Advanced Migraine Treatments: CGRP Monoclonal Antibodies, Gepants and Botox

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HEADACHE ACADEMY

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Preventive Treatments for Migraine: Current Options

ORAL TREATMENTS

- **Antidepressants**
  - TCAs: Amitriptyline*
  - SNRIs: Venlafaxine
- **Beta-blockers**
  - Propranolol*.
- **Angiotensin-based**
  - Candesartan*
- **Anticonvulsants**
  - Topiramate*, Valproate
- **Ca Channel blockers**
  - Flunarizine
- **Serotonin antagonists**
  - Pizotifen
- **Nutraceuticals (metabolic)**
  - Magnesium, Riboflavin*, CoEnzyme Q10

INJECTABLE TREATMENTS

- **Botulinum toxin type A (chronic migraine)***
- **CGRP monoclonal antibodies***
  - Erenumab
  - Fremanuzemab
  - Galcanezumab
  - Eptinezumab infusion

EMERGING TREATMENTS

- **CGRP antagonists***
  - Rimegepant (Episodic migraine)
  - Atogepant

Evidence for efficacy for most traditional oral preventive treatments derived mainly from studies in Episodic Migraine
*Recommended by NICE and/or RCT evidence base available

Guidelines on Preventive Treatments for Migraine

	NICE[1]	BASH[2]	AHS[3]
Antidepressants			
TCAs: Amitriptyline*	Consider	Yes	Probably effective
SNRIs: Venlafaxine			Probably effective
Beta-blockers			
Propranolol*.	Offer	Yes	Established efficacy
Serotonin antagonists			
Pizotifen			
Anticonvulsants			
Topiramate*	Offer	Yes	Established efficacy
Valproate			Established efficacy
Ca Channel blockers			
Flunarizine	NICE Evidence summary: flunarizine is as effective as propranolol and topiramate[4]		
Angiotensin-based			
Candesartan*		Yes	Established efficacy
Nutriceuticals (metabolic)			
Magnesium			
Riboflavin*	Consider		
CoEnzyme Q10			

1. NICE, National Institute for Health and Care Excellence; https://www.nice.org.uk/guidance/cg150
2. BASH, British Association for the Study of Headaches; https://www.bash.org.uk/guidelines/
3. AHS, American Headache Society; The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache. 2019;59(1):1-18
4. NICE Evidence Summary on Flunarzine: https://www.nice.org.uk/advice/esuom33/chapter/Key-points-from-the-evidence

Specific and/or Emerging Preventive Treatments

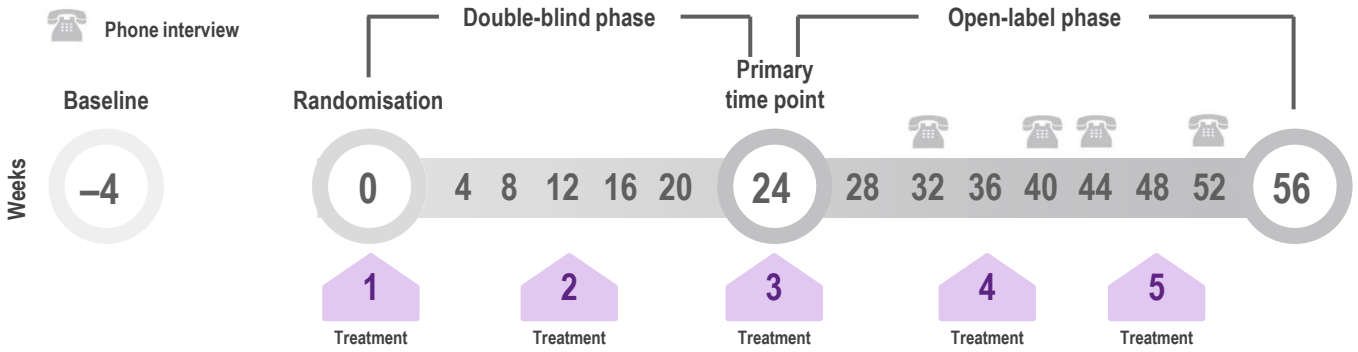
Class	Drug	Dose	Cautions
Botulinum toxin	OnabotulinumtoxinA	155–195 units to 31–39 sites every 12 weeks	Neuromuscular disorder
CGRP monoclonal antibodies	Erenumab	70 mg or 140 mg SC once monthly	Stroke, ischaemic heart disease, Raynaud's syndrome
	Fremanezumab	225 mg SC once monthly or 675 mg SC 3 monthly	
	Galcanezumab	240 mg SC loading dose, then 120 mg SC once monthly	
	Eptinezumab	100 mg or 300 mg IV 3 monthly	
CGRP receptor antagonists	Rimegepant	75 mg every alternate day	Severe liver or renal disease; CYP3A4 inhibitors/inducers
	Atogepant	60 mg daily	

Please refer to SmPC of each product for complete information
CGRP, calcitonin gene-related peptide; SC, subcutaneously; IV, intravenously.
Eigenbrodt AK, *et al*. *Nat Rev Neurol*. 2021;17(8):501–514.

Botulinum Toxin Type A in Chronic Migraine

PREEMPT studies[1,2]

- Two trials: PREEMPT 1 and PREEMPT 2
- Phase 3, parallel-group, placebo-controlled studies of Botulinum toxin A 155-195U in Chronic Migraine
- 1384 patients randomised (Botulinum toxin A 688, Placebo 696)
- Headache symptoms and medications were recorded in a daily telephone diary[2]

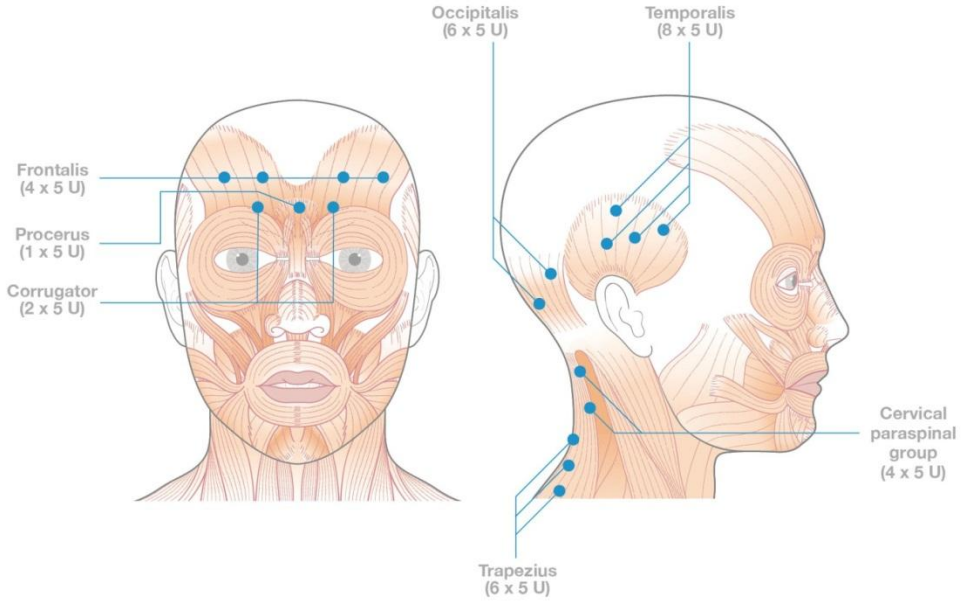


PREMPT = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy clinical program.

1. Dodick DW et al. *Headache* 2010;**50**:921–36

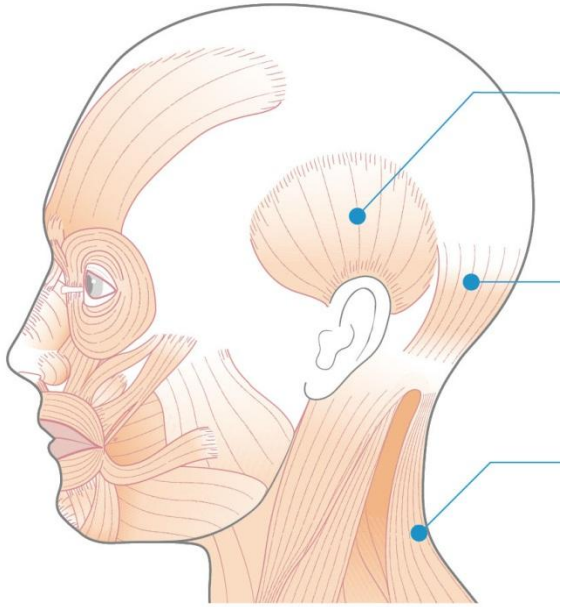
PREEMPT Injection Paradigm

Fixed-site fixed-dose injections



A total of 31 injections across seven specific head and neck muscles, with a minimum dose of 155 U of BOTOX® injected per patient

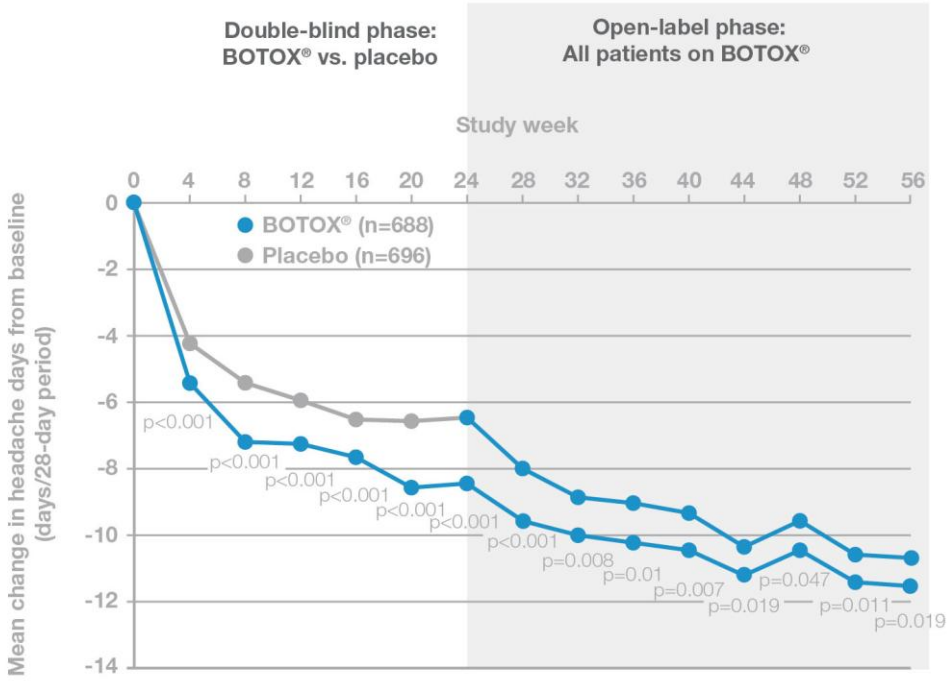
Follow-the-pain injections

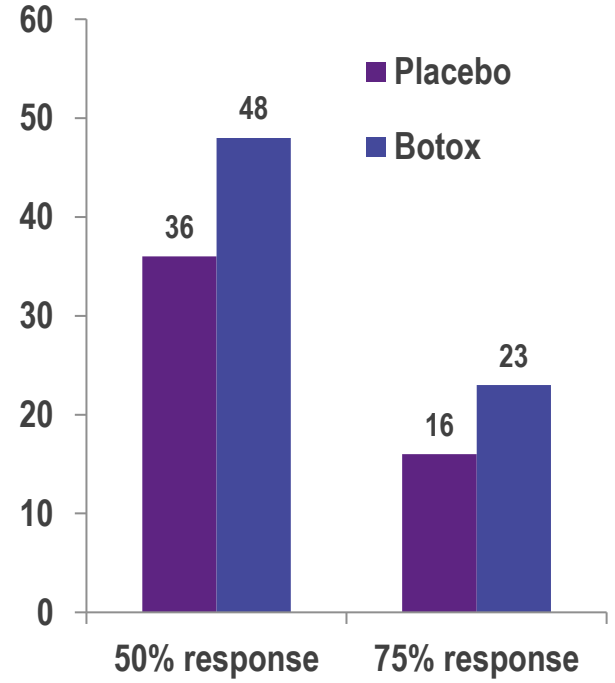


Option of 8 extra injections in three specific head and neck muscles, with a maximum dose of 195 U of BOTOX® injected per patient

Botulinum toxin type A (Botox) in Chronic Migraine

- Two trials: PREEMPT1 and PREEMPT 2
- Phase 3, parallel-group, placebo-controlled studies of Botulinum toxin A 155-195U in Chronic Migraine
- 1384 patients randomised (Botulinum toxin A 688, Placebo 696)



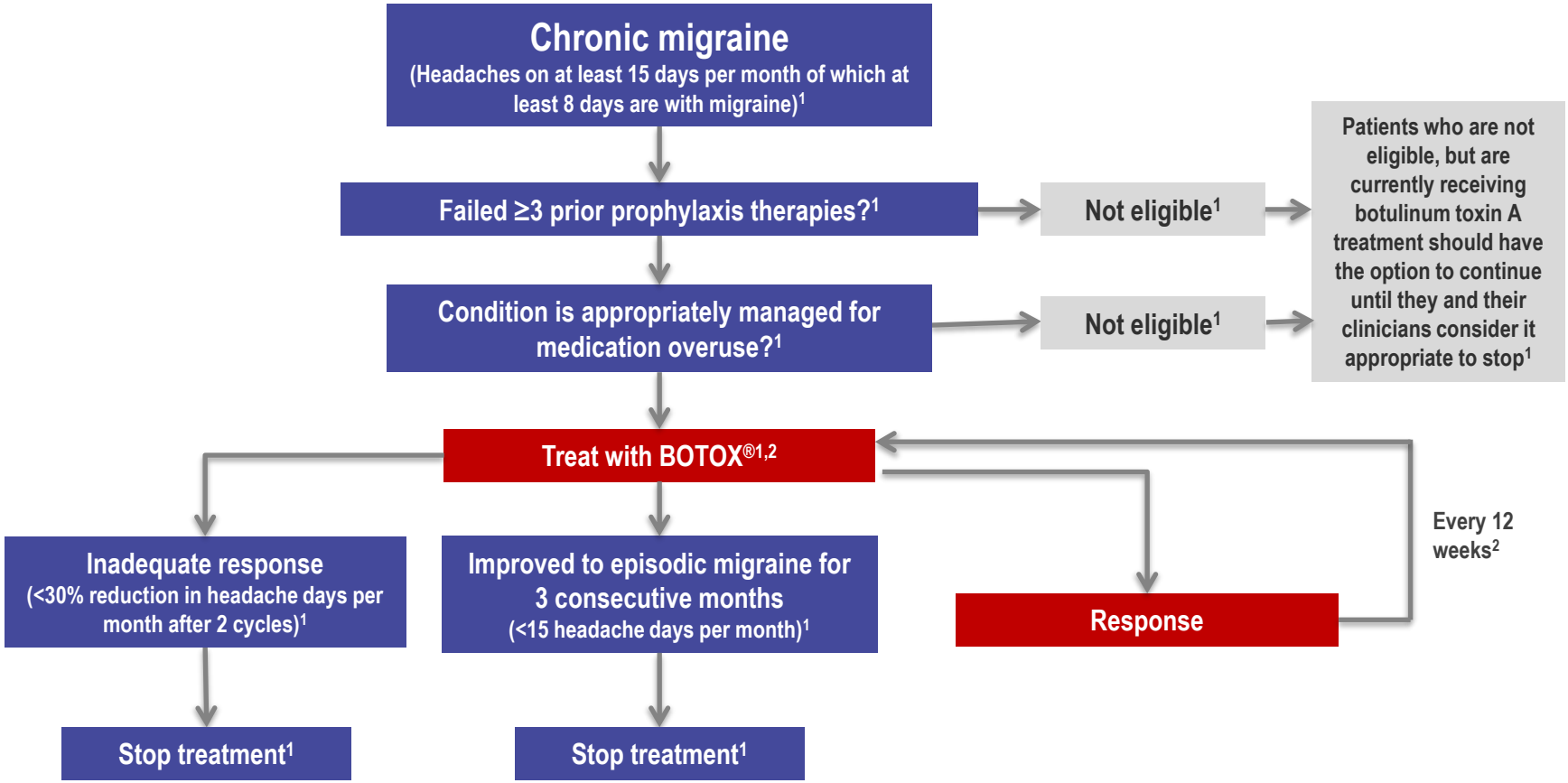


Aurora SK *et al*. Headache 2011;51:1358-1373; Dodick DW *et al. Headache* 2010;**50**:921–936; Silberstein et al, Headache 2007;47(2):170-180.

PREEMPT pooled analysis: treatment-related adverse events (AEs) reported in ≥2% of patients at Week 24 (%)

Treatment-related AEs*	Double-blind phase (24 weeks)		Open-label phase (32 weeks)
	BOTOX® (n=687) n (%)	Placebo (n=692) n (%)	Total (N=1205) n (%)
Total treatment-related AEs	202 (29.4)	88 (12.7)	245 (20.3)
Neck pain	46 (6.7)	15 (2.2)	55 (4.6)
Muscular weakness	38 (5.5)	2 (0.3)	47 (3.9)
Eyelid ptosis	23 (3.3)	2 (0.3)	30 (2.5)
Musculoskeletal pain	15 (2.2)	5 (0.7)	13 (1.1)
Injection-site pain	22 (3.2)	14 (2.0)	24 (2.0)
Headache	20 (2.9)	11 (1.6)	17 (1.4)
Myalgia	18 (2.6)	2 (0.3)	15 (1.2)
Musculoskeletal stiffness	16 (2.3)	5 (0.7)	20 (1.7)
Muscle tightness	9 (1.3)	1 (0.1)	26 (2.2)

NICE treatment pathway



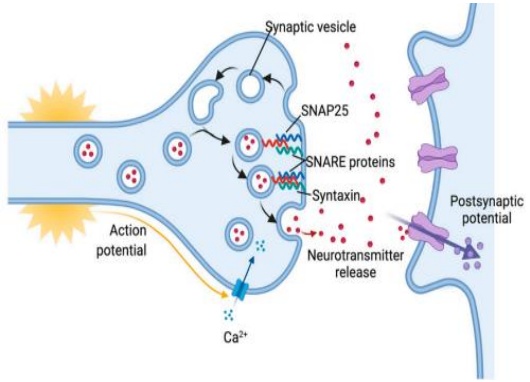
1. NICE technology appraisal guidance 260. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. June 2012
2. BOTOX®. Summary of product characteristics. Allergan Ltd

BOTOX®: sensorimotor mechanism of action

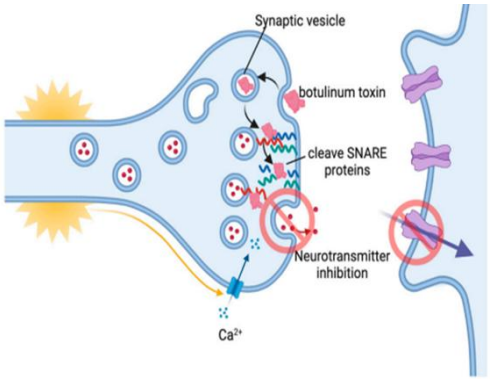
- The antinociceptive effect of BOTOX® is distinct from its neuromuscular activity[1]
- The biochemical effect of BOTOX® (cleavage of SNAP-25 to impair synaptic vesicle fusion and neurotransmitter release) is the same at both sensory and motor nerve terminals[1]

	Motor	Sensory
Mechanism of action	• BOTOX® blocks cholinergic transport by preventing the release of acetylcholine[2]	• BOTOX® blocks the release of neurotransmitters associated with the genesis of pain[2] • BOTOX® reduces the cell surface expression of ion channels and sensory receptors[3]
Treatment benefit	• Muscle relaxation[3]	• Pain reduction[3] • BOTOX® also blocks peripheral signals, thereby possibly inhibiting central sensitisation[2]

A) Normal synaptic transmission



B) Neuronal uptake of BOTOX

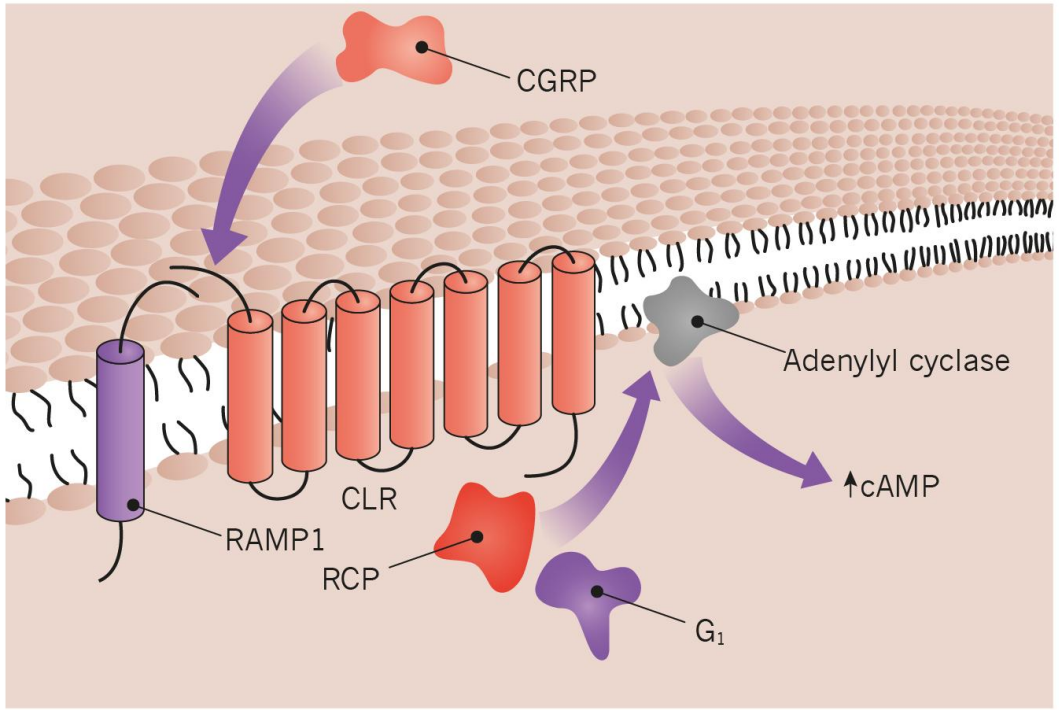


SNAP-25, synaptosomal-associated protein, 25kDa.

1. Aoki KR. Headache. 2003;43(Suppl 1):S9−15; 2. BOTOX® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/medicine/112. Accessed August 2023; 3. Whitcup AM, et al. Ann NY Acad Sci. 2014;1329:67–80.

Calcitonin Gene-Related Peptide (CGRP)

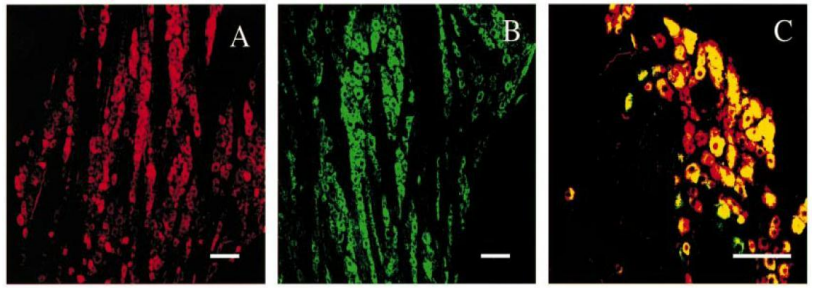
- 37 amino acid peptide
- Brain: alpha form; Gut: beta form (3 amino acids differ)
- CGRP and CGRP receptors are widely expressed in the central nervous system (CNS) and throughout the trigeminovascular system.
- CGRP is a potent vasodilator of cerebral arteries
- In the trigeminocervical complex, CGRP acts on second-order neurons to activate spinothalamic pathways
- Trigeminal ganglion stimulation increases CGRP in the cranial circulation



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

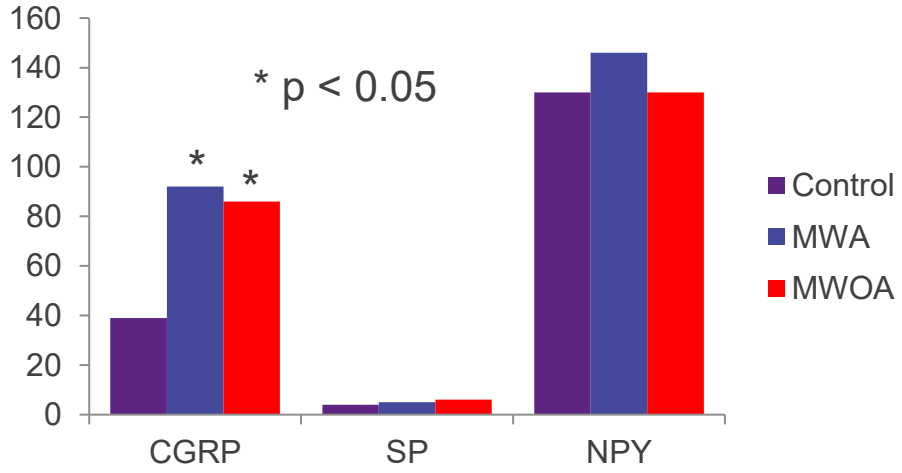
Calcitonin gene related peptide (CGRP) and Headache

- CGRP co-localizes with $5HT_{1B/1D}$ receptors in rat trigeminal ganglion
- Triptans suppress CGRP release



- CGRP elevated during migraine attack
- Elevated CGRP returns to normal when migraine attack treated with triptans

- CGRP infusion causes a delayed migrainous headache in migraine subjects



Zagami et al, Neuropeptides 1990; Goadsby et al, Ann Neurol 1988; Ma et al, EJN 2001; Goadsby, *Ann Neurol*. 1990; Goadsby, Headache 1994; Lassen, Cephalalgia 2002

CGRP-Based Therapies in Migraine Management

CGRP (Calcitonin Gene-Related Peptide) therapies include two main classes:

- **CGRP monoclonal antibodies: Used primarily for migraine prevention.**
- **CGRP antagonists (Gepants): These are small molecules that block CGRP receptors, offering more flexibility as both acute and preventive treatments.**

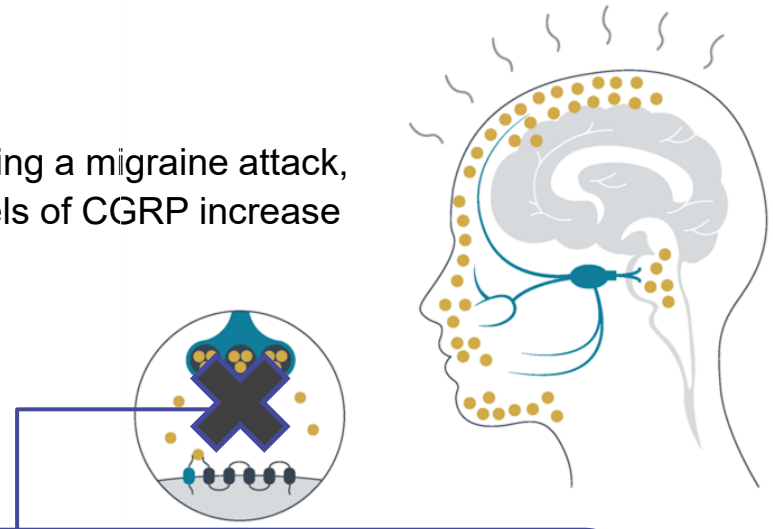
CGRP Antagonists (Gepants):

- **Gepants are oral or nasal CGRP receptor antagonists that inhibit the binding of CGRP to its receptor**

Uses:

- **Acute Treatments:**
  - **Rimegepant**
  - **Ubrogepant**
  - **Zavegepant** (nasal spray)
- **Preventive Treatments:**
  - **Rimegepant** (dual use: acute and preventive)
  - **Atogepant**

During a migraine attack, levels of CGRP increase



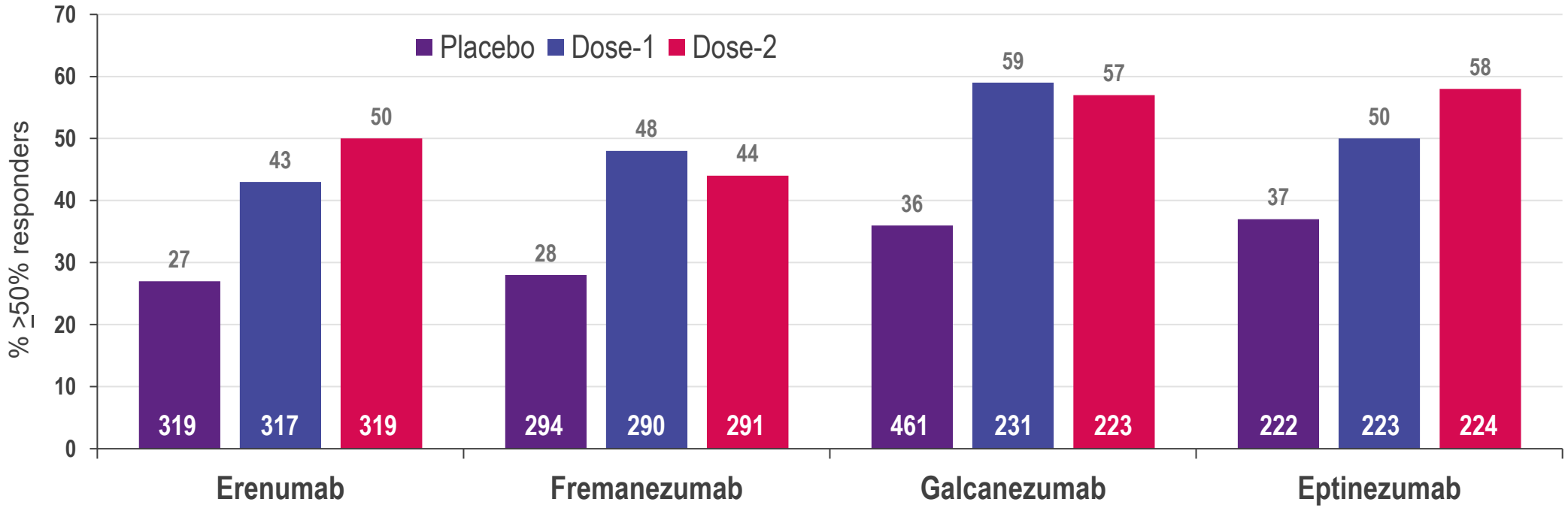
Gepants blocks the binding of CGRP to the receptor and antagonises CGRP receptor function, preventing migraine attacks

CGRP Monoclonal Antibodies and Migraine

	Eptinezumab	Erenumab	Galcanezumab	Fremanezumab
Antibody-IgG	1	2	4	2a
Type	Humanised Rabbit	Human	Humanised	Humanised
Target	CGRP	CLR/RAMP1	CGRP	CGRP
Half-life (days)	28	21	25-30	45
Phase III dosing	100mg or 300 mg IV 3 monthly No loading dose	70 mg or 140 mg SC monthly No loading dose	Loading dose 240 mg SC followed by 120 mg monthly	225 mg SC monthly or 675mg/3 monthly No loading dose
Other	Yeast production			

CGRP: calcitonin gene-related peptide
CLR: calcitonin receptor-like receptor
RAMP1: receptor activity-modifying protein

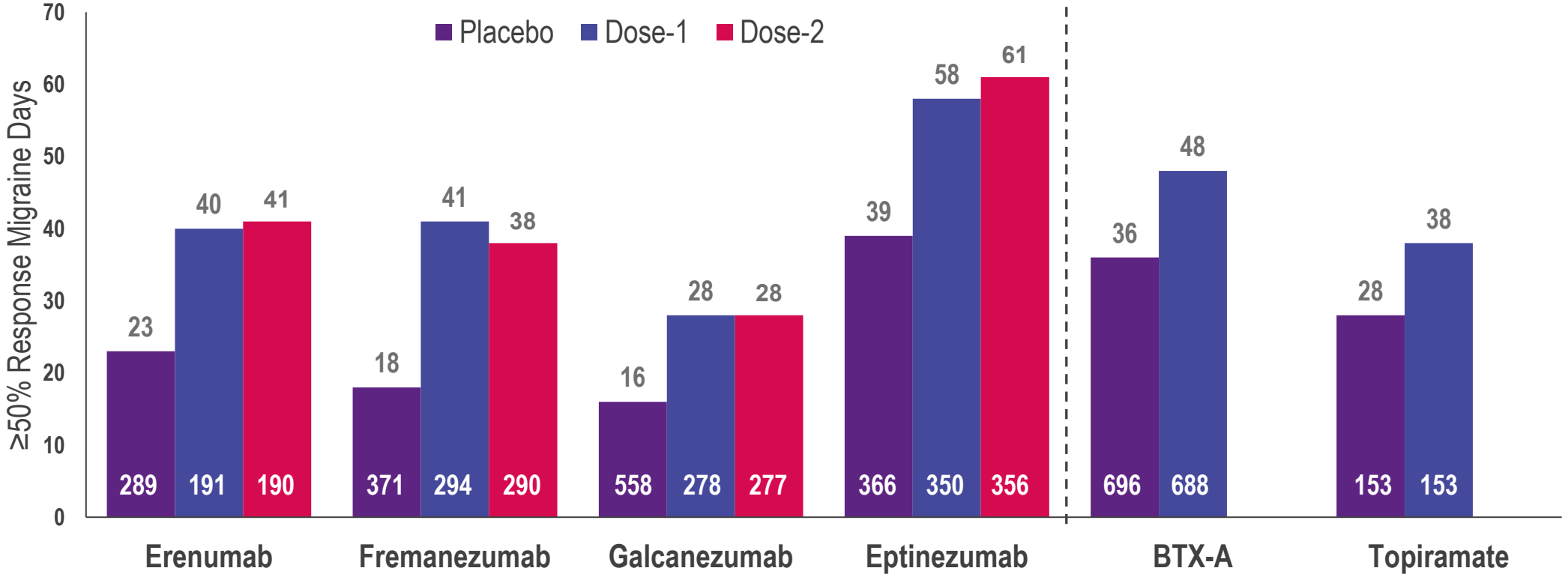
Episodic Migraine treated with CGRP Monoclonal Antibodies: Phase III Results[1]



	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Dose-1:	70mg/4 weeks, sc	225mg/4 weeks, sc	120mg/4 weeks, sc	100mg/12 weeks, iv
Dose-2:	140mg/4 weeks, sc	675mg/12 weeks, sc	240mg/4 weeks, sc	300mg/12 weeks, iv
	(2)	(3)	(4)	(5)

(1) Ray JC, et al. J Neurol Neurosurg Psychiatry. 2021. (2) Goadsby PJ, et al. N Engl J Med. 2017;377(22):2123-32. (3) Dodick DW, et al. JAMA. 2018;319(19):1999-2008.
(4) Skljarevski V, et al. Cephalalgia. 2018;38(8):1442-54. (5) Ashina M, et al. Cephalalgia. 2020;40(3):241-54.

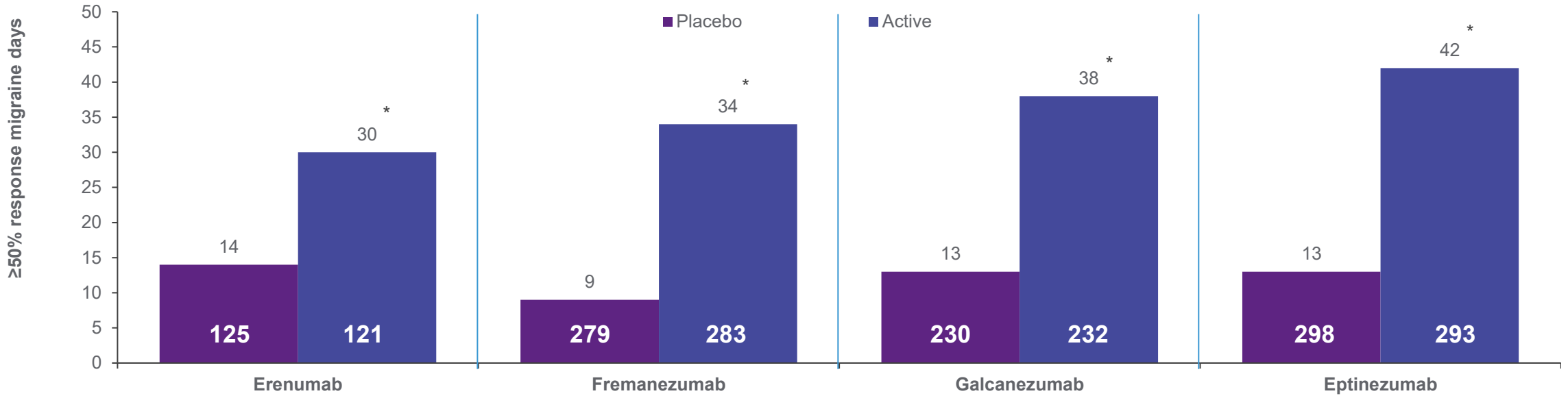
Chronic Migraine treated with CGRP Monoclonal Antibodies
Phase III Results compared to Current Therapies[1]



	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab	BTX-A	Topiramate
Dose-1:	70mg/4 weeks, sc	225mg/4 weeks, sc	240mg LD; 120mg/4 weeks, sc	100mg/12 weeks, iv	PRE-EMPT	100mg daily
Dose-2:	140mg/4 weeks, sc (2)	675mg/12 weeks, sc (3)	240mg/4 weeks, sc (4)	300mg/12 weeks, iv (5)	(6)	7)

(1) Ray JC, et al. J Neurol Neurosurg Psychiatry. 2021. (2) Tepper S, et al. Lancet Neurol. 2017;16(6):425-34. (3) Silberstein SD, et al. New England Journal of Medicine. 2017;377(22):2113-22. (4) Detke HC, et al. Neurology. 2018;91(24):e2211-e21. (5) Lipton RB, et al. Neurology. 2020;94(13):e1365-e77.(6) Aurora SK, et al. Headache. 2011;51(9):1358-73. (7) Silberstein SD, et al. Headache. 2007;47(2):170-80. LD, Loading dose

CGRP Monoclonal Antibodies in Treatment-Resistant Migraine (2–4 prior preventive treatments)



	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Dose:	140 mg, SC[1]	225 mg, SC[2]	240 mg LD; 120 mg SC[3]	100 mg, IV[4]
Study population:	Episodic migraine (4–14 days/month)	Episodic and chronic migraine (≥4 days/month)	Episodic and chronic migraine (≥4 days/month)	Episodic and chronic migraine (≥4 days/month)

This figure is for illustrative purposes only and should not be used to compare across studies.

* Statistically significant difference vs placebo

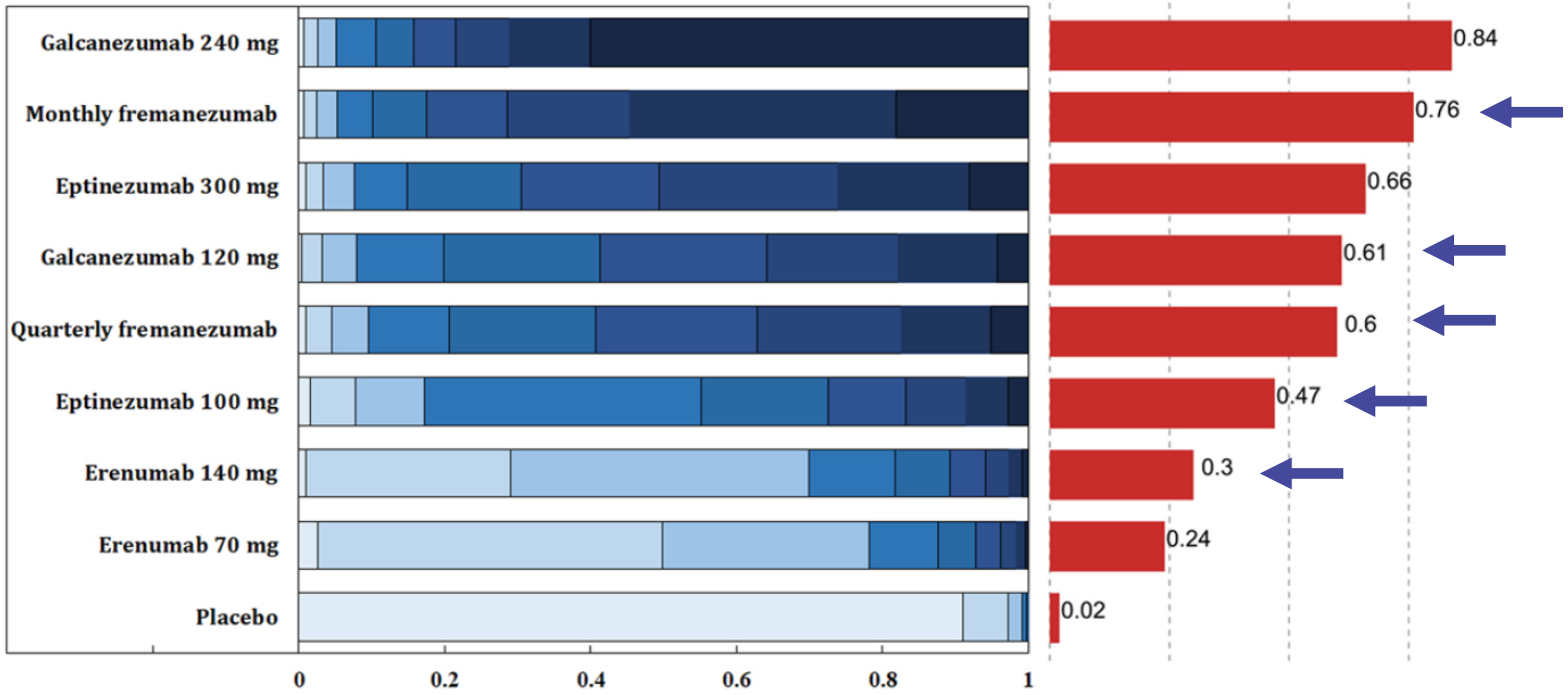
CGRP, calcitonin gene-related peptide; LD, loading dose, IV, intravenously, SC, subcutaneously.

1. Reuter U, *et al. Lancet*. 2018;392(10161):2280–2287; 2. Ferrari MD, *et al. Lancet*. 2019;394(10203):1030–1040; 3. Mulleners WM, *et al. Lancet Neurol*. 2020;19(10):814–825; 4. Ashina M, *et al. Lancet Neurol*. 2022;21(7):597–607.

Which CGRP monoclonal antibody is the most effective one?

- Network meta-analysis of CGRP monoclonal antibody (mAb) RCTs in migraine patients with previous treatment failure (2-4 preventive treatments)
- Primary efficacy outcome was change in monthly migraine days (MMDs)
- Seven studies totalling 3,052 patients were included.

Ranking probabilities graph of each treatment agent.



- CGRP mAbs was superior to CGRP receptor mAbs in reducing MMDs
- Fremanezumab or eptinezumab 300 mg provides a significant advantage over erenumab 140 mg

Wang X et al. J Headache Pain. 2022;23(1):105.

← CGRP monoclonal antibodies available in NHS

Real world experience: side effect profile[1,2]

- **Constipation (5-20%)**
- **Cold and flu-like symptoms (3-15%)**
- **Fatigue/lethargy (5-7%)**
- **Pruritus/Itching(1-5%)**
- **Injection site reactions (5%)**
- **Development of hypertension and worsening of pre-existing hypertension**
  - Transiently elevated BP in 5%
  - 362 cases identified from >245,000 patient-years of exposure; Incidence of hypertension was 0.144 per 100 patient-years
  - FDA warning: BP monitoring will be required with Aimovig
- **Muscle spasms (1-2%)**
- **Others (4-9%): hair loss, autoimmune conditions, anxiety, insomnia, joint pain**


CASE REPORT Open Access

Inflammatory complications of CGRP monoclonal antibodies: a case series

Check for updates

Jason C. Ray[1,2,3*], Penelope Allen[4,5†], Ann Bacsi[6†], Julian J. Bosco[7,8†], Luke Chen[3,9†], Michael Eller[10,11†], Hock Kua[12†], Lyndell L. Lim[4,5†], Manjit S. Matharu[13†], Mastura Monif[3,14,15†], Martin Ruttledge[16†], Richard J. Stark[1,3†] and Elspeth J. Hutton[1,3]

Case series of eight patients with new or significantly worsened inflammatory pathology in close temporal association with the commencement of CGRP mAb therapy

Raynaud's disease[3]

- 99 reports in Vig-iBase
- 57% of reports with erenumab
- Gangrene and extremity necrosis in 1 patient

WHILE IT IS IMPORTANT TO MAINTAIN VIGILANCE WITH THE USE OF CGRP MONOCLONAL ANTIBODIES, THE EMERGING EXPERIENCE IS THAT THEY ARE VERY WELL TOLERATED

1. Torres-Ferrús, M., *et al.* The impact of anti-CGRP monoclonal antibodies in resistant migraine patients: a real-world evidence observational study. *J Neurol* **268,** 3789–3798 (2021).
2. Lambru, G. *et al.* A prospective real-world analysis of erenumab in refractory chronic migraine. *J Headache Pain* **21,** 61 (2020). https://doi.org/10.1186/s10194-020-01127-0
3. Gérard AO, et al. Calcitonin gene-related peptide-targeting drugs and Raynaud's phenomenon: a real-world potential safety signal from the WHO pharmacovigilance database. J Headache Pain. 2022;23(1):53.

Duration of use of CGRP mAbs when treatment is effective?

European Headache Federation Guideline:[1]

- **A pause in effective treatment may be considered after 12 to 18 months**
- **The CGRP mAb should be resumed if the frequency of migraine attacks increases.**

Evidence:

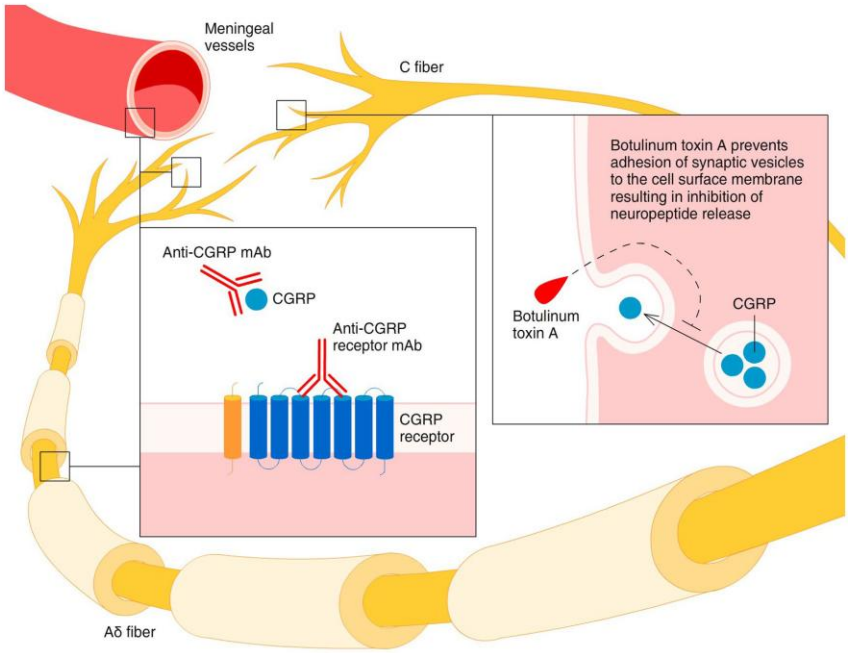
- **After ~12 months → 3-month holiday**
  - **Italian multicentre cohort** (n=154): at 3 months off, HFEM ~28% and CM ~36% still met a ≥50% responder threshold; many CM met restart criteria by month-1 (≥8 MMD). [2]
  - **Swiss real-world cohort** (n=52): mean MMD rose from 5 ± 4 at month-12 on-treatment to 11 ± 5 by month-3 off; 88.9% restarted within 3 months (≈11% remained off-drug). [3]
- **After multi-year therapy → 1-month holiday (I-GRAINE)**
  - **Prospective multicentre programme** (n=212): proportion maintaining ≥50% response during the off-month rose year-on-year — 25% after year-1 → 53.8% after year-2 → 77.8% after year-3 — with fewer relapses to CM/MOH in later holidays. [4]

(1) Sacco S, et al. J Headache Pain 23(1):67 (2) Vernieri F, et al. J Headache Pain. 2021;22(1):154; (3) Gantenbein AR, et al. Cephalalgia. 2021;41(11–12):1181–1186; (4) Barbanti P, et al. J Neurol. 2025;272(2):170.

Role for Dual Therapy with CGRP Monoclonal Antibodies and Botulinum Toxin?

Rationale[1]

- Preclinical data shows CGRP mAbs and onabotulinumtoxinA have synergistic effects
- CGRP mAbs mainly prevents the activation of Aδ-fibers, whereas botulinum toxin type A prevents the activation of C-fibers.



Open-label evidence

- USA (Cleveland Clinic), n=194: Patients on one preventive added the other class (true dual therapy). ~3 months: MMD 15→8; ≥50% responders 68%; ≥75% 46%; no new safety signals.[2]
- USA (tertiary centre), n=116: Add-on fremanezumab to established Botox. Mean overlap 17.5 ± 11.6 mo; ΔMHD −3.6 (95% CI −5.26 to −1.94); −4.6 in mAb-naïve; well tolerated.[3]
- USA (multicentre chart review), n=257: Add CGRP-mAb to Botox → extra ~3.5–4.0 fewer MHD over 6–12 months; common AE constipation ~9%; discontinuations: mAb 23% vs Botox 3%.[4]

(1) Pellesi L et al. Headache. 2020;60(6):1056-65. (2) Salim A, et al. CNS Drugs. 2024;38(6):481–491; (3) Yuan H, et al. Cephalalgia Rep. 2024;7; (4) Blumenfeld AM, et al. Pain Ther. 2021;10(2):809–826.

NICE Technology Appraisal Guidelines (TAGs)

- **Erenumab, Fremanezumab, Galcanezumab and Eptinezumab: Episodic and chronic migraine (≥4 migraine days/month)**

- **Criteria for trial:**
  - At least 3 preventive drug treatments have failed
  - Medication overuse headache does not preclude trial of CGRP mAb (Compare with Botox)

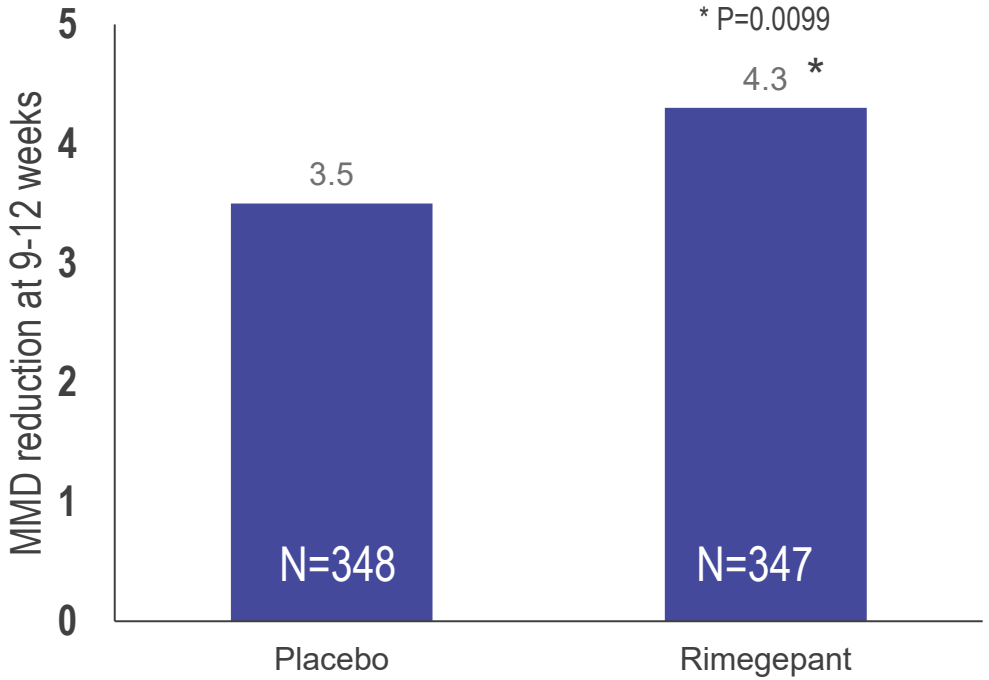
- **Stopping criteria after 12 weeks of therapy:**
  - Episodic migraine, the frequency does not reduce by at least 50%
  - Chronic migraine the frequency does not reduce by at least 30%

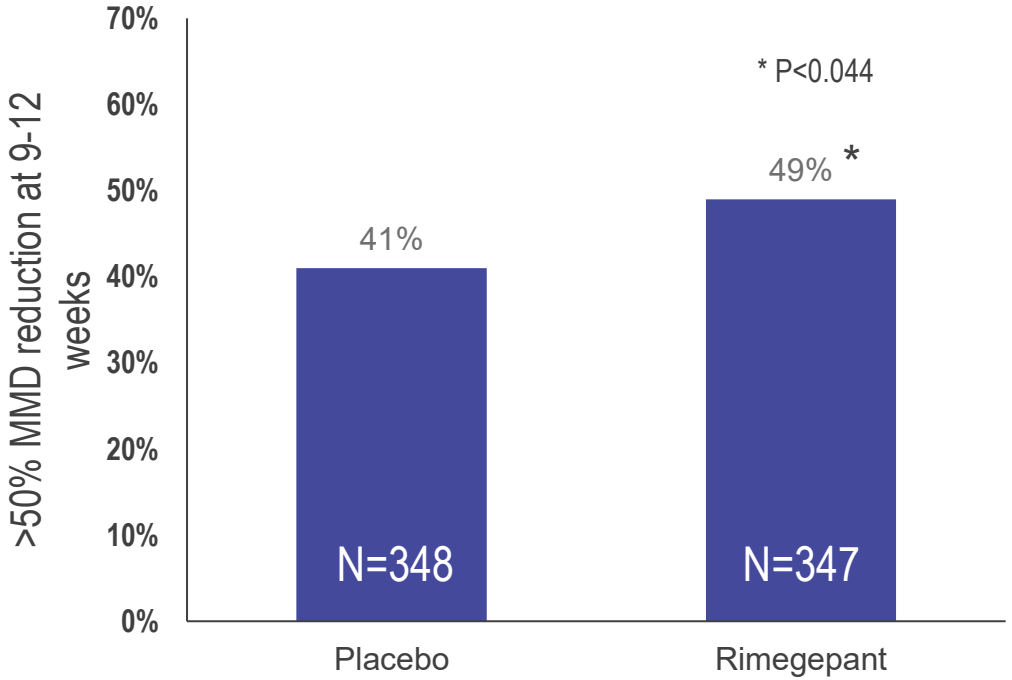
- **Treatment with a second anti-CGRP drug is not recommended (Galcanezumab)**

CGRP receptor antagonists in (Episodic) Migraine prevention

Rimegepant in migraine

- Randomised, double-blind, placebo-controlled trial of oral rimegepant 75mg every alternate day in migraine
- 747 migraine patients with headaches on 4-18 days/month; data on 695 analysed for efficacy
- Primary endpoint: Change from baseline in mean monthly migraine days during weeks 9-12 vs baseline
- Adverse events: nasopharyngitis 4%, nausea 3%, UTI 2%, URTI 2%





Croop R, et al.. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021;397(10268):51-60..

Rimegepant for the Preventive Treatment of (Episodic) Migraine

4 rimegepant and 2 placebo participants had concentrations of AST and ALT >3× the ULN

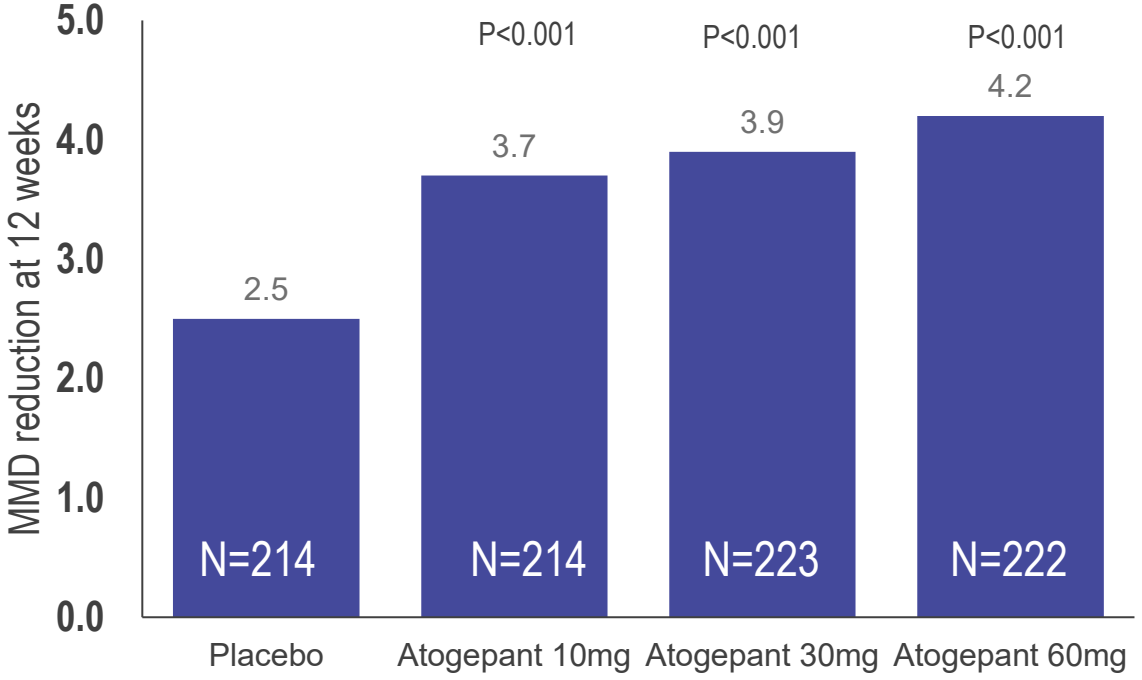
	Rimegepant 75 mg (n=370)	Placebo (n=371)
Participants with adverse events	**133 (36%)**	**133 (36%)**
Adverse events reported in ≥2% of participants treated with rimegepant		
Nasopharyngitis	13 (4%)	9 (2%)
Nausea	10 (3%)	3 (1%)
Urinary tract infection	9 (2%)	8 (2%)
Upper respiratory tract infection	8 (2%)	10 (3%)
Mild adverse events	**92 (25%)**	**91 (25%)**
Moderate adverse events	64 (17%)	62 (17%)
Serious adverse events	**3 (1%)**	**4 (1%)**
Adverse events related to treatment	40 (11%)	32 (9%)
Serious adverse events related to treatment	**0**	**1 (<1%)**
Adverse events leading to discontinuation	7 (2%)	4 (1%)

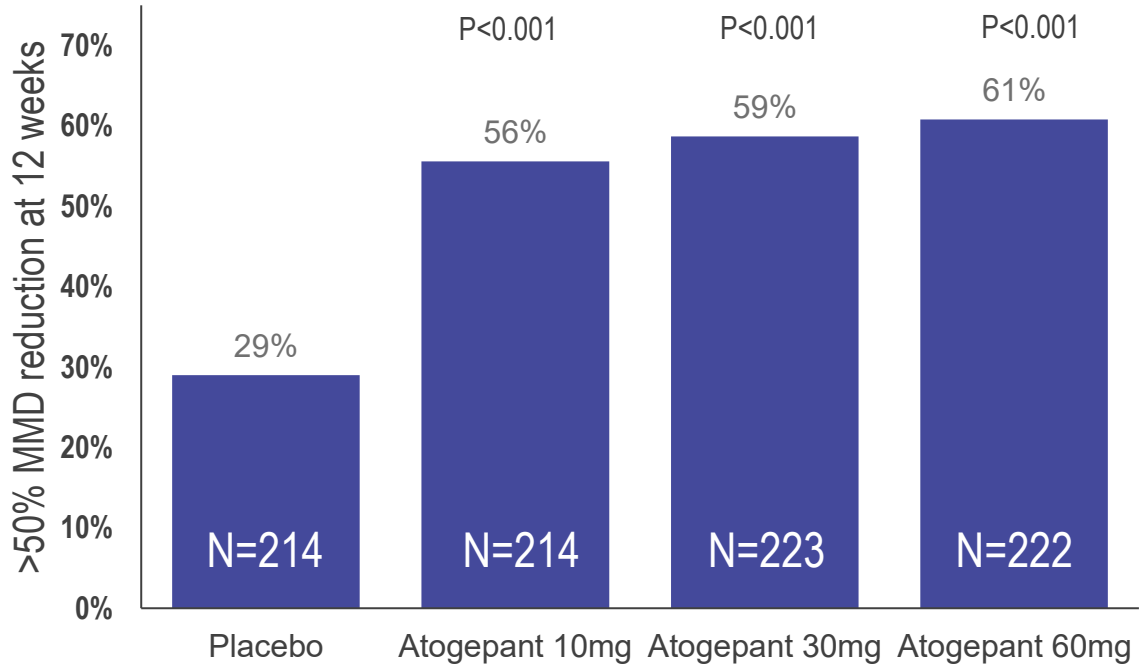
ALT, alanine aminotransferase; AST, aspartate transferase; ULN, upper limit of normal.

1. Croop R, *et al*. *Lancet*. 2021;397:51–60.

Atogepant for the Preventive Treatment of Episodic Migraine: ADVANCE Study[1]

- Randomised, double-blind, placebo-controlled, parallel-group trial in 910 episodic migraine patients
- Efficacy analyses based on modified intent-to-treat (mITT) population of 873 patients (once daily dosing data shown).
- Primary endpoint: Change from baseline in mean monthly migraine days across the 12-week treatment period
- Adverse events with Atogepant 60mg: constipation 6.9%; nausea 6.1%; fatigue 3.9%; URTI 3.9%





1. Ailani J, et al. N Engl J Med. 2021;385:695–706.

Atogepant for the Preventive Treatment of Episodic Migraine: ADVANCE Study[1-3]

In the ADVANCE trial, in patients with 4–14 migraine days per month (N=910), AQUIPTA® 60 mg o.d. (n=231) was generally well tolerated vs. placebo (n=222) across 12 weeks[1*]

Adverse events occurring in ≥4% of patients in any trial group (safety population)[1]

Adverse event, n (%)	AQUIPTA® 60 mg o.d. (n=231)	Placebo (n=222)
Constipation	16 (6.9)	1 (0.5)
Upper respiratory tract infection	9 (3.9)	10 (4.5)
Nausea	14 (6.1)	4 (1.8)

Rates of adverse reactions leading to discontinuation were similar in both treatment arms[1]

2.7% Placebo

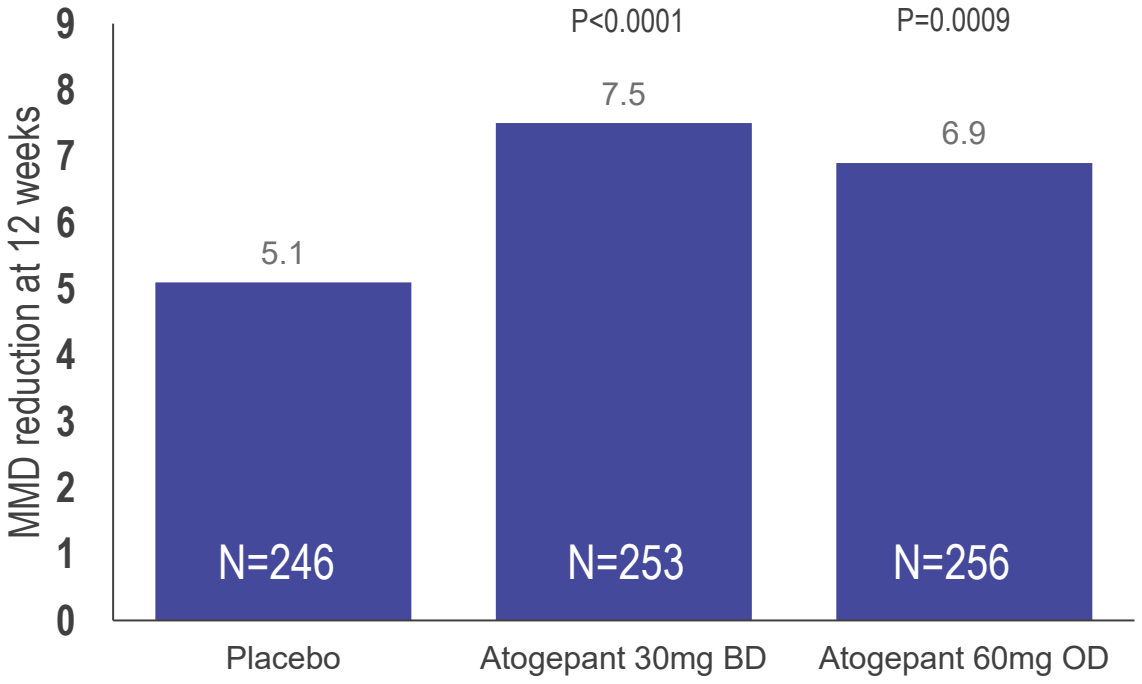
2.6% AQUIPTA® 60 mg o.d.

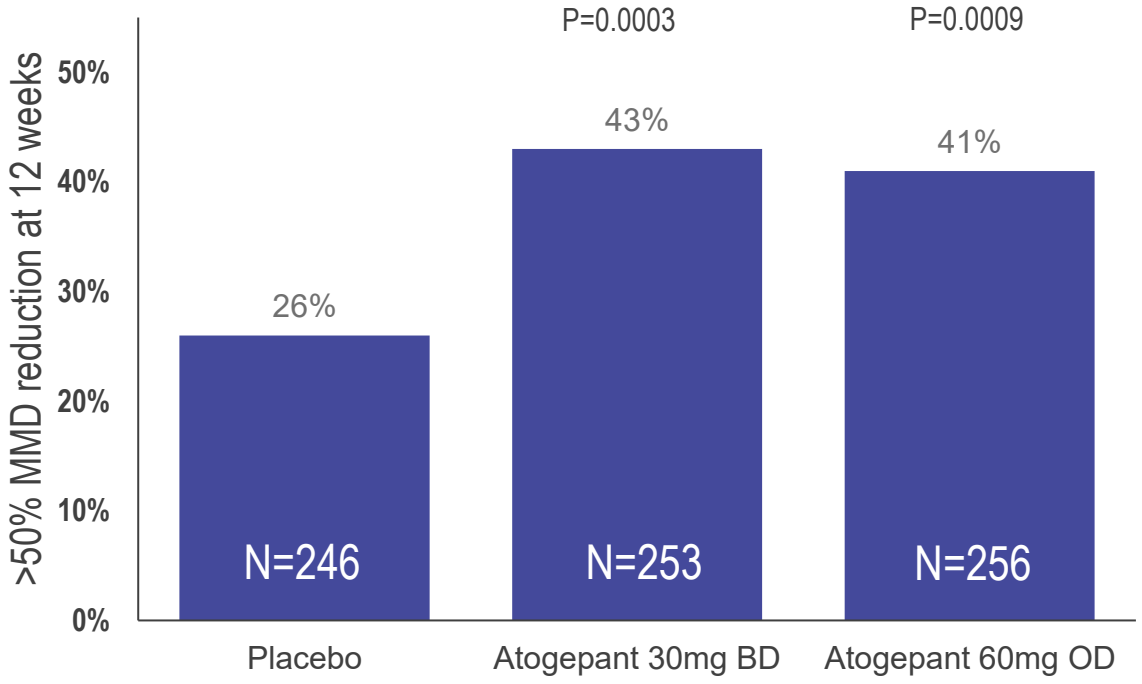
No serious adverse events related to AQUIPTA® or placebo were reported in patients in the AQUIPTA® 60 mg o.d. or placebo arm[1]

Safety population: all randomly assigned participants who received at least one dose of AQUIPTA® or placebo.[1]
*AQUIPTA® was evaluated for the prophylaxis of migraine in patients with 4–14 migraine days per month. The ADVANCE study enrolled patients who met ICHD criteria for a diagnosis of migraine with or without aura. The study excluded patients with myocardial infarction, stroke or transient ischaemic attacks within 6 months prior to screening.[1]
ICHD, international classification of headache disorders; o.d., once-daily.
1. Ailani J, et al. N Engl J Med. 2021;385:695–706; 2. AQUIPTA® (atogepant) 60 mg tablets UK Summary of Product Characteristics. September 2023; 3. AQUIPTA® (atogepant) EU Summary of Product Characteristics. August 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/aquipta. Accessed July 2024.

Atogepant for the Preventive Treatment of Chronic Migraine: PROGRESS Study[1]

- Randomised, double-blind, placebo-controlled, parallel-group trial in chronic migraine
- Efficacy analyses based on modified intent-to-treat (mITT) population of 755 patients.
- Primary endpoint: Change from baseline in mean monthly migraine days across the 12-week treatment period
- Adverse events with Atogepant 60mg od: constipation 10%; nausea 10%; dizziness 5%
- Discontinuation rates: Placebo 4%; Atogepant 60mg od 3%

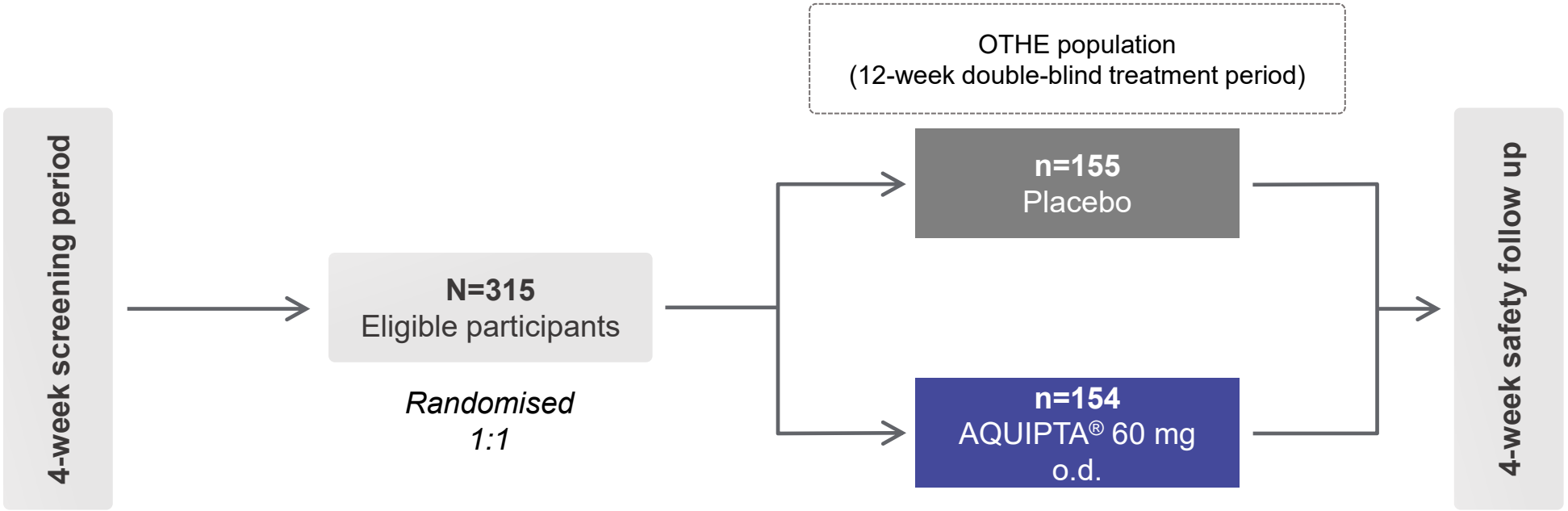




Pozo-Rosich P, et al. Lancet. 2023;402(10404):775-85.

Atogepant for the Preventive Treatment of Episodic Migraine with Prior Treatment Failure: ELEVATE Study[1]

A 12-week, multicentre, double-blind, parallel-group, randomised, placebo-controlled, Phase 3b trial to examine the safety, tolerability and efficacy of AQUIPTA® for the preventative treatment of episodic migraine in participants for whom two to four classes of conventional oral preventive treatments have failed

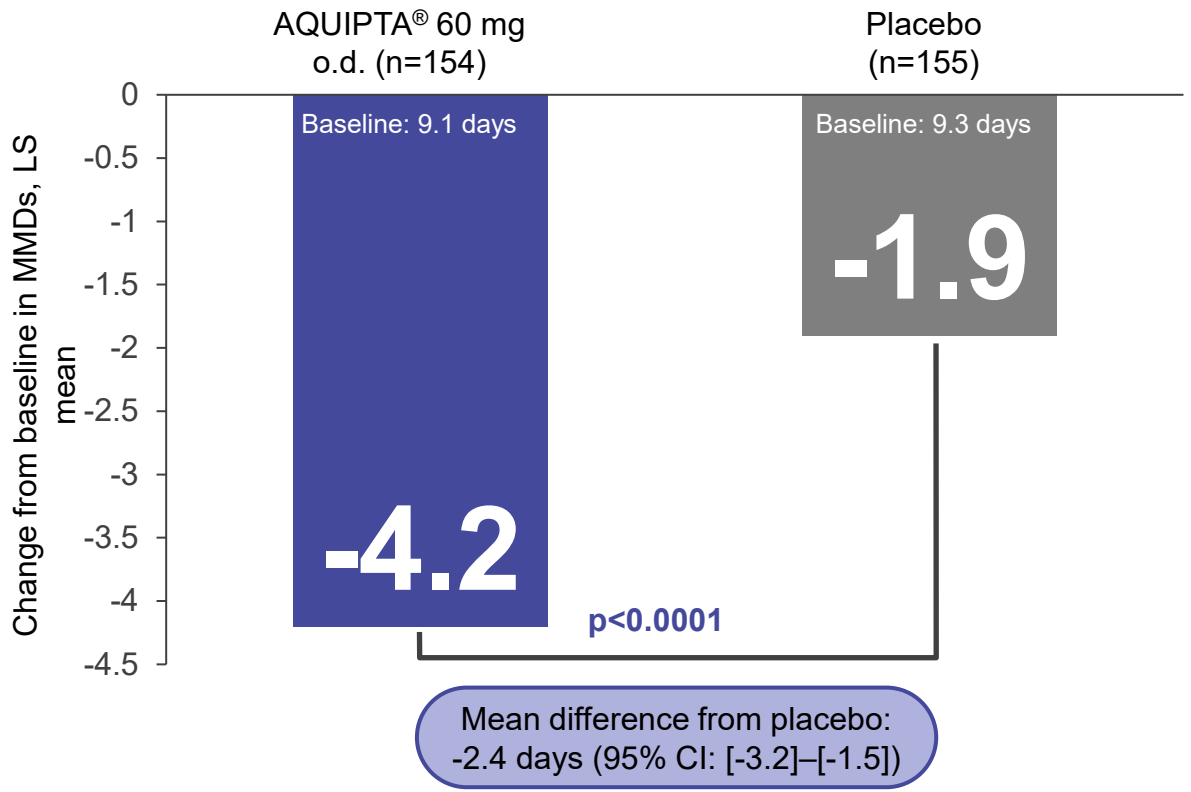


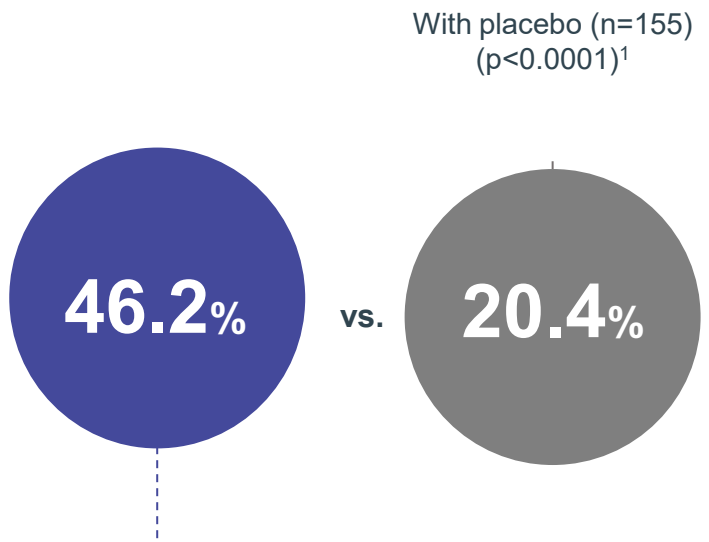
OTHE population. Included all randomised participants who received ≥1 dose of study medication, had evaluable baseline data, and had ≥1 evaluable postbaseline eDiary entry, regardless of whether on study treatment or off study treatment.
o.d., once daily; OTHE, off-treatment hypothetical estimand.
1. Tassorelli C, et al. Lancet Neurol. 2024;23:382–392.

Atogepant for the Preventive Treatment of Episodic Migraine with Prior Treatment Failure: ELEVATE Study[1]

Primary endpoint | Change from baseline in **mean MMD** across 12 weeks of treatment[1]

Change from baseline in mean monthly migraine days across 12 weeks[1]





Significant reduction from baseline in mean monthly migraine days for patients receiving AQUIPTA® 60 mg o.d. (n=154) across 12-weeks treatment[1]

1. Tassorelli C, et al. Lancet Neurol. 2024;23:382–392.

NICE Technology Appraisal Guidelines (TAGs)

Rimegepant (TA906) and Atogepant (TA10992) for preventing migraine

Criteria for trial:

- Rimegepant: Episodic migraine (4-14 migraine attacks/month)
- Atogepant: Episodic and Chronic migraine (>4 migraine attacks/month)
- At least 3 preventive drug treatments have failed
- Medication overuse headache does not preclude trial of rimegepant (Compare with Botox)

- **Stopping criteria after 12 weeks of therapy:**
  - Episodic migraine, the frequency does not reduce by at least 50%
  - Chronic migraine, the frequency does not reduce by at least 30%

- **Expense:**
  - If a range of suitable treatments available, then use the least expensive

Challenge-MIG Study: Rimegepant versus Galcanezumab

- **Randomised, Double-blind, Placebo-Controlled Phase 4 Study in Adult Patients With Episodic Migraine (4-14 Migraine Headache Days per Month)**
- **Evaluated the efficacy and safety of once-monthly injectable galcanezumab and every-other-day rimegepant ODT**
- **Primary endpoint:**
  - ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period

- **First head-to-head clinical trial comparing 2 medications targeting CGRP**
- **Both Galcanezumab and Rimegepant demonstrated robust efficacy (60% vs 61%)**
- **Galcanezumab did not achieve superiority on the primary end point**
- **The results underscore that individuals living with episodic migraine deserve broad access to effective treatment**

Schwedt TJ, et al.Neurol Ther. 2024;13(1):85-105.

Adverse events

	Botox	CGRP monoclonal antibodies	Gepants
Treatment related AEs	**28.5%** vs **12.4%** (placebo). [1]	**44–63%** vs **39–63%** (placebo). [4–7]	**36–57%** vs **36–57%** (placebo). [13–16]
Discontinue due to AEs	**3.8%** vs **1.2%** (placebo). [2]	**1–2%** vs **1–3%** (placebo). [4,8–10]	**1–3%** vs **1–2%** (placebo). [14–16,18]
Top AEs	• **Neck pain 6–9%;** • **Muscular weakness 4–6%;** • **Eyelid ptosis 3–4%;** • **Musculoskeletal stiffness 3–6%;** • Injection-site pain ~3%. [1,3]	• **Injection-site reactions ~18–45%;** • Nasopharyngitis ~6–18%; • URTI ~4–8%; • **Constipation (erenumab-weighted) ~1–3%;** • Back pain ~3–9%. [8,10–12]	• **Constipation *(atogepant)* 5–11%;** • **Nausea 3–10%;** • **Fatigue/somnolence *(atogepant)* 4–7%;** • Nasopharyngitis/URTI 6–11%; • **Abdominal pain/dyspepsia *(rimegepant)* ~2–3%.** [13–17]

(1) Aurora SK, et al. *Acta Neurol Scand Suppl.* 2014;129(S198):55–63.; (2) Dodick DW, et al. *Headache.* 2010;50(6):921–36.; (3) BOTOX® HCP (Chronic Migraine). Allergan; 2025 (accessed).; (4) Goadsby PJ, et al. *Am J Manag Care.* 2018;24(24 Suppl):S547–S559.; (5) Ashina M, et al. *Neurology.* 2020;94(13):e1365–e1377.; (6) Winner PK, et al. *Neurology.* 2020;95(13):e1730–e1742.; (7) Detke HC, et al. *Neurology.* 2018;91(24):e2211–e2221.; (8) AIMOVIG® USPI. Amgen Inc.; 2025.; (9) AJOVY® USPI. Teva Pharmaceuticals; 2025.; (10) EMGALITY® USPI. Eli Lilly and Company; 2025.; (11) CADTH Clinical Review—Galcanezumab. CADTH; 2022.; (12) Ashina M, et al. *J Headache Pain.* 2022;23:120.; (13) Ailani J, et al. *N Engl J Med.* 2021;385:695–706.; (14) Pozo-Rosich P, et al. *Lancet.* 2023;402:—.; (15) QULIPTA® USPI. AbbVie Inc.; 2021/2023.; (16) Croop R, et al. *Lancet.* 2021;397(10268):51–60.; (17) Nurtec ODT® USPI. Biohaven Pharmaceuticals; 2025.; (18) Lipton RB, et al. *J Headache Pain.* 2024;25

Selecting an Advanced Migraine Preventive Treatment

Comparison of Advanced Migraine Preventive Treatments

Factor	Gepants	CGRP Monoclonal Antibodies	Botox Injections
Dosing Regimen	Oral, once/1-2 days	Periodic injections (monthly/quarterly)	Every 12 weeks by healthcare professional
Administration	Oral	Injection/infusion	Injection
Needle Phobia	Suitable for patients with needle phobia	Not suitable	Not suitable
Half-Life	Short (approx. 11 hours)	Long	Long-lasting effect up to 12 weeks
Suitability for Preconception or Pregnancy	Suitable for pre-conception due to short half-life	Not suitable due to long half life	Suitable during preconception and pregnancy (?)
Wearing-Off Effect	Consistent daily/alt day dose, minimal wearing-off	Efficacy diminishes towards end of injection cycle	Efficacy diminishes towards end of injection cycle

Comparison of Advanced Migraine Preventive Treatments

Factor	Gepants	CGRP Monoclonal Antibodies	Botox Injections
Migraine Classification	Atogepant: EM, CM Rimegepant: EM	EM, CM	CM
Medication Overuse	Effective	Effective	Effective
Drug interactions*	Strong CYP3A4 inhibitors. Strong OATP inhibitors.	Fewer interactions	Non-systemic approach, few interactions
Cardiovascular Safety	Atogepant: avoid for first 6 months after cardiovascular event	Contraindicated	Safe
Raynaud's syndrome	Use with caution but effect can be reversed quickly	Use with caution	Safe

* Strong/Moderate CYP3A4 Inhibitors: **Azole Antifungals** (e.g., ketoconazole, itraconazole, fluconazole), **Macrolide Antibiotics** (e.g., clarithromycin, erythromycin), and **Anti-HIV Agents** (e.g., ritonavir).
Strong OATP inhibitors; **Antitubercular Agents** (single-dose Rifampin), **Calcineurin Inhibitors** (Ciclosporin), **HIV Protease Inhibitors** (Atazanavir, Ritonavir), **Cephalosporin Antibiotics** (Ceftobiprole medocaril).

Summary

- Advanced prevention now centres on Botox, CGRP monoclonal antibodies, and oral gepants; first choice can be driven by patient preference.
- Use a pragmatic personalised algorithm (balancing route, half-life, comorbidities, interactions, pregnancy planning, MOH, and needle phobia) to select the “least-cost suitable” option.
- Gepants offer flexible prevention with short half-lives suited to pre-conception, and can be used both as preventive and as acute treatments.
- Most responders need long-term therapy; brief drug holidays (e.g., 12–24 months then pause) are reasonable, but many will relapse and should promptly restart treatment.
- Combination therapy (e.g., Botox plus a CGRP mAb) shows additive benefit in real-world cohorts, though not explicitly approved in the NHS and many commissioners permit only one advanced agent at a time.