Faculty of Health and Medical Sciences

Anti-CGRPs, should I stay, or should I go?

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Disclosures

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MA serves as associate editor of Cephalalgia, associate editor of the Journal of Headache and Pain, and associate editor of Brain.

Overview of Treatment Landscape

Preventive treatments

Non- specific therapies

Metoprolol 50-200 mg
Propranolol 40-240 mg
Bisoprolol 5-10 mg
Lisinopril 20-40 mg
Candesartan 16-32 mg

Topiramate 100 (200) mg
Valproate 500-1800 mg

Flunarizine 5-10 mg
Amitriptyline 10-100 mg

Botulinum toxin type A 155U
Indication: Chronic migraine

Anti CGRP or its receptors monoclonal antibodies

Erenumab	Fremanezumab	Galcanezumab	Eptinezumab

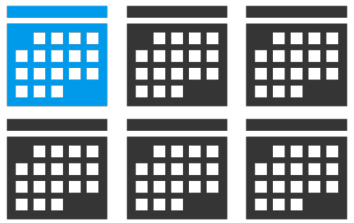
Oral CGRP-receptor antagonists

Rimegepant	Atogepant

Ashina M et al. *Lancet* 2021 Apr 17;397(10283):1505-1518.

Challenges of Nontargeted Oral Migraine Preventive Therapies

DELAYED EFFICACY



A trial of 2 to 6 months, including various titration periods, is often required **before the benefits of the oral preventive treatments can be fully realized**[1,2]

POOR TOLERABILITY

AEs of the traditional oral preventive treatments may include…[2-5]

Weight gain

Fatigue

Cognitive issues

Depression

HIGH DISCONTINUATION RATES

The **majority of patients** taking an oral preventive treatment **discontinue it within 6 months of initiation**[6]

1. Silberstein SD et al. Supplemental E-Tables. *Neurology*. 2012;78(17):1337-1345. 2. Silberstein SD et al. *Neurology*. 2012;78(17):1337-1345. 3. Amitriptyline hydrochloride. Package insert. Mylan Pharmaceuticals Inc. 4. Topamax. Package insert. Janssen Ortho LLC. 5. Divalproex sodium. Package insert. Par Pharmaceutical. 6. Hepp Z et al. *Cephalalgia*. 2017;37(5):470-485.

Phase III data have demonstrated the efficacy of anti-CGRP mAbs in patients with EM and CM

Significant improvements vs placebo across a range of endpoints:

- Reduction in MMDs/MHDs[1–7]
- ≥50% responder rates[1–7]
- Improved disability scores and/or functioning[1–4]
- Improved depression scores[8]
- Rapid onset (within 1–4 weeks)[1–7]
- Efficacy sustained long-term[1–4]
- Reduction in acute medication use[1–4,6,7]
- Improved non-headache symptoms[9]

…including in different patient subgroups

- Multiple prior preventive treatment failures[11–13]
- Medication overuse[14–16]
- From low- / moderate-frequency EM through high-frequency CM[17]
- Older age[18]
- Psychiatric and pain comorbidities[19]

CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; mAb, monoclonal antibody; MHD, monthly number of headache days; MMD, monthly number of migraine days.

1. Teva Pharmaceuticals. AJOVY®▼ (fremanezumab). Summary of Product Characteristics, 2022; 2. Novartis. Aimovig®▼ (erenumab). Summary of Product Characteristics, 2022; 3 Eli Lilly. Emgality®▼ (galcanezumab). Summary of Product Characteristics, 2021; 4. Lundbeck. Vyepti®▼ (eptinezumab). Summary of Product Characteristics, 2022; 5. Ashina M, et al. Cephalalgia 2020;40:241–254; 6.Lipton RB, et al. Neurology 2020;94:e1365–e1377;
7. Silberstein S, et al. J Headache Pain 2020;21:120; 8. Lipton RB, et al. Headache 2021;61:662–672; 9. Lipton RB, et al. Headache 2021;61:766–776; 11. Ferrari M, et al. Lancet 2019;394:1030–1040; 12. Reuter U, et al. Lancet 2018;392:2280–2287; 13. Mulleners W, et al. Lancet Neurol 2020;19:814–825; 14. Silberstein SD, et al. J Headache Pain 2020;21:114; 15. Tepper SJ, et al. Neurology 2019;92:e2309–e2320; 16. Dodick DW, et al. Cephalalgia 2021;41:340–352; 17. Simone Quintana et.al., Neurol Sci. 2022 Sep;43(9):5757-5758; 18. Nahas SJ, et al. J Headache Pain 2021;22:141; 19. Verena RC et.al., Cephalalgia 2023, Vol. 43(1S) 1–333;

Defining Patient Profiles

Understanding Migraine Variability

- Migraines aren't a one-size experience.

Personalized Medicine

- Each patient has unique characteristics.

Treatment Efficacy & Patient Profiles

- Treatment outcomes often resonate with specific profiles.

Defining Patient Profiles

Factors affecting treatment efficacy

Raffaelli *et al.*
The Journal of Headache and Pain (2023) 24:16
https://doi.org/10.1186/s10194-023-01552-x

The Journal of Headache and Pain

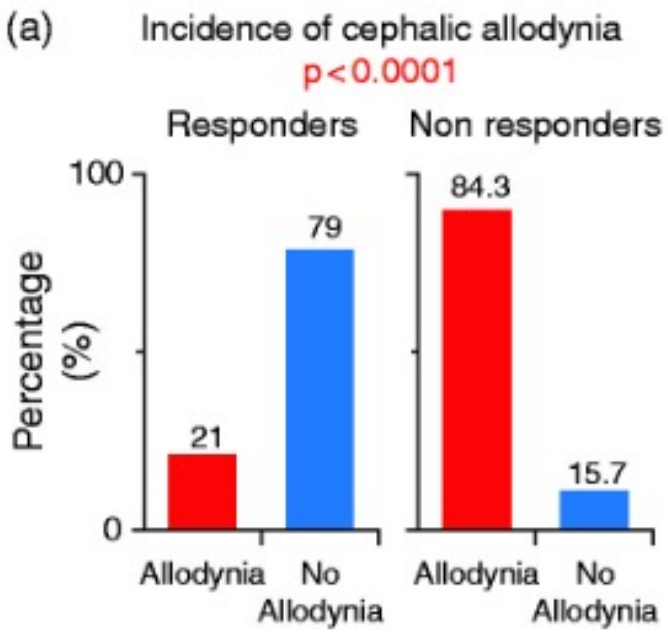
RESEARCH Open Access

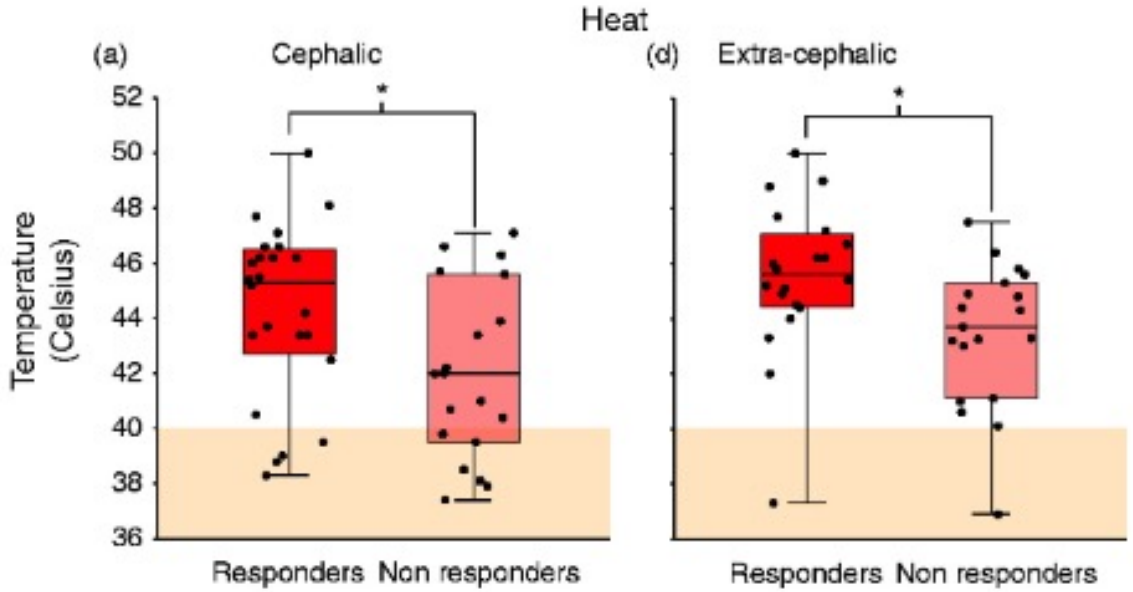
Clinical evaluation of super-responders vs. non-responders to CGRP(-receptor) monoclonal antibodies: a real-world experience

Bianca Raffaelli[1,2†], Mira Fitzek[1†], Lucas H. Overeem[1], Elisabeth Storch[1], Maria Terhart[1] and Uwe Reuter[1,3*]

	Non-Responders	MD	Super-Responders	MD
Unilateral headache, n (%)	18 (72%)	1	25 (93%)	2
Pulsating character, n (%)	19 (76%)	1	26 (93%)	1
Aggravation by physical activity, n (%)	22 (100%)	4	25 (100%)	4
Photophobia, n (%)	21 (88%)	2	26 (96%)	2
Phonophobia, n (%)	20 (87%)	3	24 (89%)	2
Nausea, n (%)	21 (88%)	2	27 (100%)	2
Vomitus, n (%)	4 (18%)	4	12 (48%)	4

Allodynia in relation to treatment response





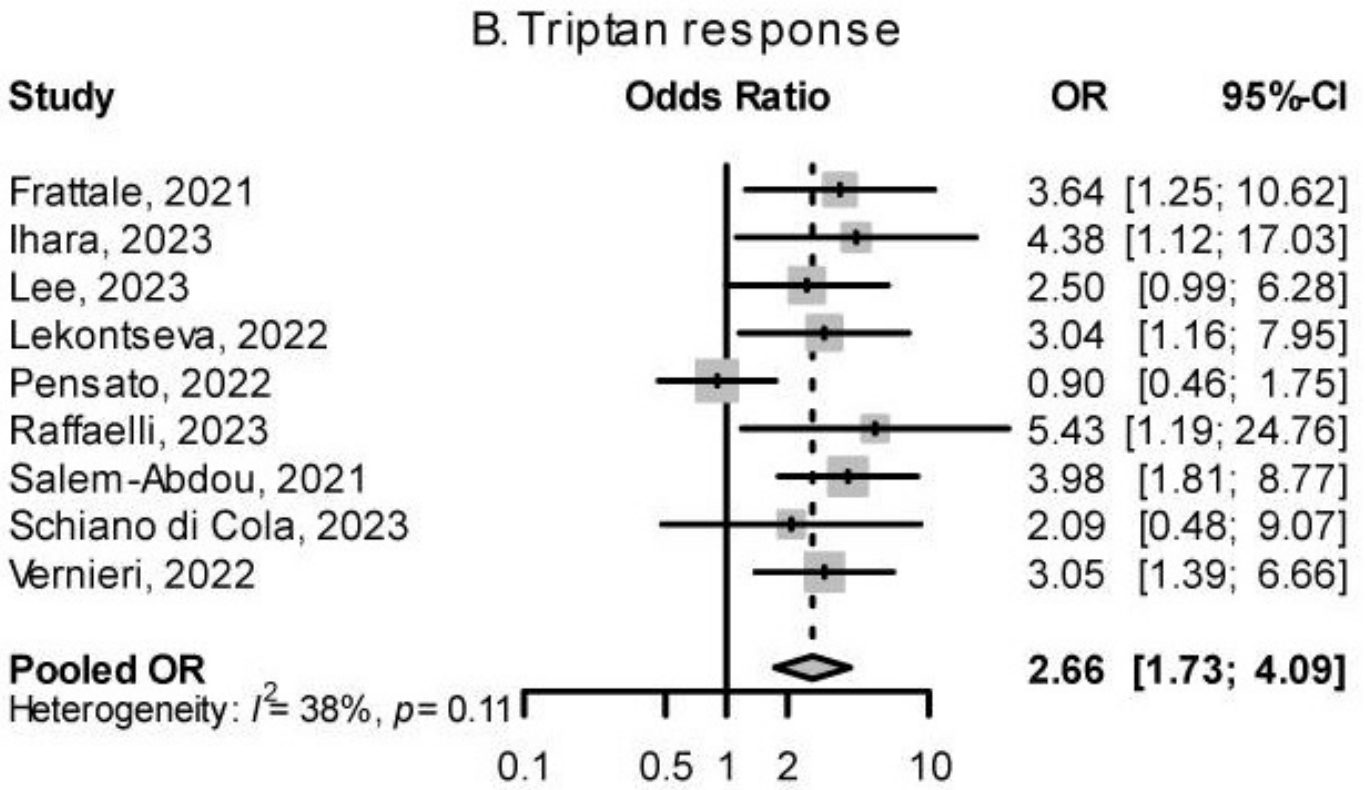
Ashina S et al. Pre-treatment non-ictal cephalic allodynia identifies responders to prophylactic treatment of chronic and episodic migraine patients with galcanezumab: A prospective quantitative sensory testing study (NCT04271202) Cephalalgia 2023 Mar;43(3):3331024221147881. doi: 10.1177/03331024221147881.

Pharmaceuticals (Basel). 2023 Jul; 16(7): 934.
Published online 2023 Jun 27. doi: 10.3390/ph16070934
PMCID: PMC10385131
PMID: 37513846

A Scoping Review and Meta-Analysis of Anti-CGRP Monoclonal Antibodies: Predicting Response

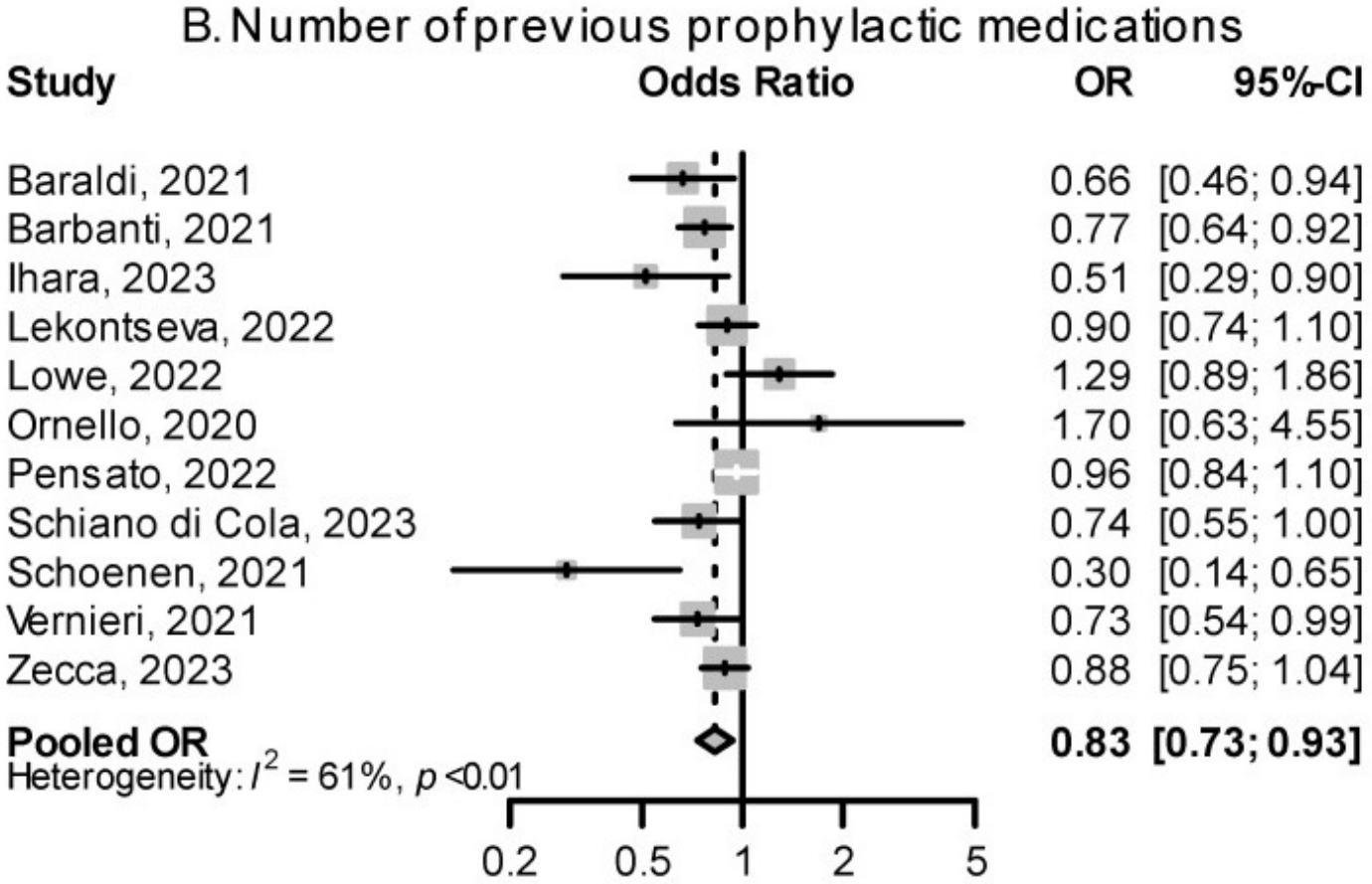
Ja Bin Hong,[1] Kristin Sophie Lange,[1] Lucas Hendrik Overeem,[1,2] Paul Triller,[1] Bianca Raffaelli,[1,3] and Uwe Reuter[1,4,*]

Migraine characteristics: triptan responders



Hong JB, Raffaelli B and Reuter U. A Scoping Review and Meta-Analysis of Anti-CGRP Monoclonal Antibodies: Predicting Response. Pharmaceuticals (Basel) 2023 Jun 27;16(7):934. doi: 10.3390/ph16070934.

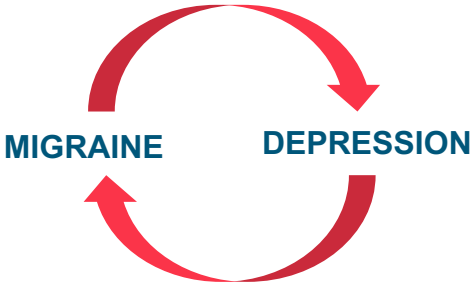
Numerous Prior Preventive Medications May Indicate Lower Treatment Efficacy



Hong JB, Raffaelli B and Reuter U. A Scoping Review and Meta-Analysis of Anti-CGRP Monoclonal Antibodies: Predicting Response. Pharmaceuticals (Basel) 2023 Jun 27;16(7):934. doi: 10.3390/ph16070934.

A bidirectional relationship exists between migraine and psychiatric comorbidities

Depression is a risk factor for migraine and migraine is a risk factor for depression[1,2]



Psychiatric comorbidities are more common in people with migraine:[a]

4–5x more likely to experience anxiety[3]

2–4x more likely to experience depression[4]

3x more likely to experience sleep disorders[3]

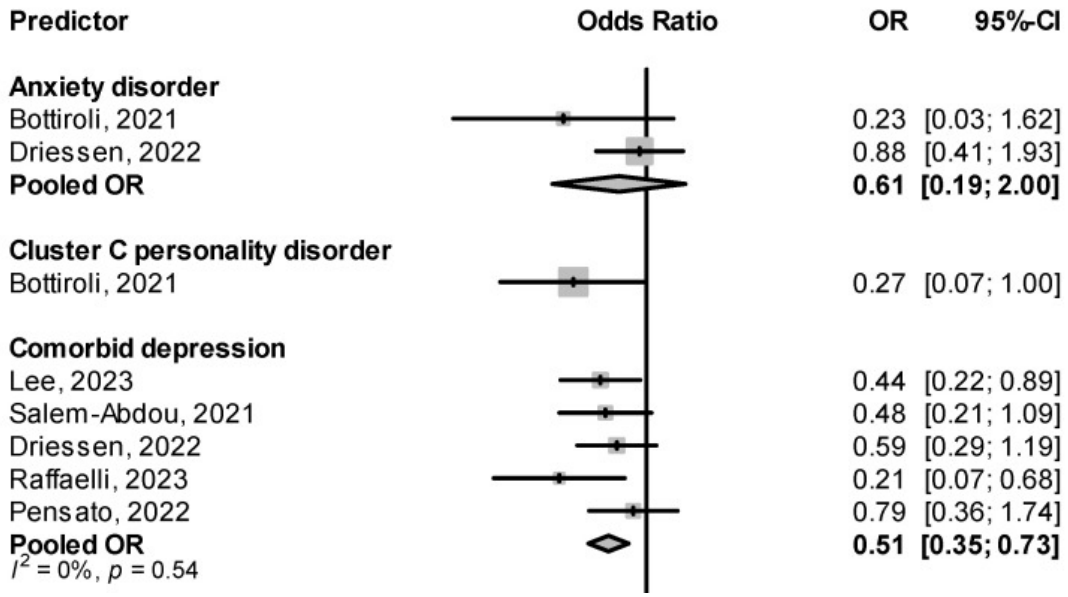
Psychiatric comorbidities are associated with poor patient outcomes:[5]

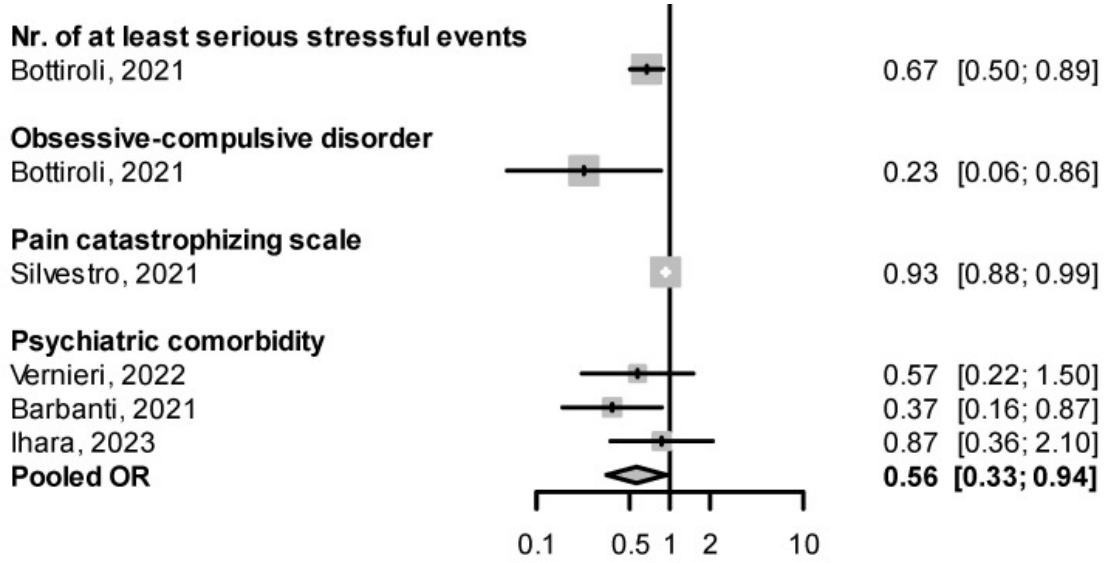
- ↑ MMDs
- ↑ Headache pain
- ↑ Disability
- ↑ Risk of chronification
- ↓ QoL

MMD, monthly migraine day; MO, medication overuse; QoL, quality of life.
[a]Compared to individuals without migraine.

1. Dresler T, et al. J Headache Pain 2019;20:51; 2. Stępień A, et al. Psychiatr. Pol. 2022; 56:711–28; 3. Burch RC, et al. Neurologic Clinics 2019;37:631–49; 4. Smitherman TA, et al. Psychiatric Times 2013;30;
5. Driessen MT, et al. J Headache Pain 2022;23:47.

Psychiatric Co-Occurrences Could Indicate Lower Treatment Efficacy





Hong JB, Raffaelli B and Reuter U. A Scoping Review and Meta-Analysis of Anti-CGRP Monoclonal Antibodies: Predicting Response. Pharmaceuticals (Basel) 2023 Jun 27;16(7):934. doi: 10.3390/ph16070934.

UNITE is the first RCT of a CGRP pathway mAb conducted in patients with comorbid MDD

UNITE is evaluating the efficacy of subcutaneous monthly 225 mg and quarterly 675 mg fremanezumab in adult patients with EM or CM and MDD[1,2]

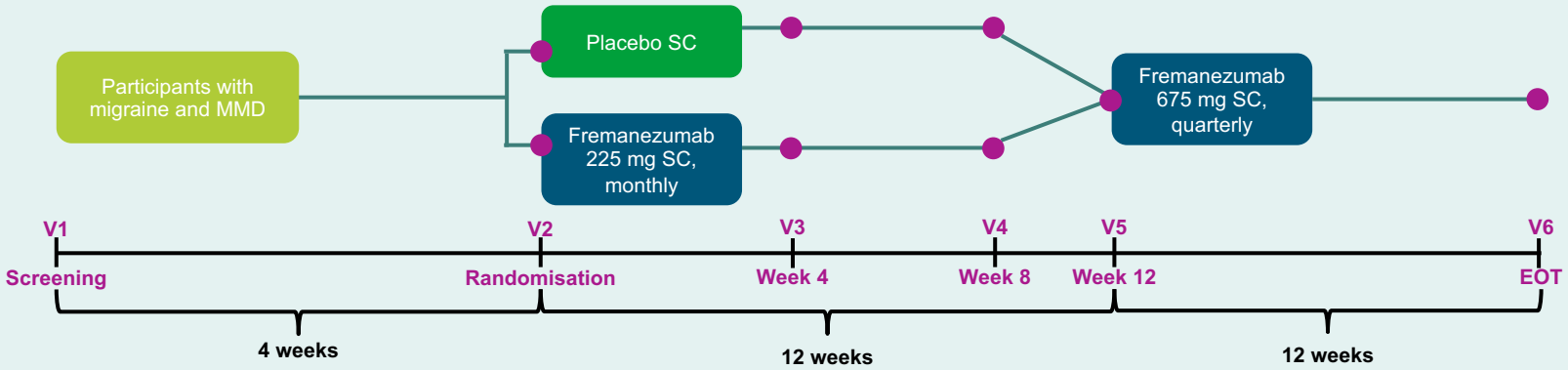
353 patients enrolled in the study[1]

12-week multicentre, double-blind, placebo-controlled, parallel-group study with a 12-week OLE period[1,2]

Primary endpoints:
- Mean change in MMDs at Week 12

Other endpoints:
- Changes in MDD symptoms
- Responder rates
- Improvements in QoL and disability
- Safety and tolerability

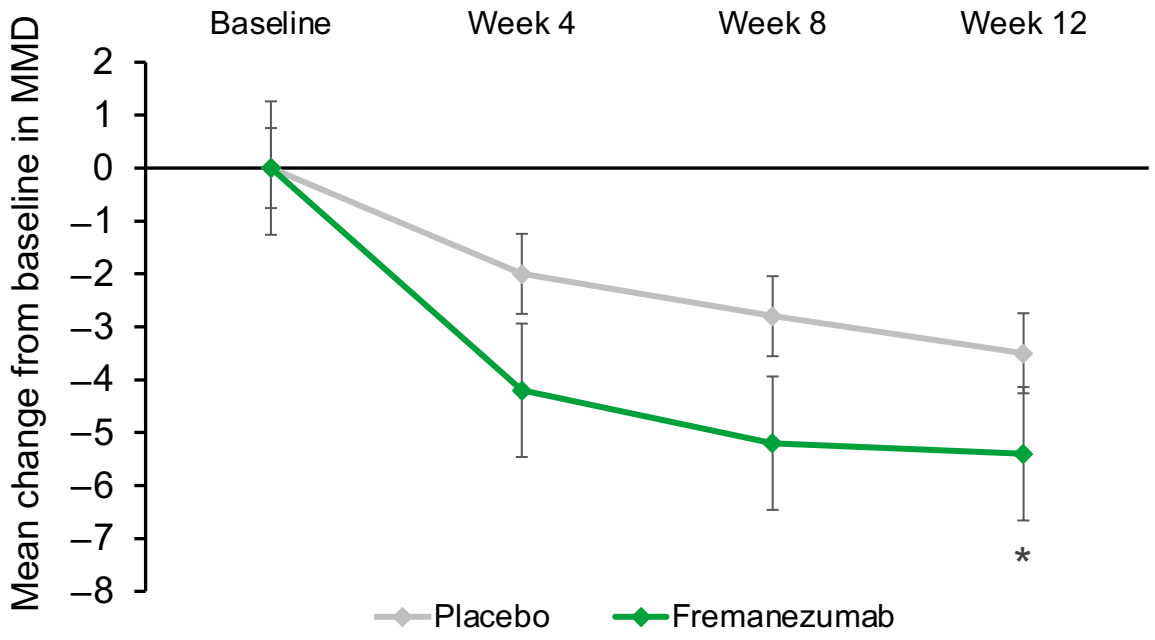
UNITE study design:[1]



CM, chronic migraine; EM, episodic migraine; EOT, end of treatment; MDD, major depressive disorder; MIDAS, Migraine Disability Assessment; MMD, monthly migraine days; OLE, open-label extension; V, visit.

1. Lipton RB. et.al., Headache: The Journal of Head and Face Pain, Volume 63, 2023, Pages 1-213; 2. Lipton RB. et. al. Cephalalgia 2022, Vol. 42(1S) 1–101

Reductions from baseline MMDs were observed with fremanezumab vs placebo over 12 weeks in UNITE



	Placebo (n = 178)		Fremanezumab (n = 175)	
	Days	Reduction	Days	Reduction
Baseline	14.4		15.1	
Week 4	12.6	–2.0	11.0	–4.2
Week 8	11.8	–2.8	10.0	–5.2
Week 12	11.2	–3.5	9.6	–5.4
Primary endpoint: Reduction from baseline over 12 weeks (p<0.0001)		**–2.9**		**–5.1**

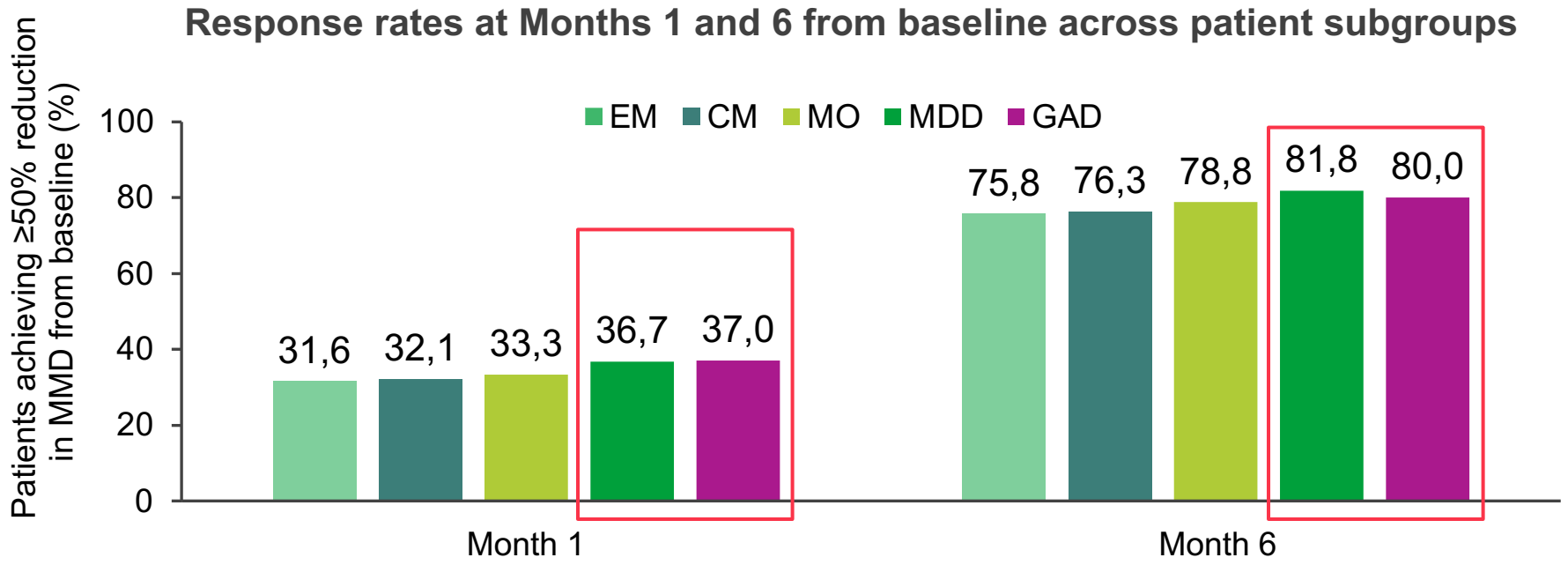
Statistically significant reductions from baseline in MMD during the 12-week double-blind period were observed with fremanezumab vs placebo

MMD, monthly migraine day.

Lipton RB et.al., Headache: The Journal of Head and Face Pain, Volume 63, 2023, Pages 1-213.

High response rates are seen with fremanezumab in different subpopulations with comorbidities in the real world

USA | Multicentre | N = 1003 | 6 months



Regardless of the type of migraine, response was seen within 1 month after initiating fremanezumab treatment, with continued improvement demonstrated over 6 months of treatment

CGRP pathway mAbs are not indicated for the treatment of migraine overuse headache.

This US-based study was a non-interventional, retrospective, online, clinician panel–based chart review. CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; GAD, generalized anxiety disorder; mAb, monoclonal antibody; MDD, major depressive disorder; MMD, monthly migraine day; MO, medication overuse.

Driessen MT, et al. J Headache Pain 2022;23:56.

Prescribing guidelines and criteria for initiating and discontinuing anti-CGRP monoclonal antibody treatment differs across countries

INITIATION

In many countries, people with migraine are required to fail multiple preventive treatments before they are prescribed an anti-CGRP monoclonal antibody

CONTINUING ANTI-CGRP TREATMENT

Depending on the country, patients with migraine must have ≥30% or ≥50% reduction in MMDs after multiple cycles to continue anti-CGRP treatment

RESPONSE ACROSS THRESHOLDS

Given differences in prescribing guidelines and criteria, it is important to understand the potential trajectory of response for patients treated with these medications across a variety of thresholds

1. Stovner LJ, et al. *Lancet Neurol*. 2018;17(11):954-976.
2. Ashina M, et al. *Lancet*. 2021;397 :1505–1518.
3. Vyepti [package insert]. Lundbeck Seattle BioPharmaceuticals, Inc.; 2022.
4. Ashina M, et al. *Lancet Neurol*. 2022;21:597-607.
5. Silberstein S, et al. *Cephalalgia*. 2008;28(5):484-495.
6. Tassorelli C, et al. *Cephalalgia*. 2018;38(5):815-832.

anti-CGRP, anti-calcitonin gene-related peptide
MMDs, monthly migraine days

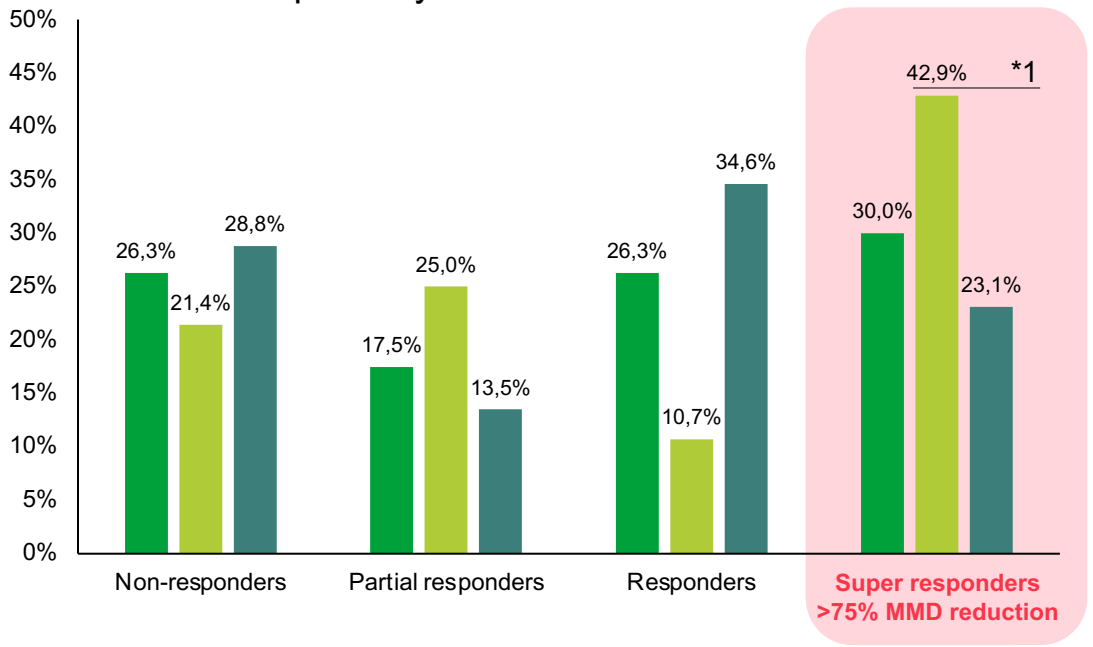
Proportion of super-responders was higher with ligand- vs receptor-targeted CGRP pathway mAbs

Retrospective observational study on patients treated with CGRP pathway mAbs

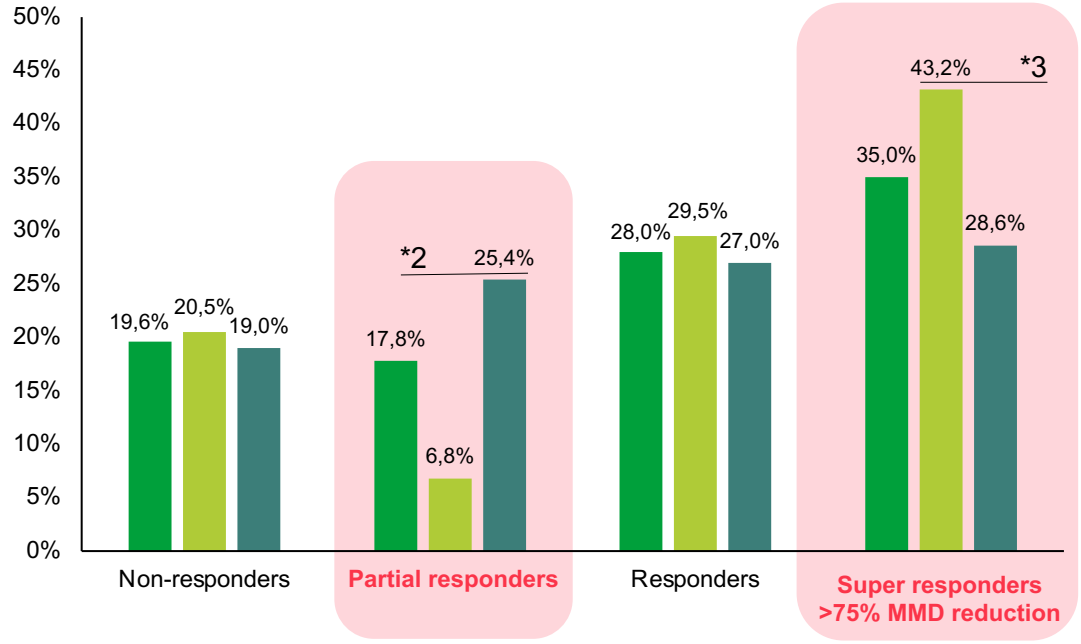
N = 152 | 6 months | Single centre

*1 p = 0.041
*2 p = 0.049
*3 p = 0.047

Response rates during treatment with CGRP pathway mAbs after 3 months



Response rates during treatment with CGRP pathway mAbs after 6 months



All patients | CGRP-ligand targeting | CGRP-receptor targeting

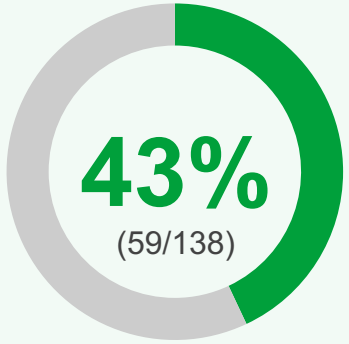
Non-responders: <30% MMD reduction; partial responders: 30%–50% MMD reduction; responders: 50%–75% MMD reduction; super-responders: >75% MMD reduction.
CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody.
Schiano di Cola, et al. Eur J Neurol 2023;30:1764–73.

Data suggest that switching from receptor- to ligand-targeting CGRP pathway mAbs may lead to a reduction in migraine frequency

FINESSE[1]

Prospective, non-interventional study[1]

N = 153[a] | 3 months – subgroup analysis

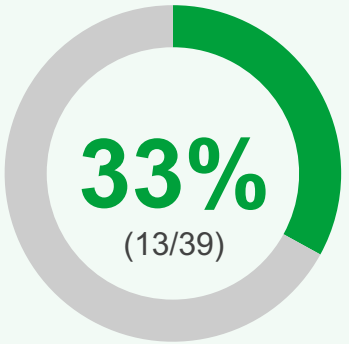


≥50% reduction in MMDs from baseline to Month 3

Prospective multi-centre real world study[2]

N = 39 **refractory CM patients** | 12 months follow-up analysis | Average number of preventatives failed: **7.5** (6.0–11.0)

Patients who failed erenumab were started on fremanezumab



- ↓ Reduction of MMD: from 21.4 to 8.6
- ↓ Reduction in headache days: from 30.0 to 8.6
- ↓ Reduction in HIT-6 score: from 66 to 62

Side effects: 20.5% (1 patient discontinued)

≥50% reduction in MMDs from baseline to Month 12

Please note that these data are not from head-to-head studies; therefore, no direct comparisons should be made.

[a]153/867 patients with a history of anti-CGRP pathway mAb treatment prior to initiation of fremanezumab were analysed.

CGRP, calcitonin gene-related peptide; CM, chronic migraine; mAb, monoclonal antibody.

1. Straube A, et al. J Headache Pain 2023;24:59; 2. Lambru G, et al, Neurotherapeutics (2023) 20:1284–1293

Biomarkers: Is Serum CGRP an Indicator for Treatment Efficacy?

de Vries Lentsch *et al.*
The Journal of Headache and Pain (2022) 23:120
https://doi.org/10.1186/s10194-022-01483-z

The Journal of Headache and Pain

RESEARCH Open Access

Serum CGRP in migraine patients using erenumab as preventive treatment

Simone de Vries Lentsch[1], Ingrid M. Garrelds[2], A. H. Jan Danser[2], Gisela M. Terwindt[1†] and Antoinette MaassenVanDenBrink[2*†]

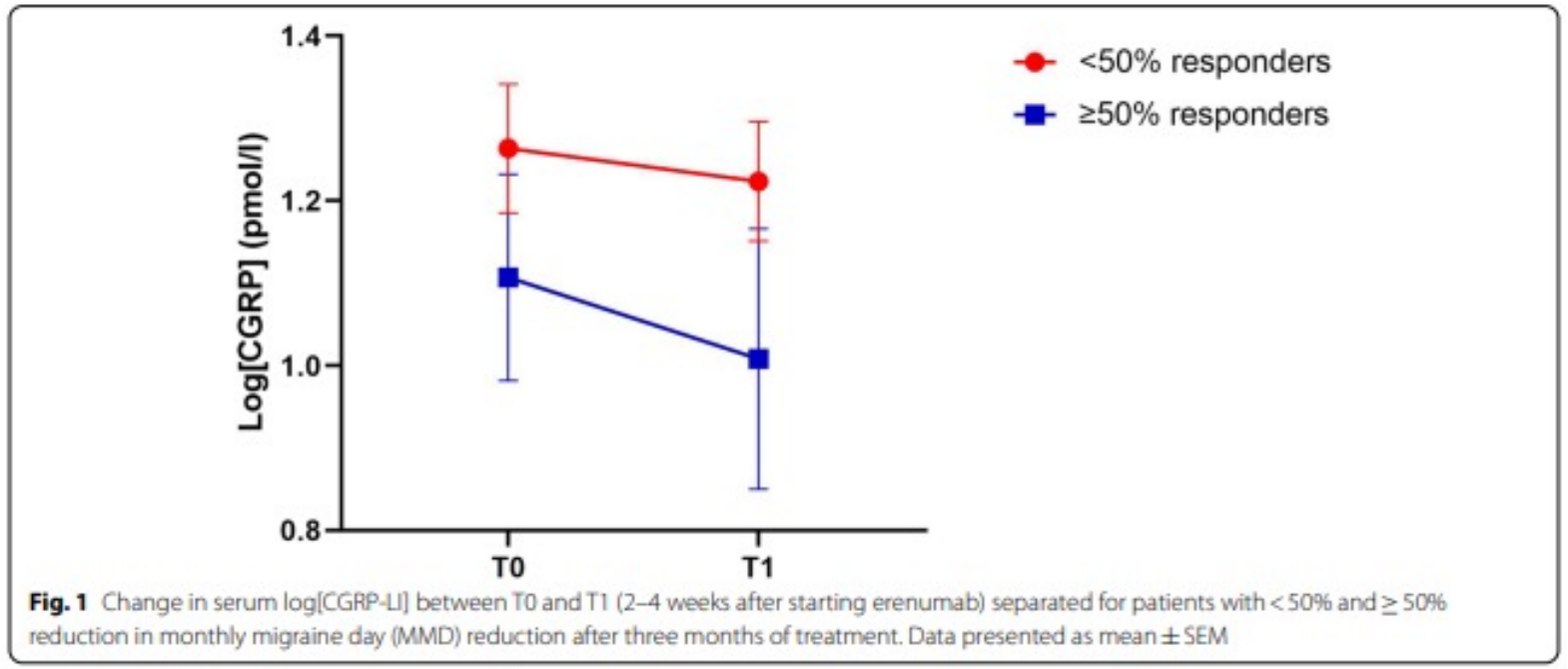


Fig. 1 Change in serum log[CGRP-LI] between T0 and T1 (2–4 weeks after starting erenumab) separated for patients with < 50% and ≥ 50% reduction in monthly migraine day (MMD) reduction after three months of treatment. Data presented as mean ± SEM

Biomarkers: Does Salivary CGRP Reflect Treatment Outcomes?

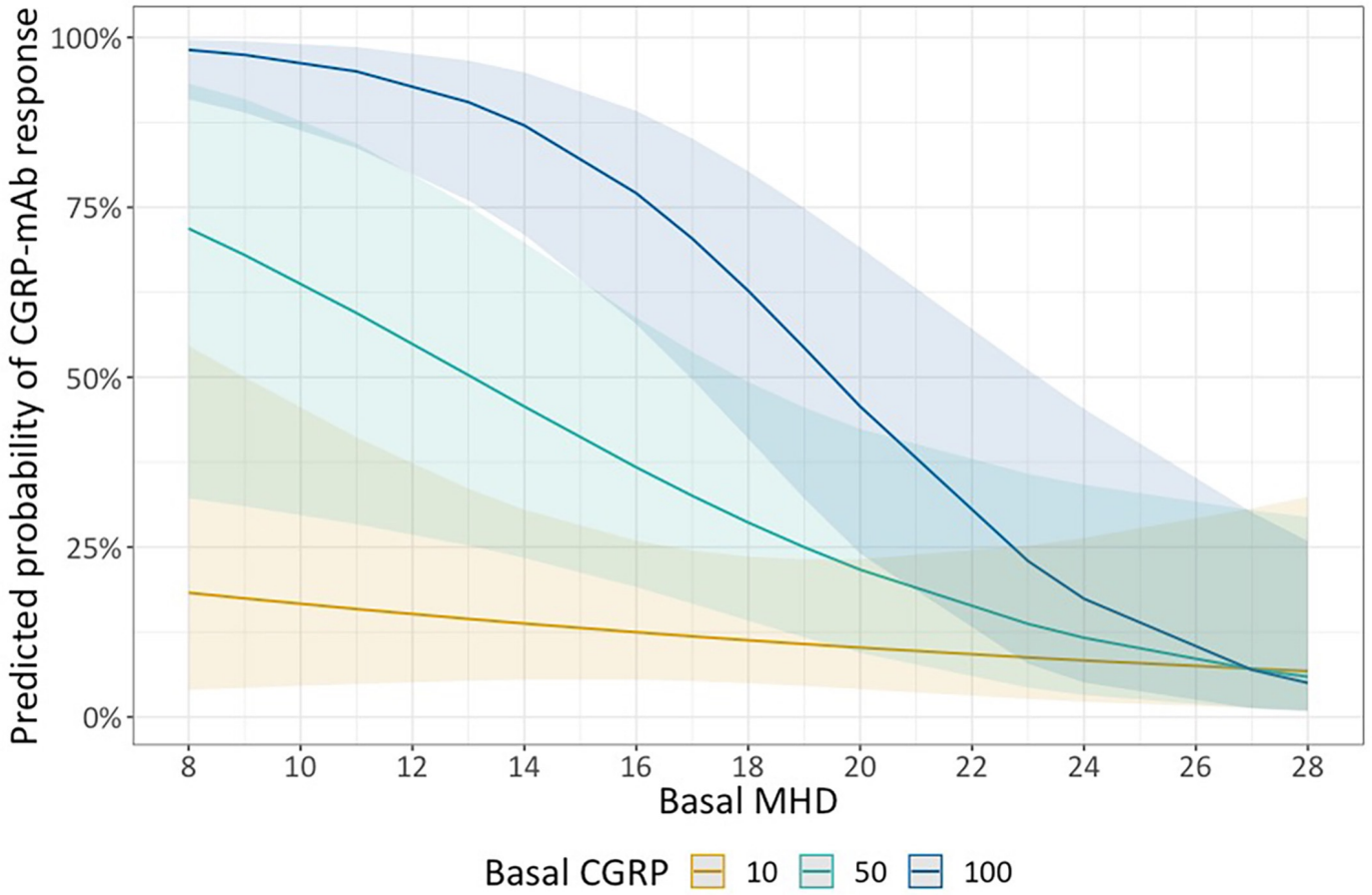
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA AMERICAN NEUROLOGICAL ASSOCIATION

Research Article | Full Access

Salivary CGRP and Erenumab Treatment Response: Towards Precision Medicine in Migraine

Alicia Alpuente MD, Victor J Gallardo MSc, Laila Asskour MLT, Edoardo Caronna MD, Marta Torres-Ferrus MD, PhD, Patricia Pozo-Rosich MD, PhD

A visual representation comparing salivary CGRP levels with monthly headache frequency (MHD) at the start of the study to see if they can predict treatment success (whether patients responded or didn't respond to treatment).



Ann Neurol. 2022 Nov;92(5):846-859

The updated EHF guidelines suggest tailoring treatment decision to the individual patient's needs

	Expert opinion
Treatment initiation	**In individuals with migraine who require preventive treatment**, we suggest mAbs targeting the CGRP pathway to be included as a **first-line treatment option** First-line treatment option should be carefully chosen by physicians **considering the patient's history, comorbidities, and burden of the disease** Headache experts must be able to choose, **after discussion with the patient**, the therapy that is most appropriate
Migraine and medication overuse	In individuals with **migraine and medication overuse**, we suggest **offering mAbs targeting the CGRP pathway**
Non-responders	In individuals with **migraine with inadequate response to one mAb targeting the CGRP pathway**, there is insufficient evidence on the potential benefits of antibody switch but **switching may be an option**
Careful considerations	We suggest **caution and decision on a case-by-case basis** in the **presence of vascular disease or risk factors and Raynaud phenomenon** We suggest **caution in erenumab use** in individuals with migraine with **history of severe constipation**

Real-world data can provide insights on treatment individualisation and management of safety signals

CGRP, calcitonin gene-related peptide; EHF, European Headache Federation; mAb, monoclonal antibody.
Sacco S, et al. J Headache Pain 2022;23:67.