraine	922	Gal 120mg, Gal 140mg, Placebo	−4.3 −4.2 −2.3	59.3% 56.5% 36%	6 months
	REGAIN	Chronic migraine with or without MOH	1113	Gal 120mg (loading dose), Gal 140mg, Placebo	−4.8 −4.6 −2.7	27.6% 27.5% 15.4%	3 months
Framanezumab (Fre)	HALO - EM	Episodic migraine	875	Fre 225mg monthly, Fre 675mg quarterly, Placebo	−4.6 −4.3 −2.5	41% 38% 18%	3 months
	HALO - CM	Chronic migraine with or without MOH	1136	Fre 675mg at baseline + 225mg monthly, Fre 675mg quarterly, Placebo	−3.4 −3.7 −2.2	44.4% 47.7% 27.9%	3 months
Eptinezumab (Ept)	PROMISE-1	Episodic Migraine	898	Ept 100mg, Ept 300mg, Placebo	−3.9 −4.3 −3.2	49.8% 56.3% 16.2%	3 months
	PROMISE-2	Chronic Migraine with or without MOH	1121	Ept 100mg, Ept 300mg, Placebo	−7.7 −8.2 −5.6	57.6% 61.4% 39.3%	3 months

Mascarella D, Neurol Sci 2022

REAL-WORLD PROSPECTIVE STUDIES

	Patients included				Mean Previous Failed Prophylaxes	Anti-CGRP mAb	MMD reduction	Fifty-percent responders	Follow-up
	Total	*Episodic migraine*	*Chronic migraine*	*Medication overuse headache*					
Barbanti et al. (EARLY)	372	103 (27%)	269 (72%)	268 (72%)	3.5 in EM 5.4 in CM	Erenumab	−4.5 in EM −9.3 in CM	59.4% in EM 55.5% in CM	3 months
Barbanti et al. (EARLY-2)	242	57 (23%)	164 (67%)	133 (54%)		Erenumab	−4.4 in EM −12.8 in CM	56% in EM 75% in CM	48 weeks
Belvis et al. (MAB-MIG)	210	10.5%	89.5%	70%	7.8	Erenumab	−8.6	37% responder rate	3 months
Caronna et al.	139	0	139 (100%)	99 (71%)	>3	Erenumab Galcanezumab	−8.3 in CM −10.3 in MOH	57.5% in CM 63.6% in MOH	6 months
Cheng et al.	170	0	179 (100%)	85 (50%)	5–9 in 68%	Erenumab	−8.5 at 3 months −9.2 at 6 months	58.8% at 3 months 46.5% at 6 months	3 and 6 months
De Vries Lentsch et al.	100	54 (54%)	46 (46%)	0	5	Erenumab	−4.8	22–43%	6 months
Lambru et al.	162	0	162 (100%)	84 (51%)	8.4	Erenumab	−6.0 at 3 months −7.5 at 6 months	35% at 3 months 38%. at 6 months	3 and 6 months
Pensato et al.	149	0	149 (100%)	149 (100%)	7	Erenumab	−11.3	51%	3 months
Schoenen et al.	156	80 (51%)	76 (49%)	50 (32%)	>2 in 74%	Erenumab	−4.2 in EM −7.8 in CM	55% in EM 43% in CM	3 months
Torres Ferrus et al.	155	20	135	97	>4 in 89%	Erenumab Galcanezumab	−9.1	51.6%	3 months
Vernieri et al. (GARLIT)	163	33	130	117	4 in EM 5 in CM	Galcanezumab	−8 in EM −13 in CM	76.5% in EM 66.7% in CM	6 months

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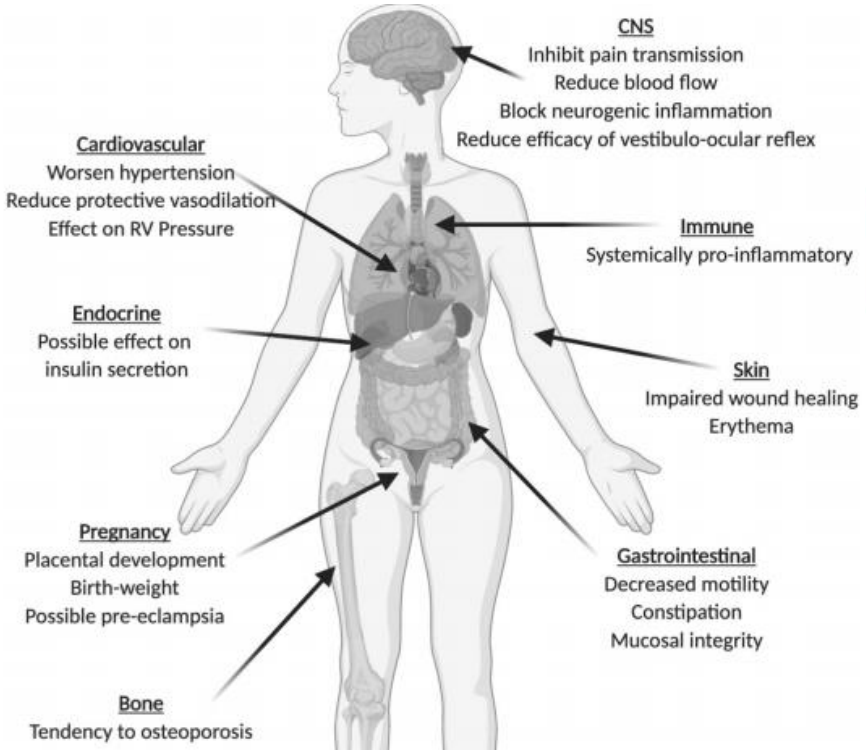
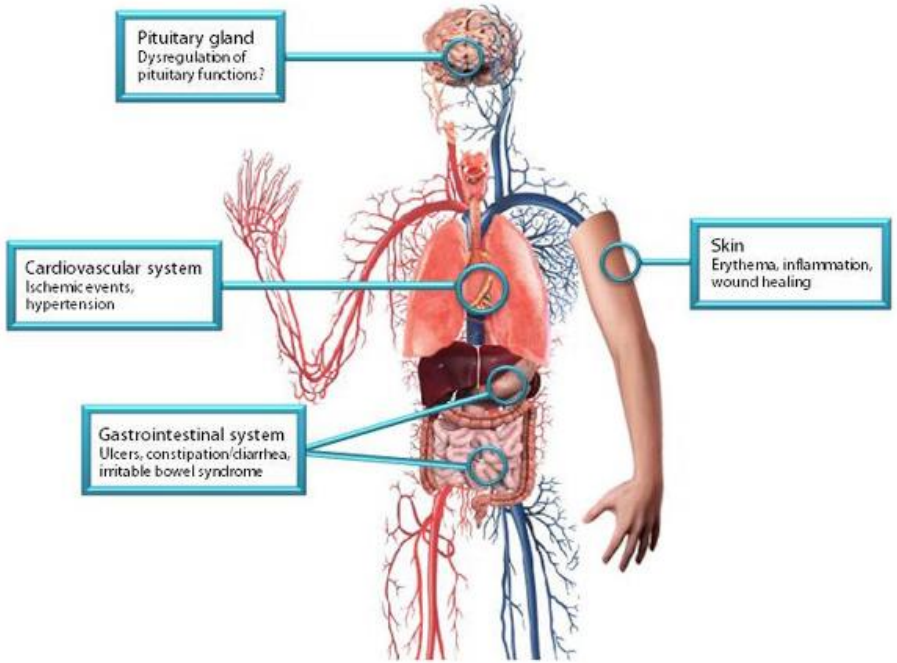
DISEASES AND CONDITIONS POTENTIALLY RELATED TO CGRP BLOCK





System	Possible benefit	Possible caution/consider
Family history		SAH Osteoporosis
Neurological		Multiple sclerosis Stroke
Gastrointestinal		Constipation Peptic ulcer disease Inflammatory bowel disease
Cardiovascular		Hypertension Pulmonary hypertension Vascular disease
Endocrinological		Osteoporosis Pituitary dysfunction
Skin		Psoriasis Atopic dermatitis
Rheumatological	Osteoarthritis Rheumatoid arthritis	

In conclusion, based on current knowledge, we believe that the benefits of blocking CGRP – including the perspectives of improving the lives of those suffering from frequent headaches – seems to be greater than the disadvantages.

Russell Physiol Rev 2014 Deen Journal of Headache and Pain 2017 Ray JNNP 2021

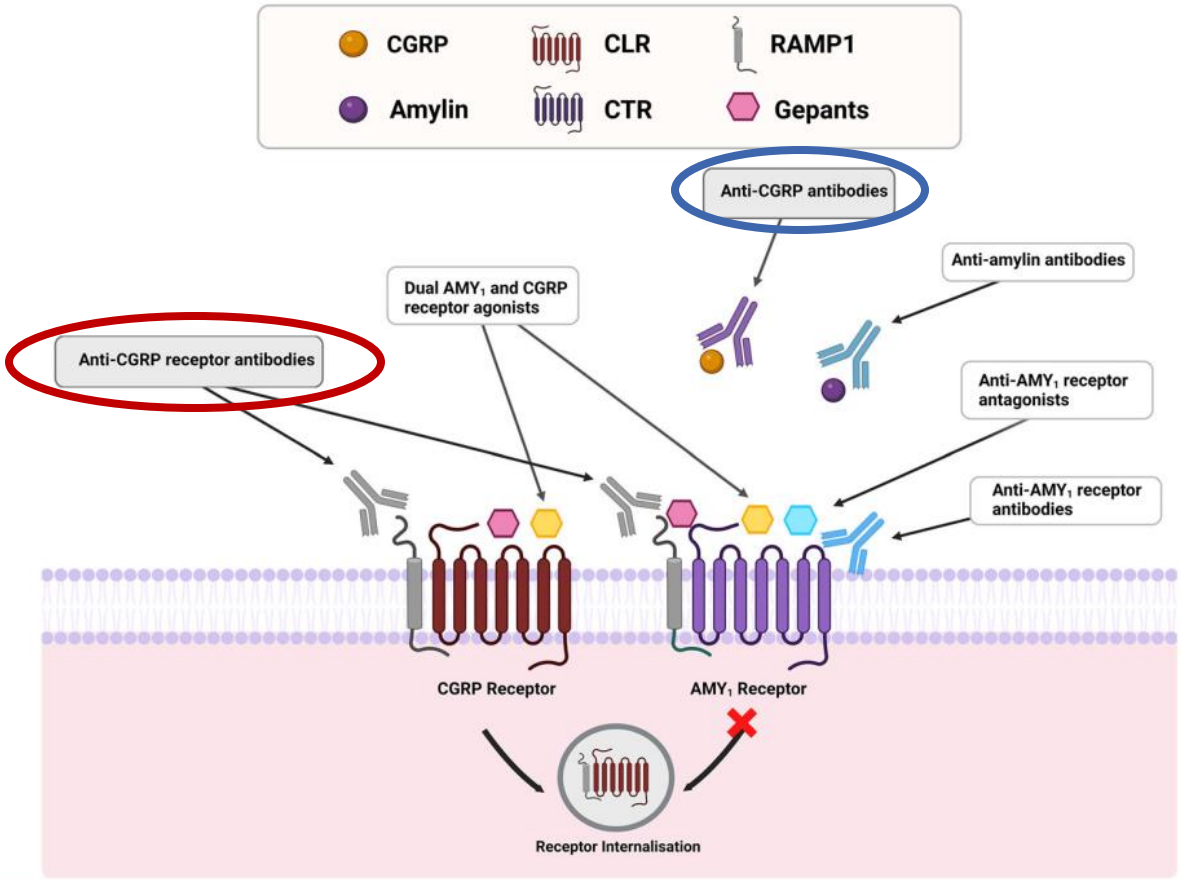
CONCLUSION AND OPEN QUESTIONS

- Main peripheral action of Ab anti-CGRP
- Fremanezumab, eptinezumab, galcanezumab block CGRP
- Erenumab blocks RAMP1/CLR and also RAMP1/CTR
- Eptinezumab peak in hours
- Ab anti-CGRP/R class switch
- Ab anti-CGRP/R and Gepants switch

- Ab anti-CGRP/R and Onabotulintoxin A add-on
- Outcome predictors
- Use in children and adolescents
- Long-term treatment adherence and persistence
- Effect persistence after discontinuation

GRAZIE!

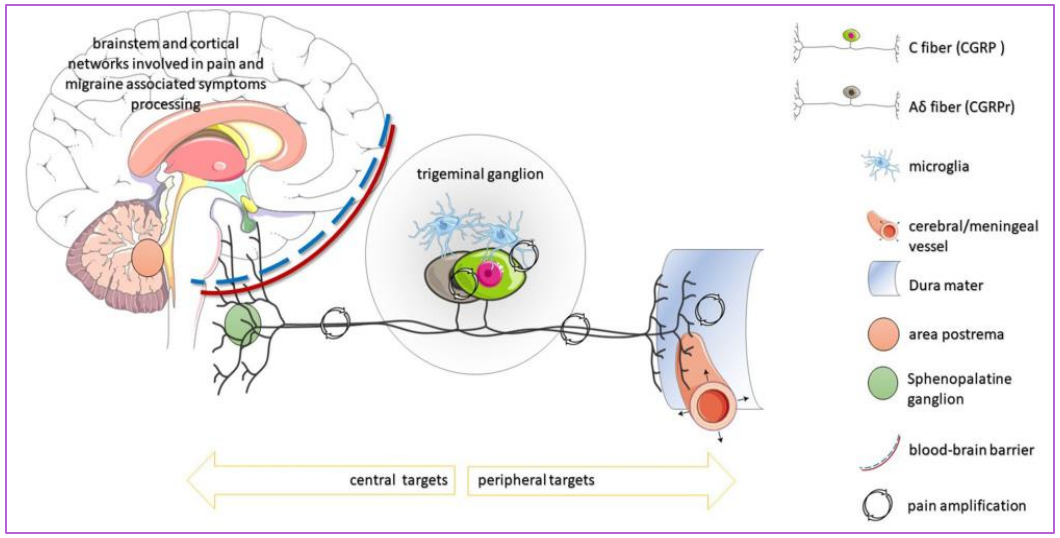
CROSSTALK BETWEEN CGRP AND AMYLIN



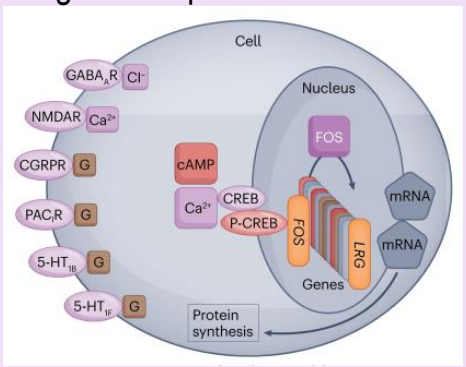
- CGRP and amylin 1 (AMY1) receptors are formed by association of either CLR or CTR with RAMP1, respectively.
- **CGRP and amylin are equipotent at the AMY1 receptor,** while **CGRP is more potent at the** canonical **CGRP receptor.**
- These receptors have a **distinct internalization profile**. Current antimigraine drugs targeting CGRP (blue boxes) and potential antimigraine amylin drugs (white boxes) are shown.

Labastida-Ramírez The Journal of Headache and Pain 2023

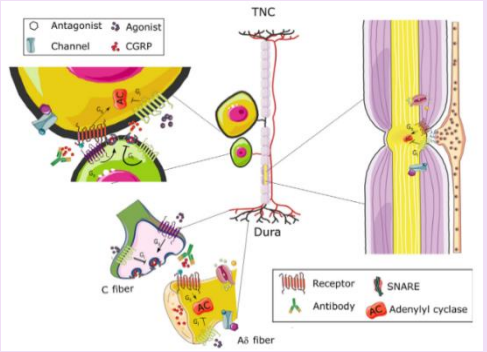
CGRP PATHWAYS AND CGRP RECEPTOR ANTAGONISM WITHIN TRIGEMINOVASCULAR PATHWAY

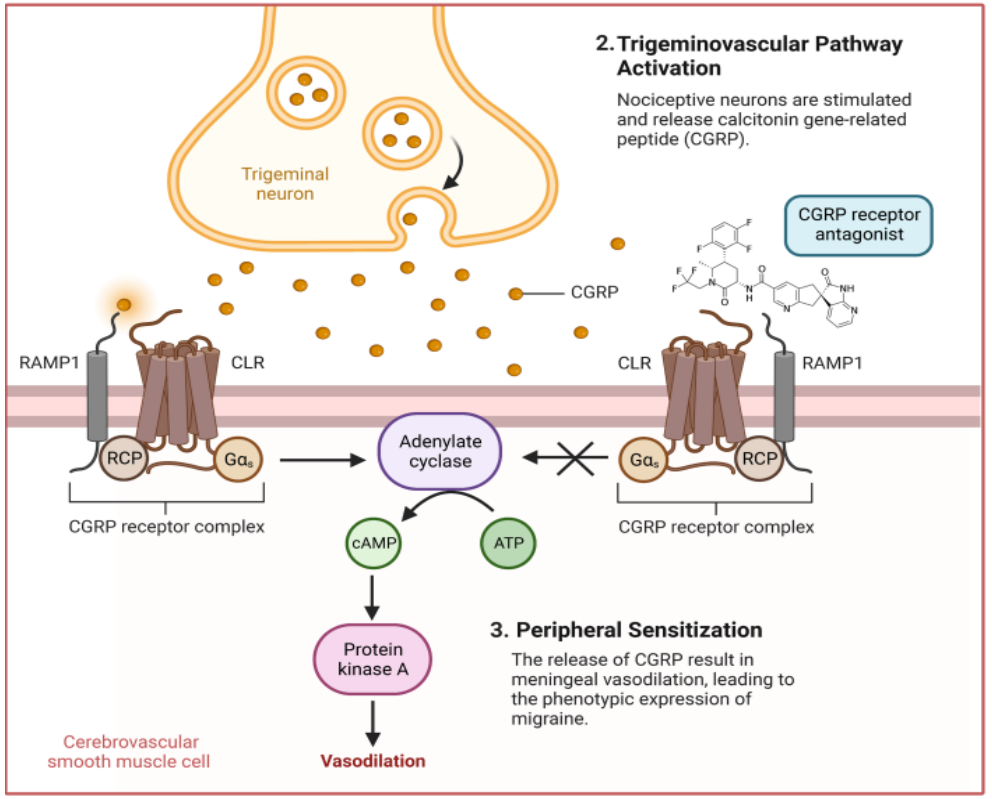


Trigeminal spinal nucleus



Trigeminal spinal ganglion

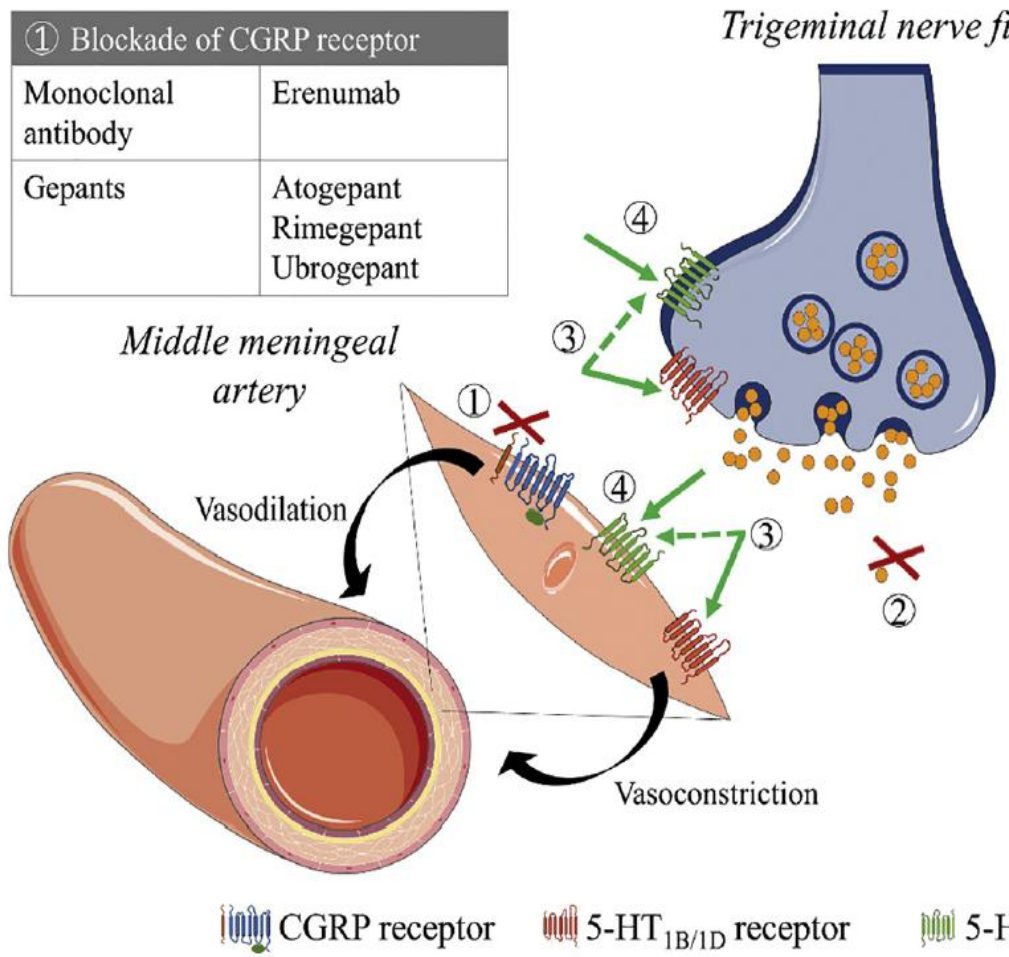




ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CLR, calcitonin receptor-like receptor; RAMP1, receptor activity-modifying protein; RCP, receptor component protein

Edvinsson Trends In Pharmacological Sciences 2021
Mitsikostas DD Nature Rev Neurol 2023
Boinpally R Clin Transl Sci 2024
Altamura C Neurological Sciences 2022

① Blockade of CGRP receptor	
Monoclonal antibody	Erenumab
Gepants	Atogepant Rimegepant Ubrogepant



② Blockade of CGRP	
Monoclonal antibody	Eptinezumab Fremanezumab Galcanezumab

③ Stimulation of 5-HT$_{1B/1D(/1F)}$ receptor	
Triptans	Almotriptan Eletriptan Frovatriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan

④ Stimulation of 5-HT$_{1F}$ receptor	
Ditans	Lasmiditan

De Vries- Pharm. And Ther. 2021

Generic drug name	Indication	Dosage and administration	T_{max}	$t_{1/2}$
Small molecule CGRP receptor antagonists				
Atogepant	• Preventive treatment of migraine in adults	10, 30, or 60 mg taken orally daily	~1–2 h	~11 h
Rimegepant	• Acute treatment of migraine with or without aura in adults, and • Preventive treatment of episodic migraine in adults	Acute: 75 mg taken orally, as needed; maximum 24-h dose is 75 mg preventive: 75 mg taken every other day	1.5 h	~11 h
Ubrogepant	• Acute treatment of migraine with or without aura in adults	50 or 100 mg taken orally, as needed; maximum 24-h dose is 200 mg	1.7 h	5–7 h
Zavegepant	• Acute treatment of migraine with or without aura in adults	10 mg single intranasal spray taken as needed; maximum 24-h dose is 10 mg	~30 min	6.55 h
mAb targeting the CGRP receptor				
Erenumab	• Preventive treatment of migraine in adults	70 or 140 mg monthly single dose s.c. injection	4–6 days[a]	28 days
mAbs targeting the CGRP ligand				
Eptinezumab	• Preventive treatment of migraine in adults	100 or 300 mg i.v. infusion over 30 min every 3 months	End of infusion	~27 days
Fremanezumab	• Preventive treatment of migraine in adults	225 mg monthly, or 675 mg every 3 months s.c. injection	5–7 days[a]	~31 days
Galcanezumab	• Preventive treatment of migraine, and • Treatment of episodic cluster headache	240 mg s.c. injection loading dose, followed by monthly doses of 120 mg	5 days[a]	27 days

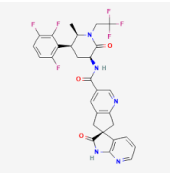
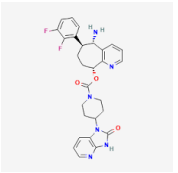
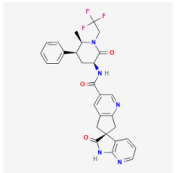
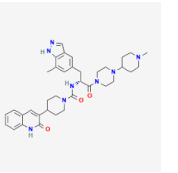
Boinpally R Clin Transl Sci 2024

ACUTE TREATMENT

- *Three gepants*
  - ubrogepant
  - rimegepant
  - zavegepant

PREVENTIVE TREATMENT

- *Two gepants*
  - atogepant
  - rimegepant

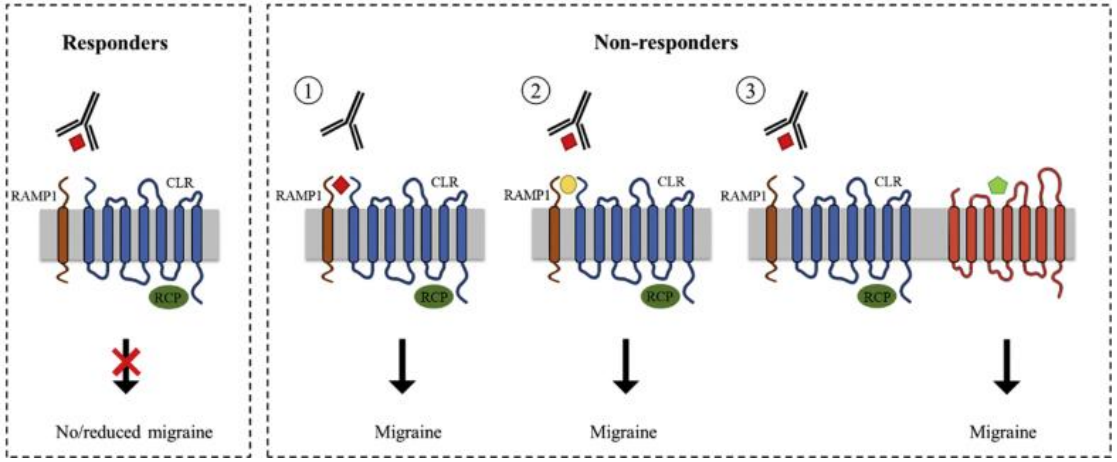





	Gepants	Anti-CGRP monoclonal antibodies
Target	CGRP receptor	CGRP receptor or ligand
Clearance	Liver, kidney	Reticuloendothelial system
Half-life	5–11 h	3–7 weeks
Size	0.5–0.6 kDa	143–146 kDa
Ability to cross blood–brain barrier	Low (1.4% CSF/plasma ratio)	No
Administration	Oral, intranasal	Parenteral
Immunogenicity	No	Yes

Linda Al-Hassany Lancet Neurol 2022

Medication targeting CGRP

Monoclonal antibodies (eptinezumab, fremanezumab, galcanezumab)

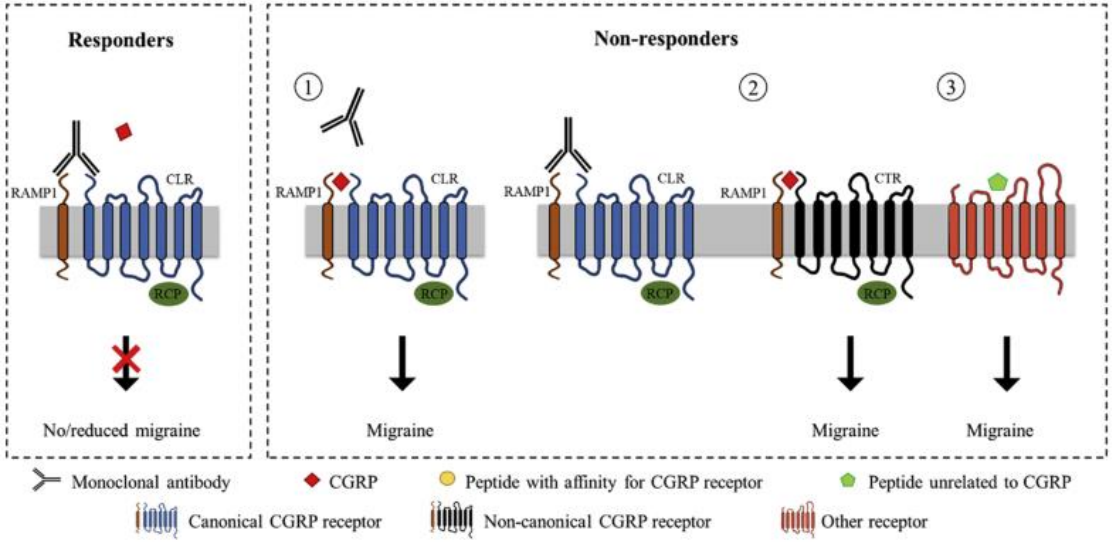


In responders to medications targeting CGRP (eptinezumab, fremanezumab and galcanezumab), CGRP is sufficiently blocked, leading to a reduction in migraine.

In non-responders, multiple situations are possible 1) **Blocking of CGRP is insufficient**. 2) Blocking of CGRP is sufficient, but **other peptides** (e.g. amylin) **can activate the CGRP receptor**. 3) Blocking of CGRP is sufficient, but migraine is induced **via a different pathway**.

Medication targeting the CGRP receptor

*Monoclonal antibody (erenumab) and gepants (atogepant, rimegepant, ubrogepant)**



In responders to medications targeting the CGRP receptor (erenumab or the gepants; atogepant, rimegepant, ubrogepant, zavegepant), the receptor is sufficiently blocked. Migraine persists in non-responders. 1) **Blocking of the CGRP receptor is insufficient**. 2) Blocking of the CGRP receptor is sufficient but **CGRP can activate related receptors** (e.g. AMY1 receptor). 3) Migraine is induced **via a different pathway**

De Vries T Pharmacology & Therapeutics 2020