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When to evaluate effectiveness? – Anti-CGRPs and gepants

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Trondheim, Norway

Conflicts of Interest

Industry:

Lectures/ advisory boards:
- Amgen
- Novartis
- Eli Lilly
- Abbvie
- TEVA
- Roche
- Lundbeck
- Pfizer
- Biogen

Stocks and IP + Consulent : Man & Science AS
Stocks and IP: Nordic Braintech AS
Stocks and IP: Keimon Medical AS

Other:

- Board Member European Headache Federation
- Board Member Norwegian Headache Federation
- Board Member Ottar Sjaastad Migraine Foundation
- Member Headache Panel European Academy of Neurology
- Associate Editor Cephalalgia

Largest funders:

- Norwegian Research Council
- Norwegian Health Trusts and Universities
- European Commission (EU funding programs)

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We dont know for certain

When to evaluate effectiveness? – Anti-CGRPs and gepants

We dont know for certain

But what do we know?

When to evaluate?

	EHF Guidelines:	AHS Guidelines:
mAbs	- After 3 months - In selected cases an additional 3 months	- After 3 months (monthly treatments) - After 6 months (quarterly treatments)
Gepants		- After 8 weeks and if not effective, switching treatment is recommended - Partial responders could benefit from 6-12 months treatment

Sacco, S. et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 23, 67 (2022).

Ailani J, et al. Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039.

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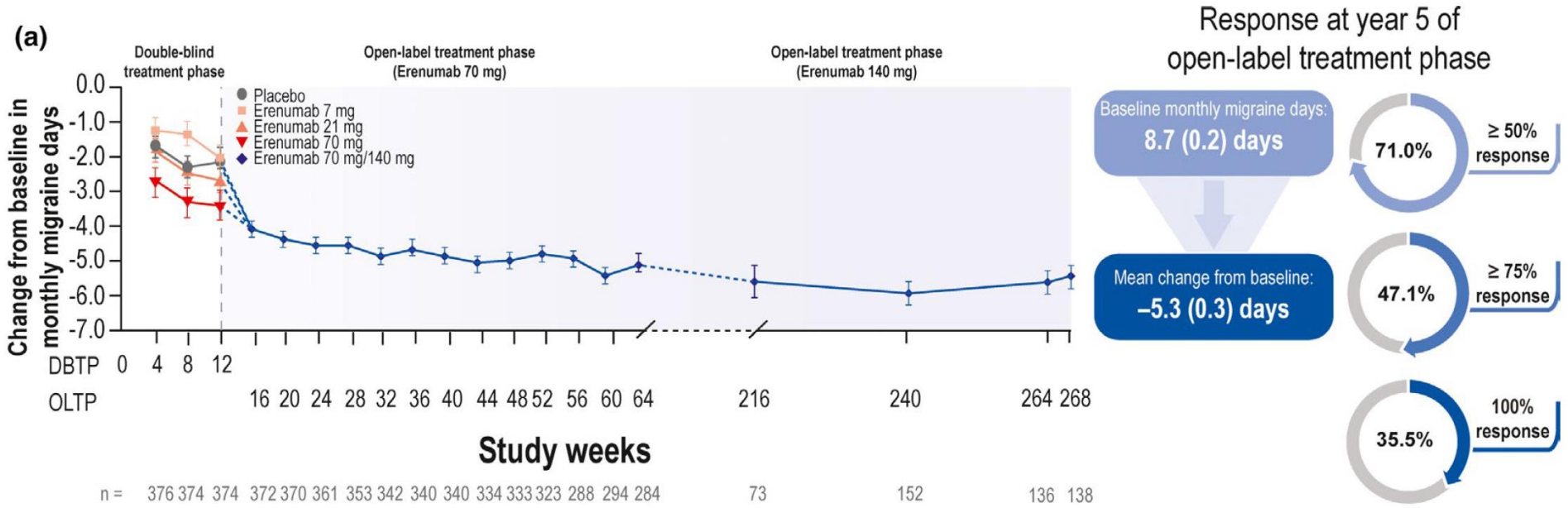
Open label and observational data



Ashina M et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. Eur J Neurol. 2021 May;28(5):1716-1725.

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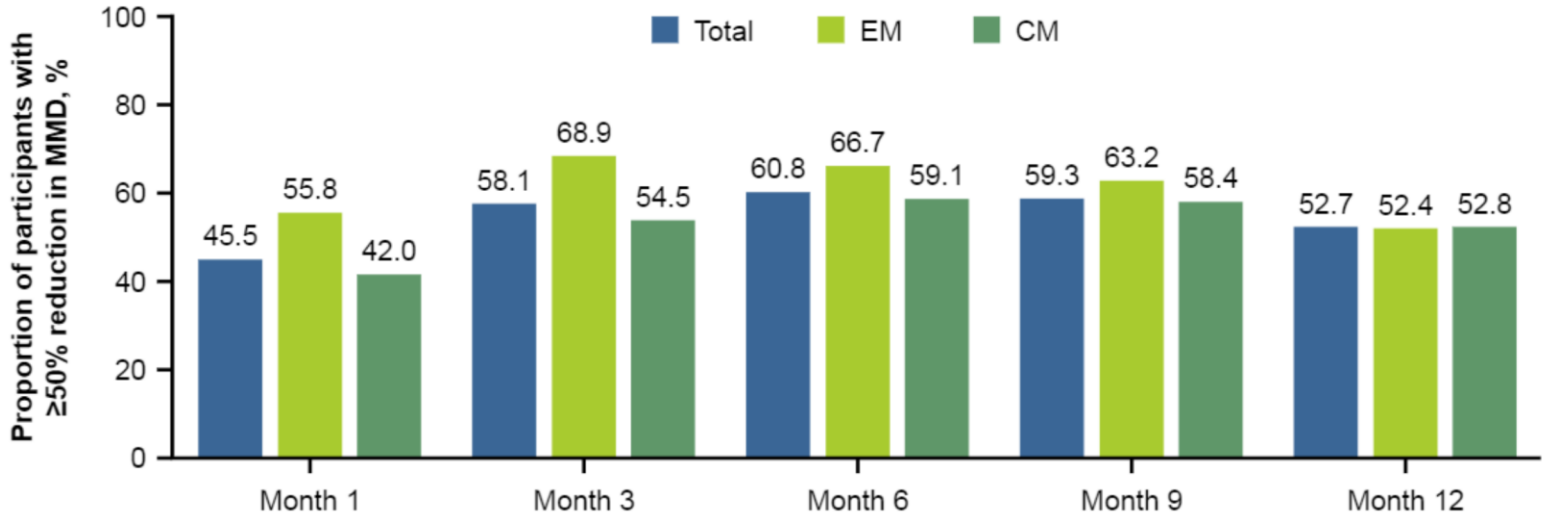
50% responders MMD in fremanezumab over 12 months



Total participants, *N*	552	473	309	216	146
EM participants, *n*	138	119	72	38	21
CM participants, *n*	414	354	237	178	125

CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days.

Ashina M, et al. Real-world effectiveness of fremanezumab for the preventive treatment of migraine: Interim analysis of the pan-European, prospective, observational, phase 4 PEARL study. Cephalalgia. 2023;43(11).

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Monthly or quarterly inj (blinded) - Fremanezumab

Follow-up 12 months

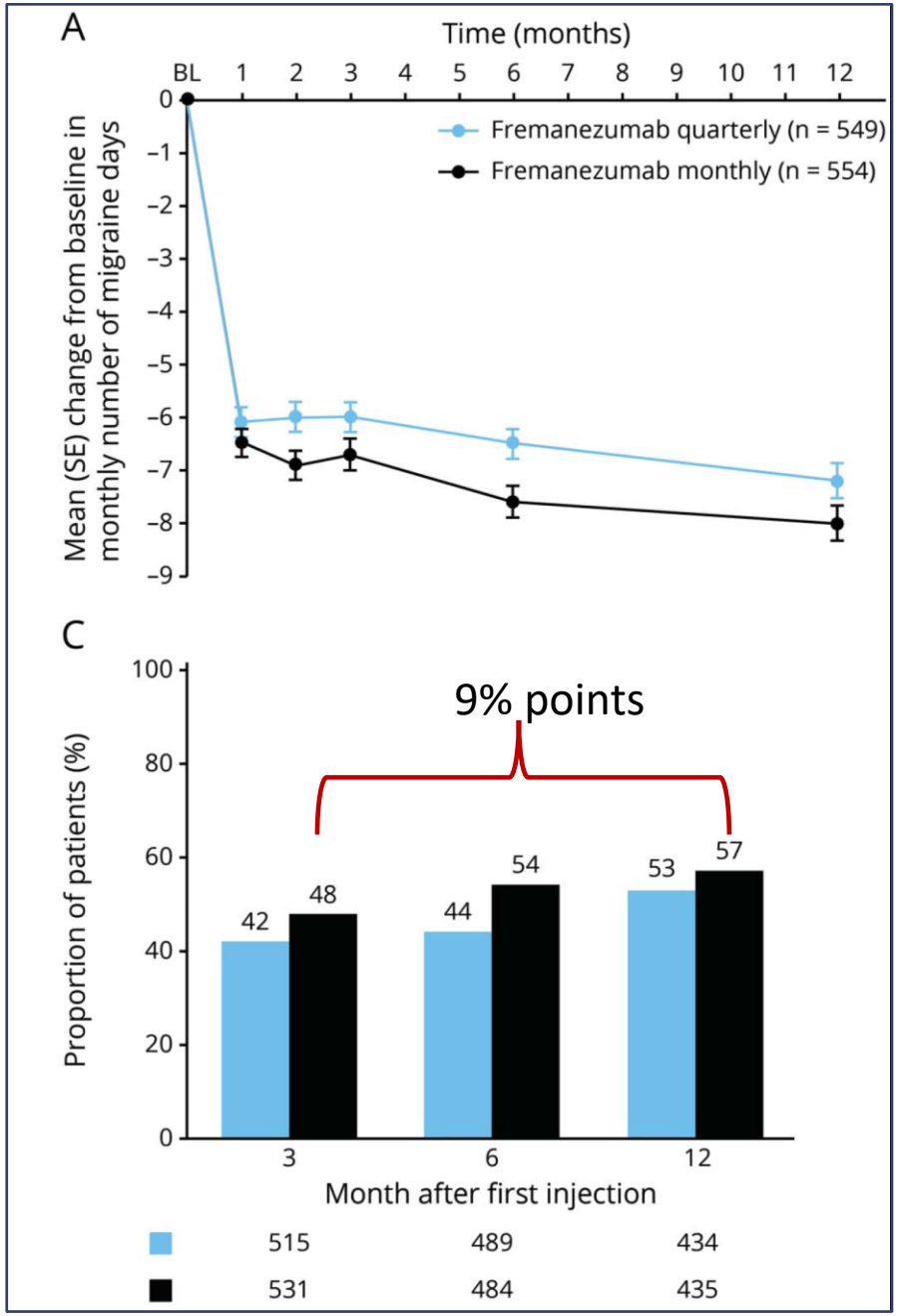
NB ! No Placebo group

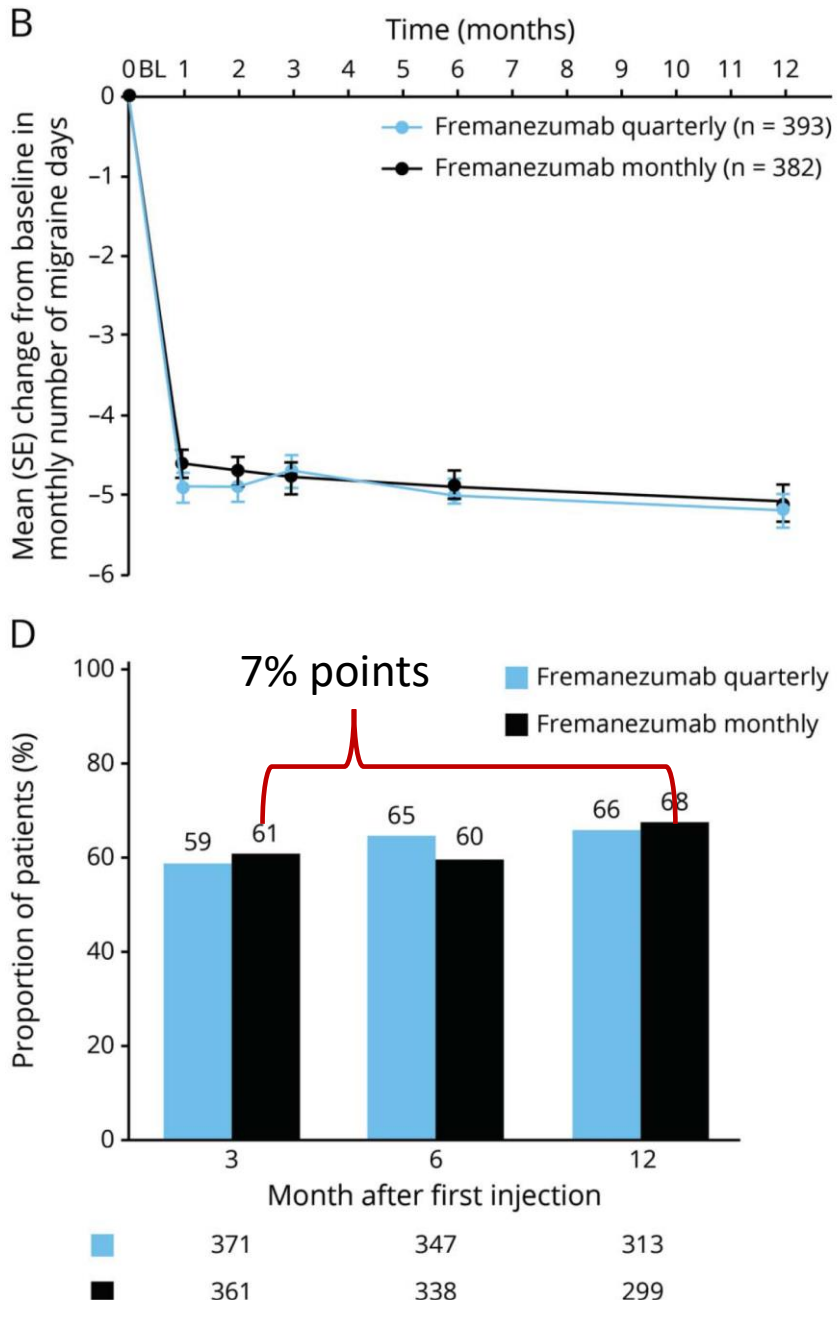
Reduction in MMD

Proportion of 50% responders

CHRONIC MIGRAINE

EPISODIC MIGRAINE





Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R, Dodick DW. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. Neurology. 2020 Nov 3;95(18):e2487-e2499.

Double – blinded data ≥ 6 months

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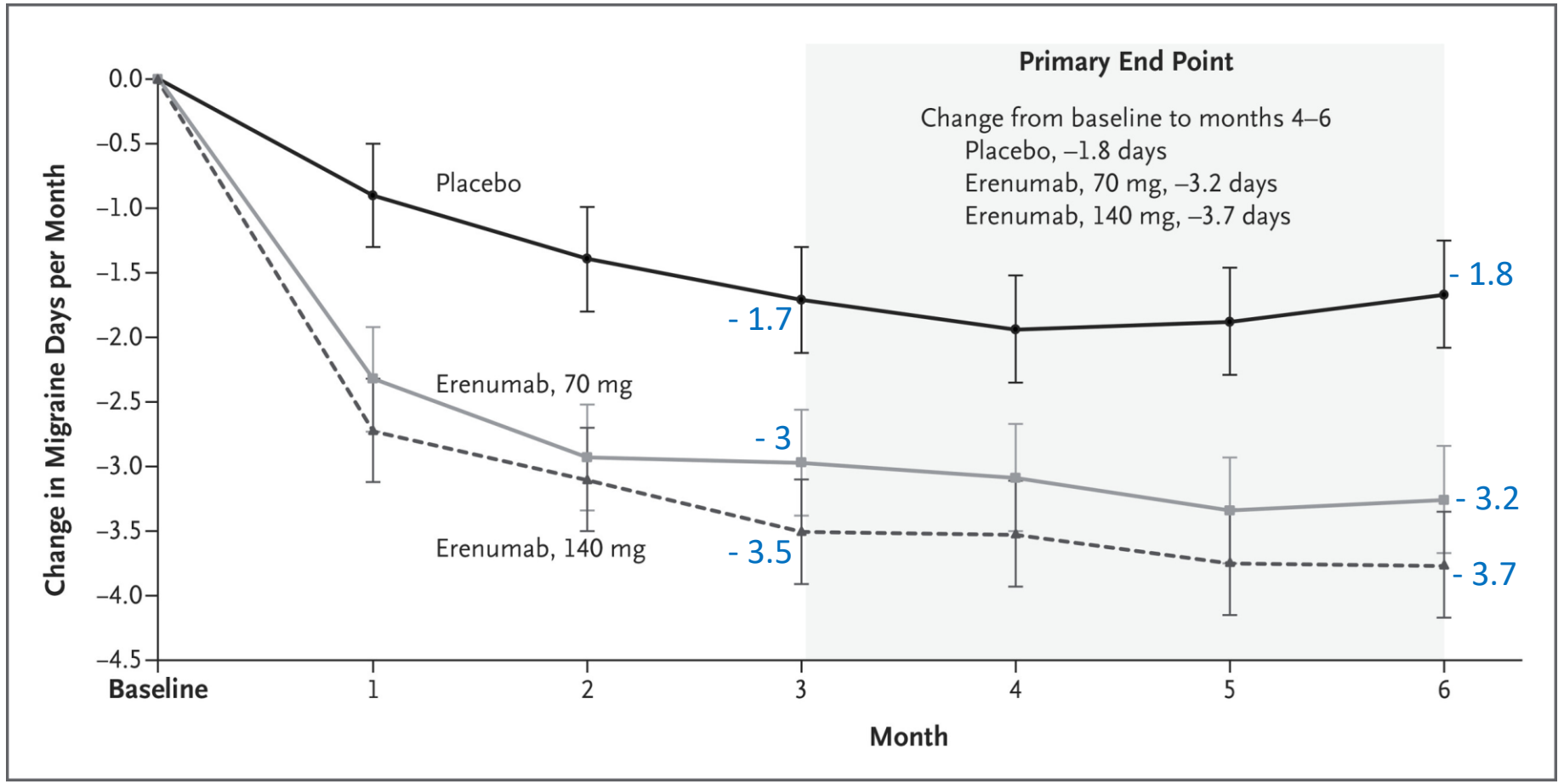
STRIVE study – Episodic migraine – Double blind for 6 months



3 vs. 6 month

70mg: △ = - 0.2 MMD

140mg: △ = - 0.2 MMD

Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017 Nov 30;377(22):2123-2132.

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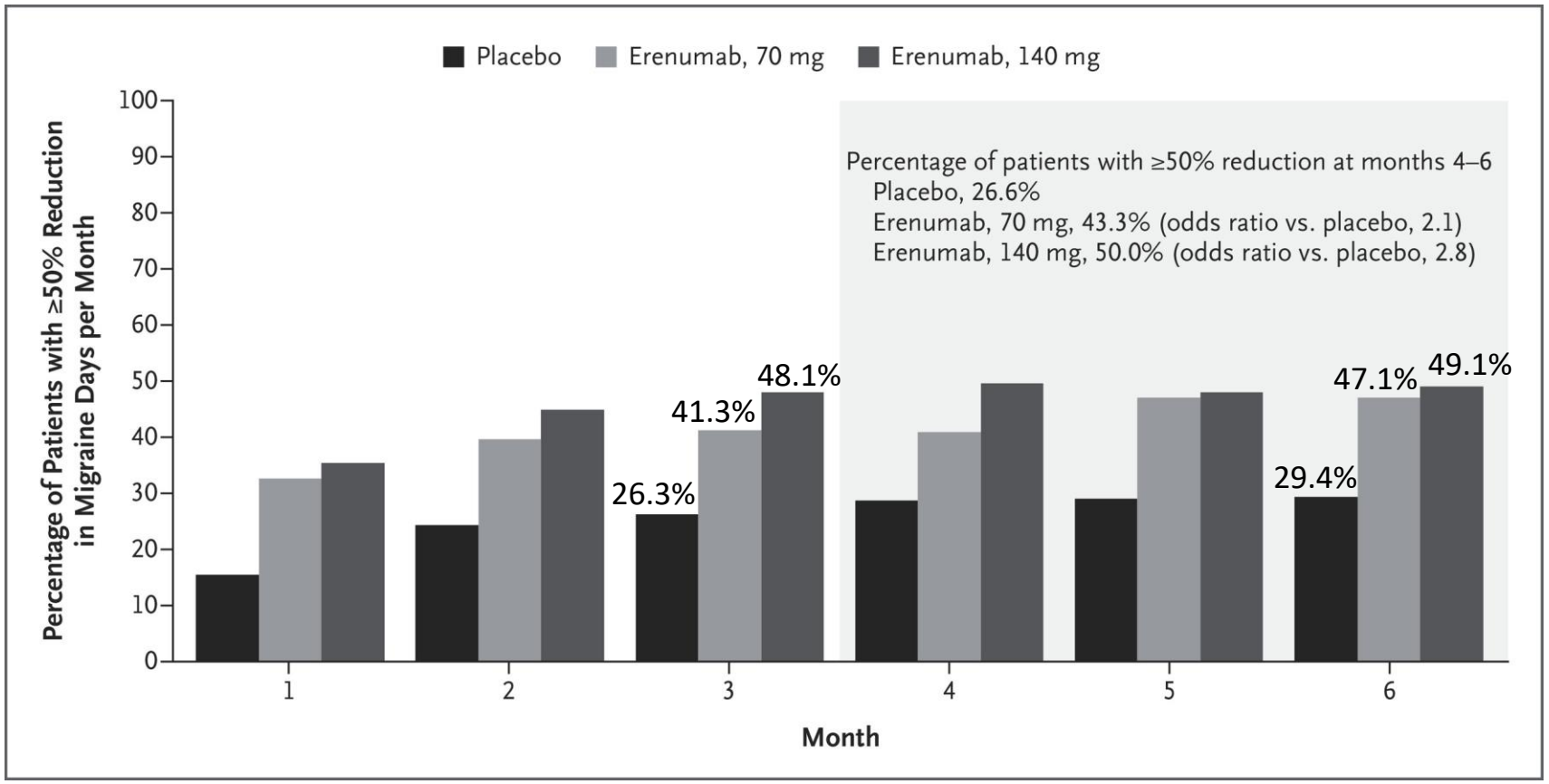
STRIVE study – Episodic migraine – Double blinded for 6 months



50% response month 3 vs. 6

70mg: 41.3% -> 47.1%

140mg: 48.1% -> 49.1%

Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017 Nov 30;377(22):2123-2132.

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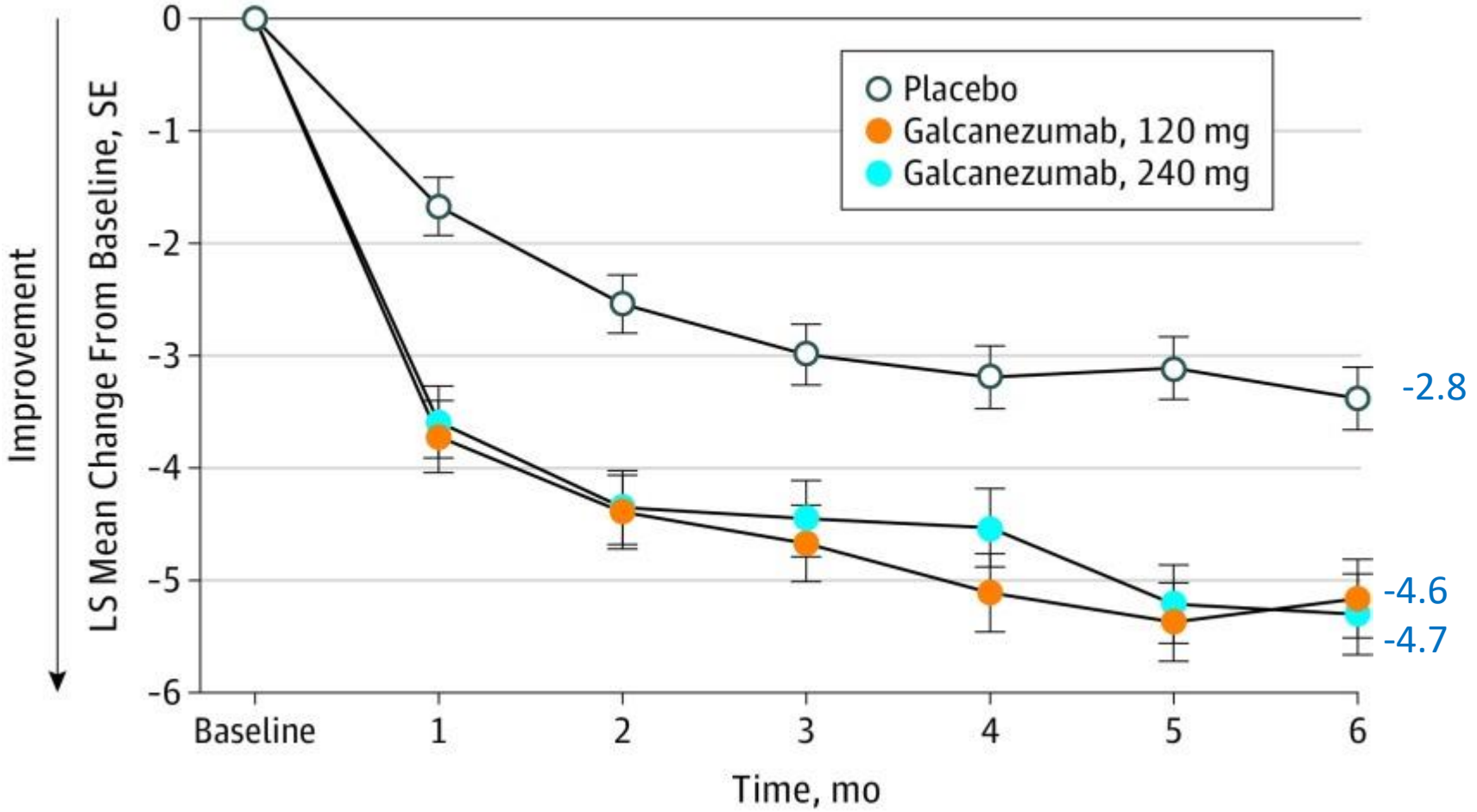
EVOLVE-1 Galcanezumab - EM - 6 months double-blind



MMD

Stauffer VL, et al. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018 Sep 1;75(9):1080-1088.

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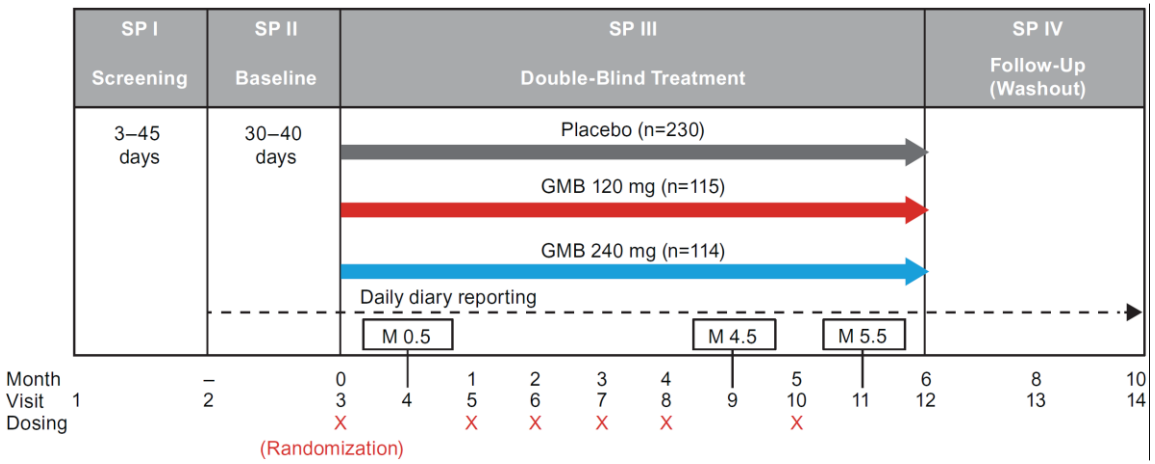
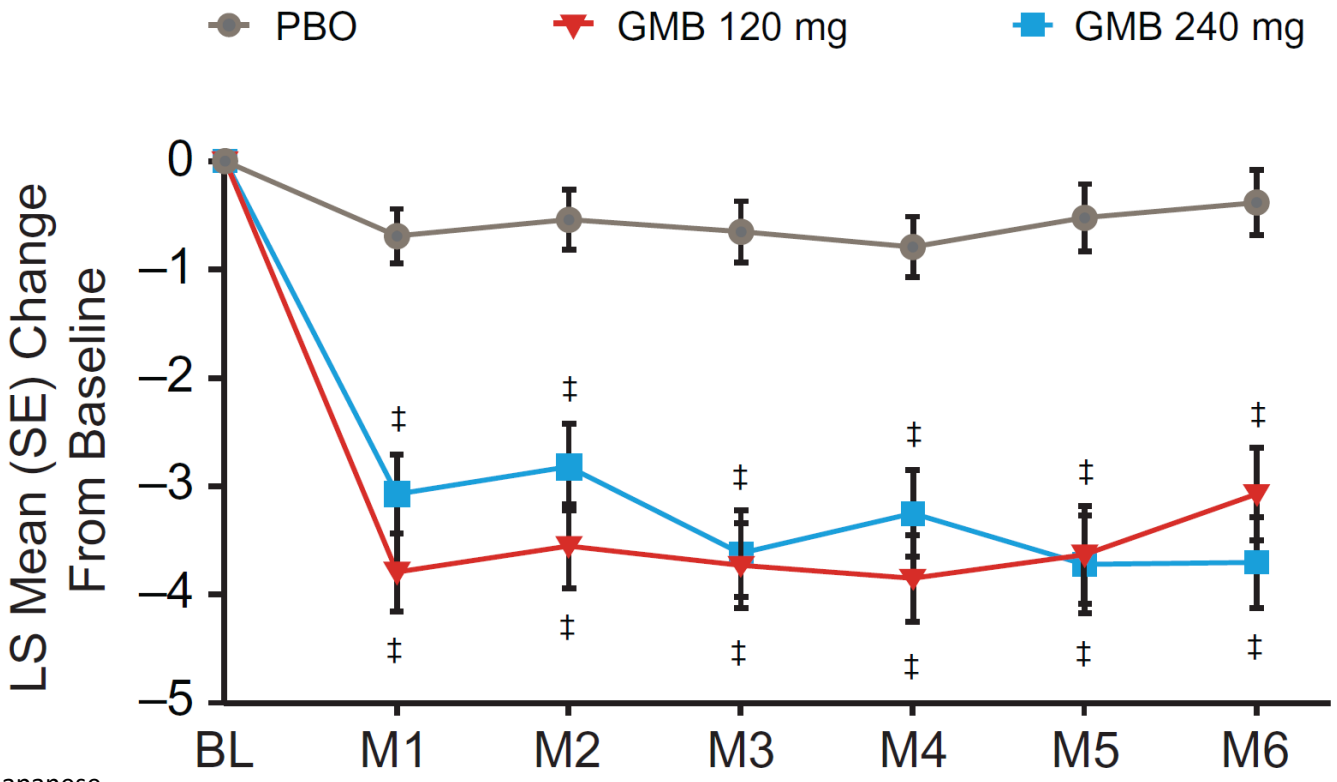


Galcanezumab (GMB) over 6 months- EM- double - blind



Sakai F, et al. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial. Cephalalgia Reports. 2020;3.

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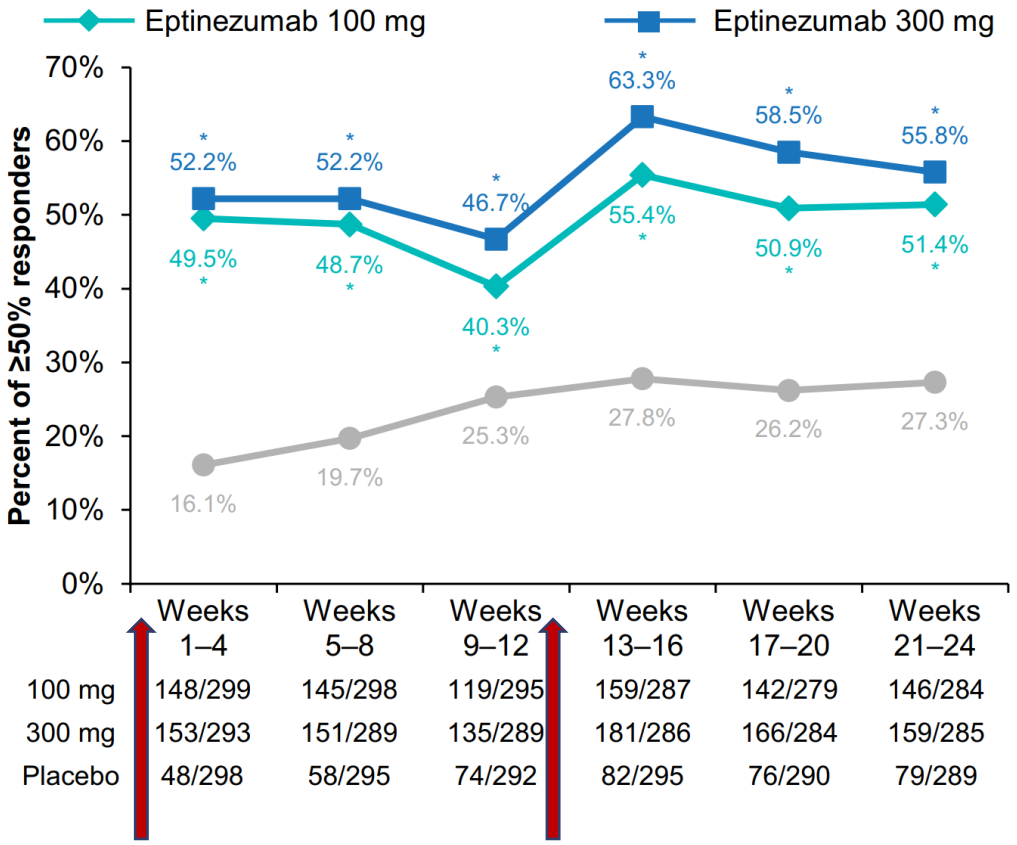
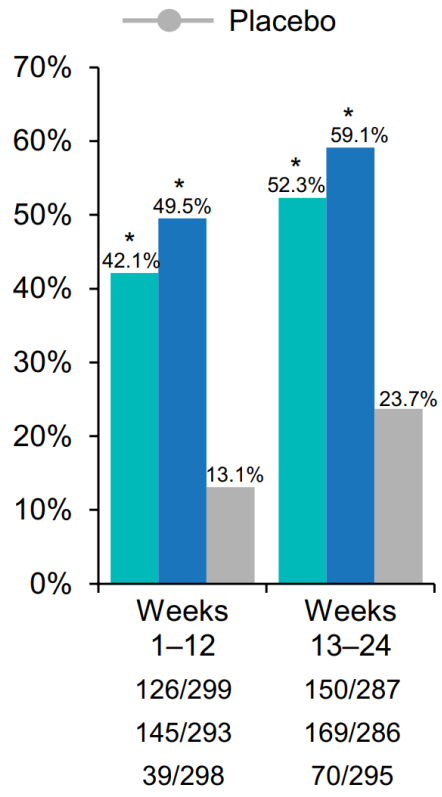
DELIVER study – eptinezumab – EM + CM posthoc analysis on 50% responder rates





Therapeutic gain month 1-3

Epti 100mg: 29% points
Epti 300mg: 36% points

Therapeutic gain month 4-6

Epti 100mg: 29% points
Epti 300mg: 35% points

Ashina M, et al. Responder rates with eptinezumab over 24 weeks in patients with prior preventive migraine treatment failures: post hoc analysis of the DELIVER randomized clinical trial. Eur J Neurol. 2024 Feb;31(2):e16131.

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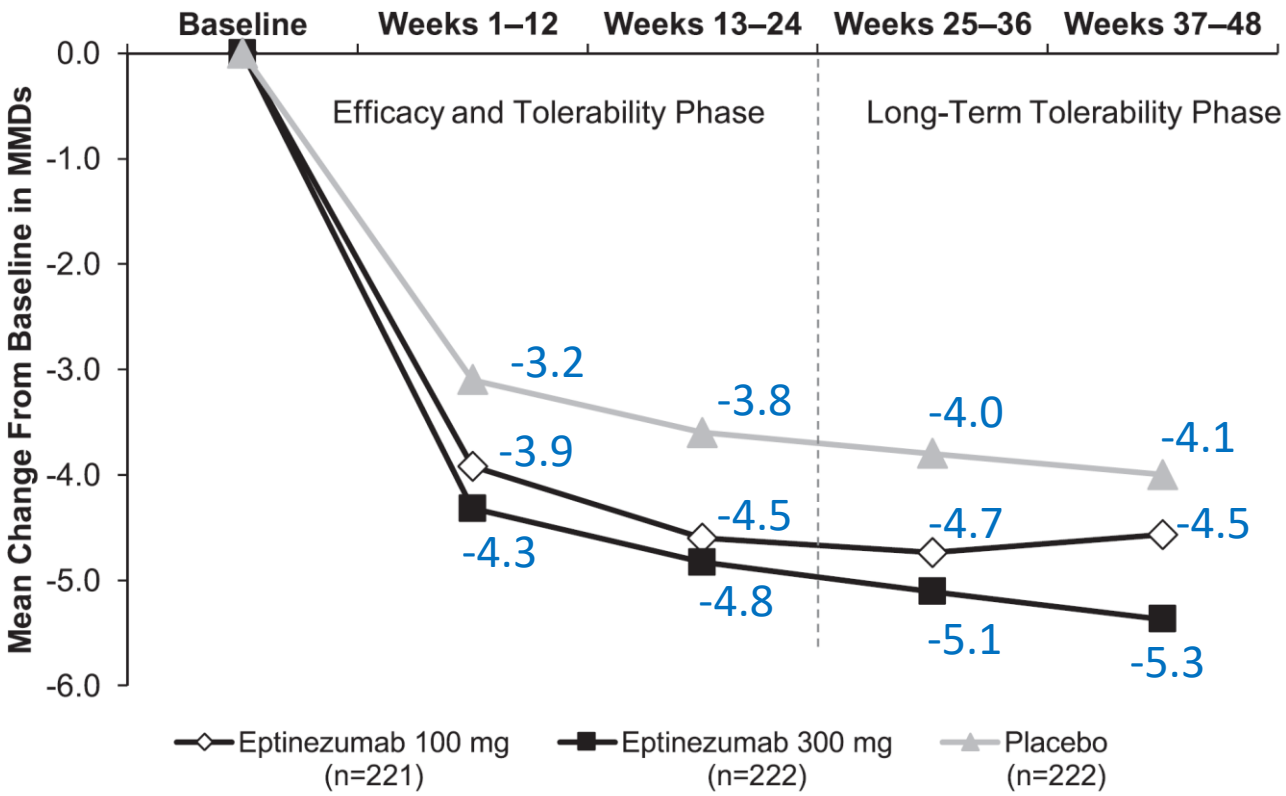
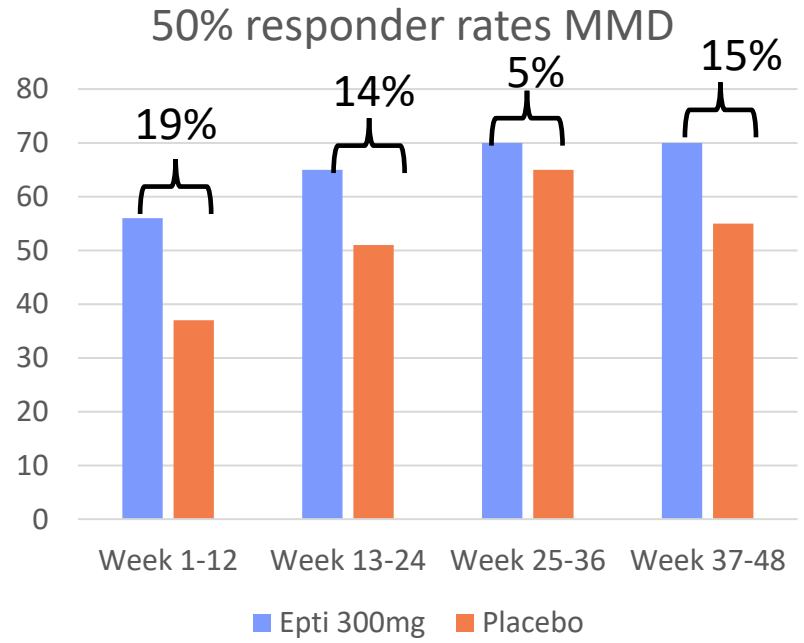
PROMISE-1 study. Eptinezumab - EM - placebo controlled for 48 weeks





Ashina M, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia. 2020 Mar;40(3):241-254.

Smith TR, et al. Eptinezumab for the Prevention of Episodic Migraine: Sustained Effect Through 1 Year of Treatment in the PROMISE-1 Study. Clin Ther. 2020 Dec;42(12):2254-2265.e3.

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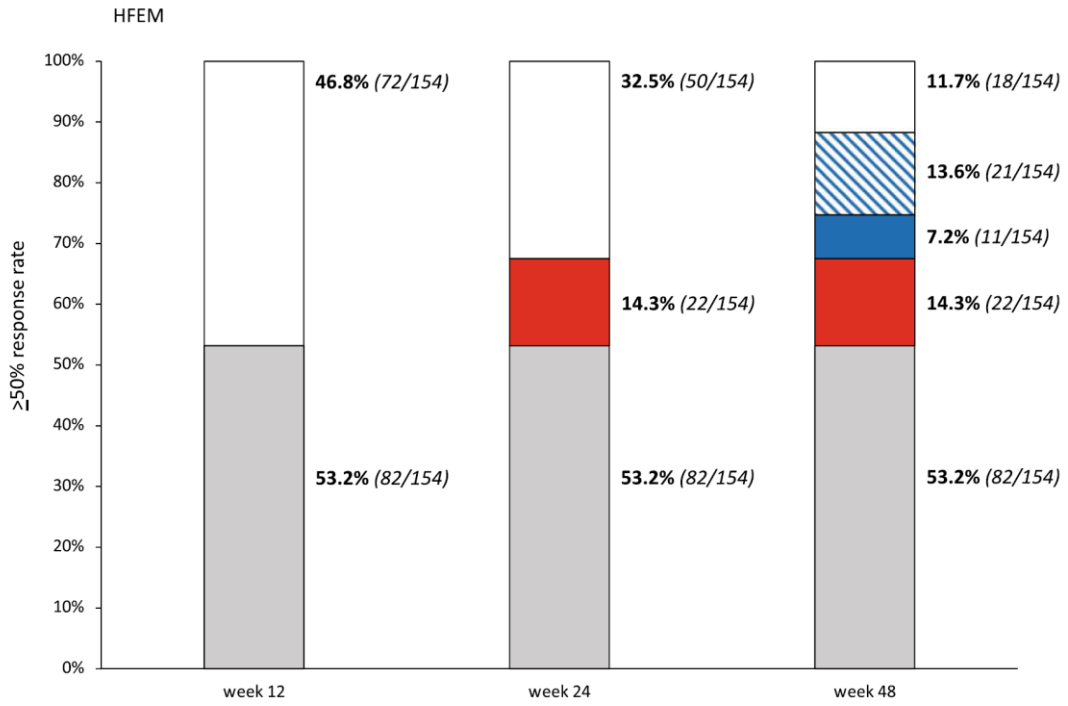
Italian registry data

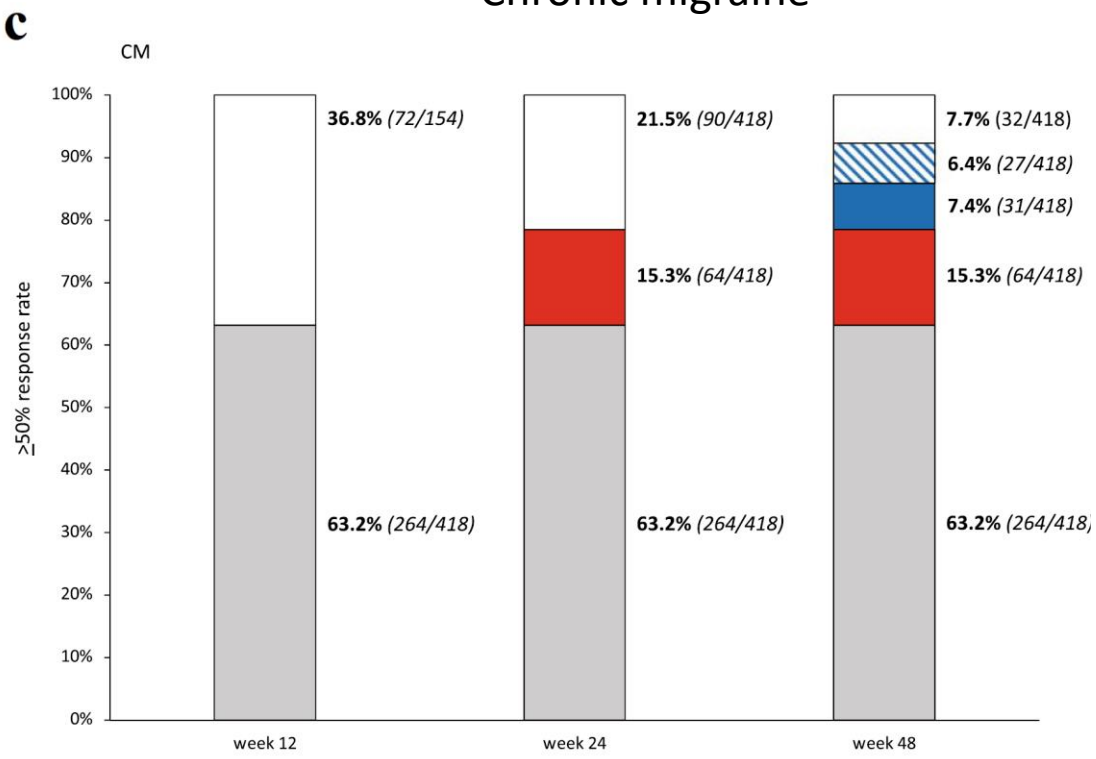
Registry data. 50% responders to MMD (HEF>8d/m) and MHD (CM)

- Non-responders
- Responders ≤ 12w
- Late responders >12w
- Ultra- Late responders >24w – persistent
- Ultra- Late responders >24w - not persistent

High-frequency episodic migraine



Chronic migraine



Barbanti P,; ERT; for the Italian Migraine Registry study group. Ultra-late response (> 24 weeks) to anti-CGRP monoclonal antibodies in migraine: a multicenter, prospective, observational study. J Neurol. 2024 May;271(5):2434-2443.

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RWE data predictors for efficacy of mAbs:

≥50% MHD reduction associated with:

- Older age
- Unilateral headache
- No depression
- Less concomitant oral medication

Late responders:

- higher BMI
- more frequent treatment failures
- psychiatric comorbidities
- less common unilateral pain
- with unilateral cranial autonomic symptoms
- allodynia

Caronna E, Pozo-Rosich P; EUREkA study group. Redefining migraine prevention: early treatment with anti-CGRP monoclonal antibodies enhances response in the real world. J Neurol Neurosurg Psychiatry. 2024 Sep 17;95(10):927-937.

Barbanti P,et al; Italian Migraine Registry study group. Late Response to Anti-CGRP Monoclonal Antibodies in Migraine: A Multicenter Prospective Observational Study. Neurology. 2023 Sep 12;101(11):482-488

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Evaluating time for effectiveness in gepants

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ADVANCE study – Atogepant vs placebo for prevention - EM – double blind – 12w

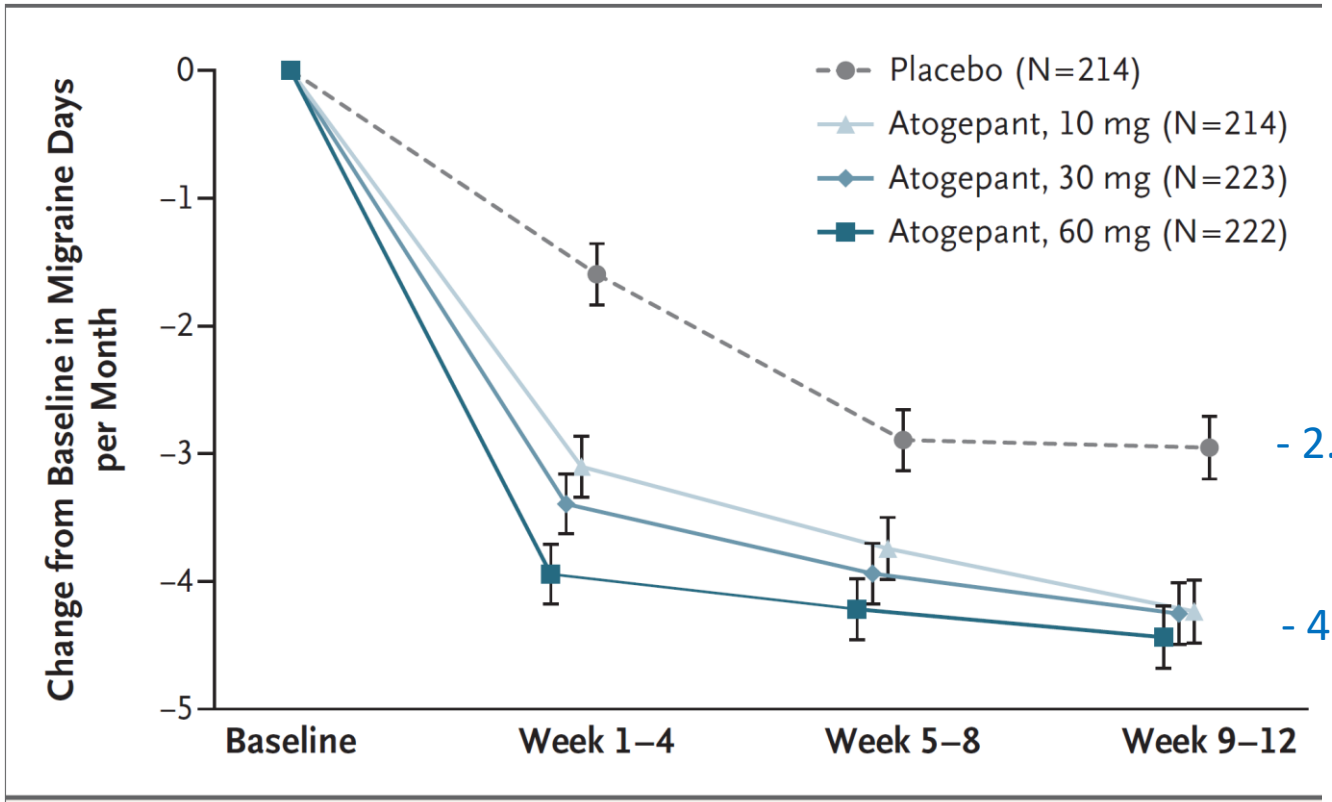

Figure 2. Time Course of Efficacy (Modified Intention-to-Treat Population).
Shown is the least-squares mean change from baseline in migraine days per month. I bars indicate standard errors.

<u>50% responders MMD :</u>

Placebo: 29%
60mg Atogepant 61%

Ailani J, et al. ADVANCE Study Group. Atogepant for the Preventive Treatment of Migraine. N Engl J Med. 2021 Aug 19;385(8):695-706

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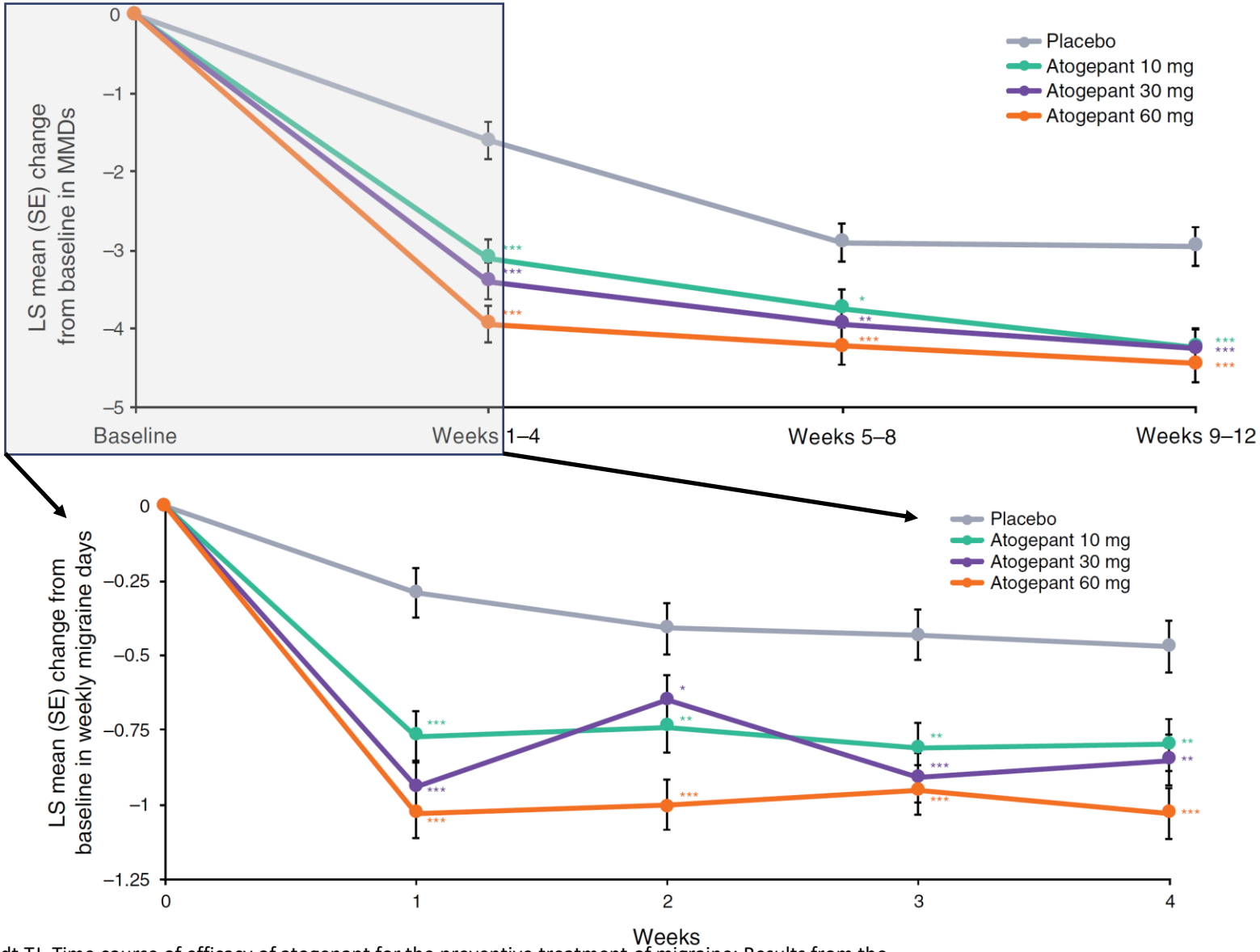
ADVANCE study – Looking at the first 4 weeks



MMD

Weekly migraine days

Schwedt TJ. Time course of efficacy of atogepant for the preventive treatment of migraine: Results from the randomized, double-blind ADVANCE trial. Cephalalgia. 2022 Jan;42(1):3-11.

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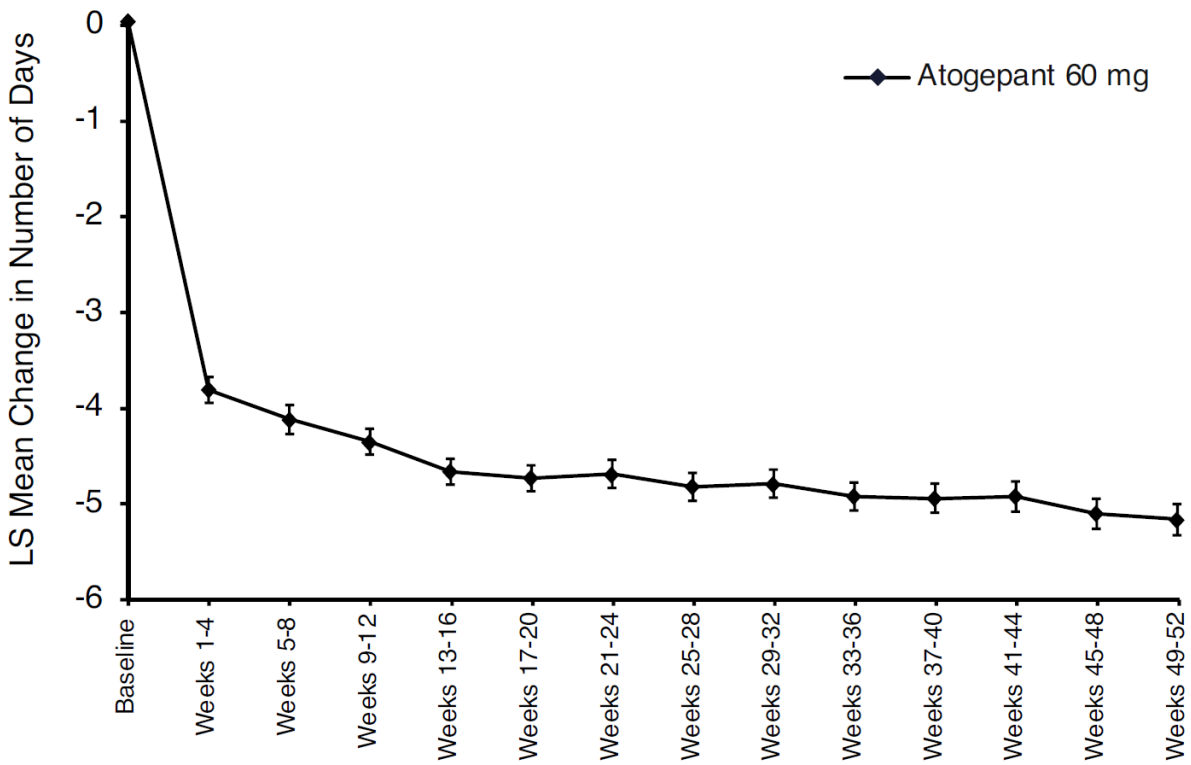
Open-label - EM – 60 mg Atogepant – 12 months



Baseline
monthly migraine days
7.3 (2.6) days

LS mean change from
baseline at 52 weeks
-5.2 (0.2) days

- 3.8 MMD (week 1-4)

- 5.2 MMD (week 49-52)

Ashina M, et al. Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial. Headache. 2023 Jan;63(1):79-88.

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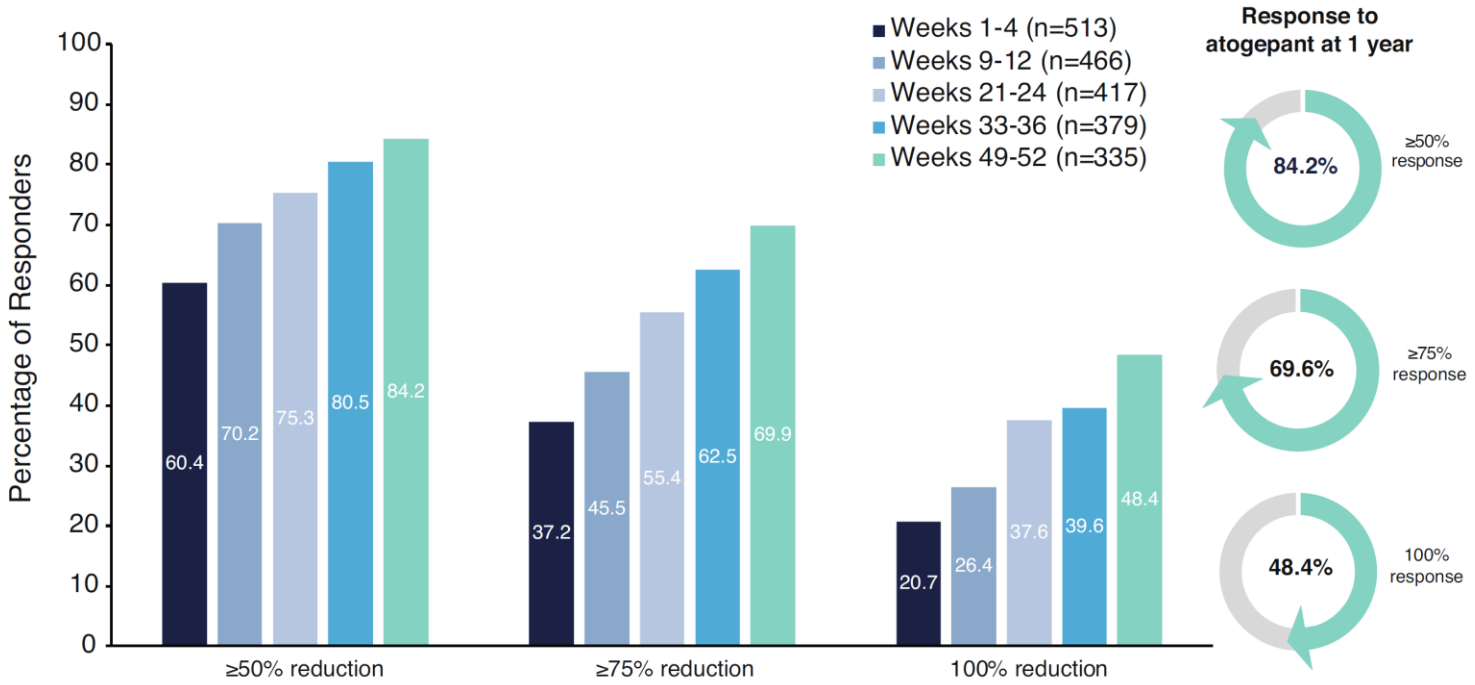
Open-label - EM – 60 mg Atogepant – 12 months

50% responders



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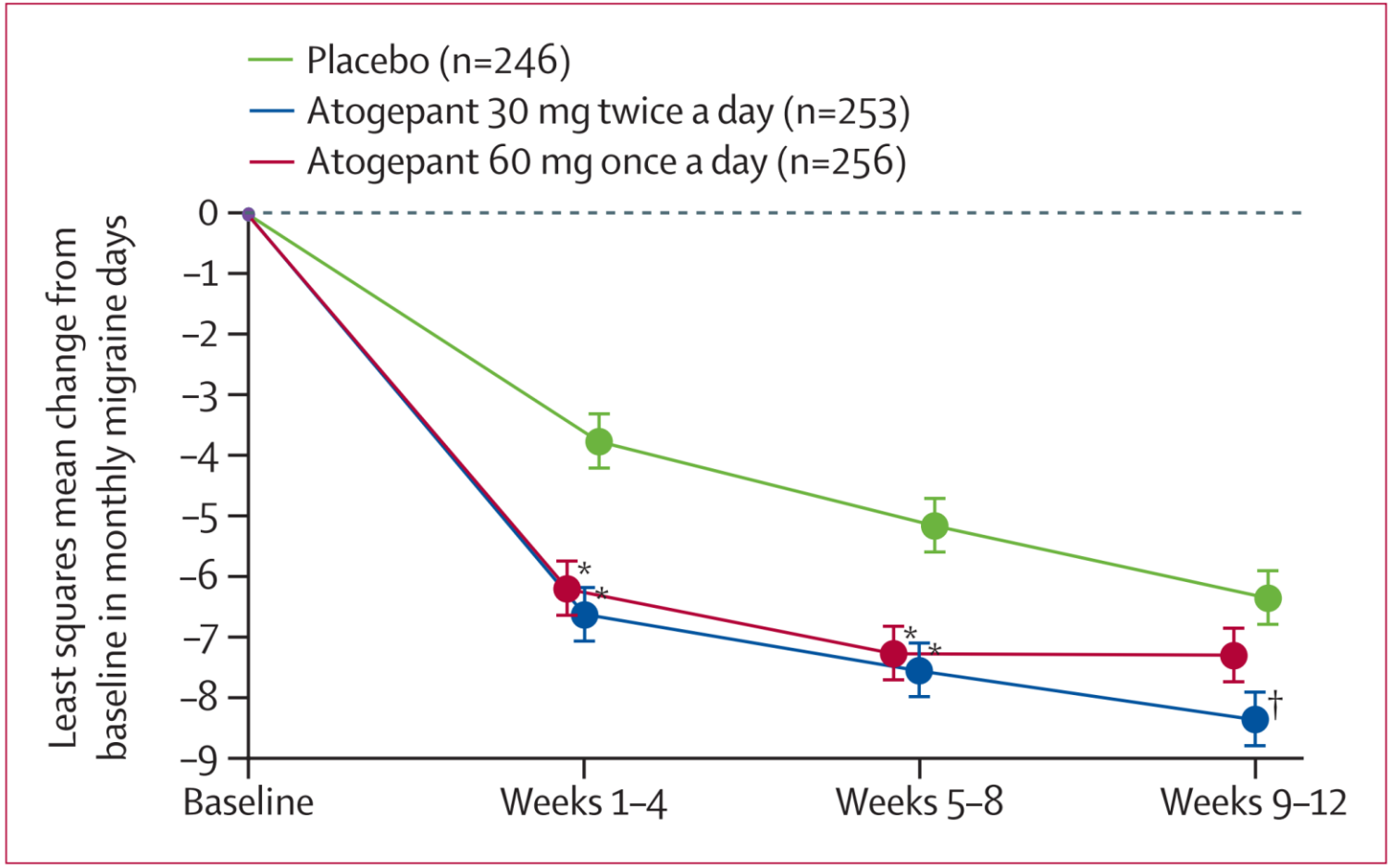
PROGRESS-study Atogepant in CM – 12w double-blind



Placebo: - 5.1 MMD

Atogepant 60mg: - 6.9 MMD

Pozo-Rosich P, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023 Sep 2;402(10404):775-785.

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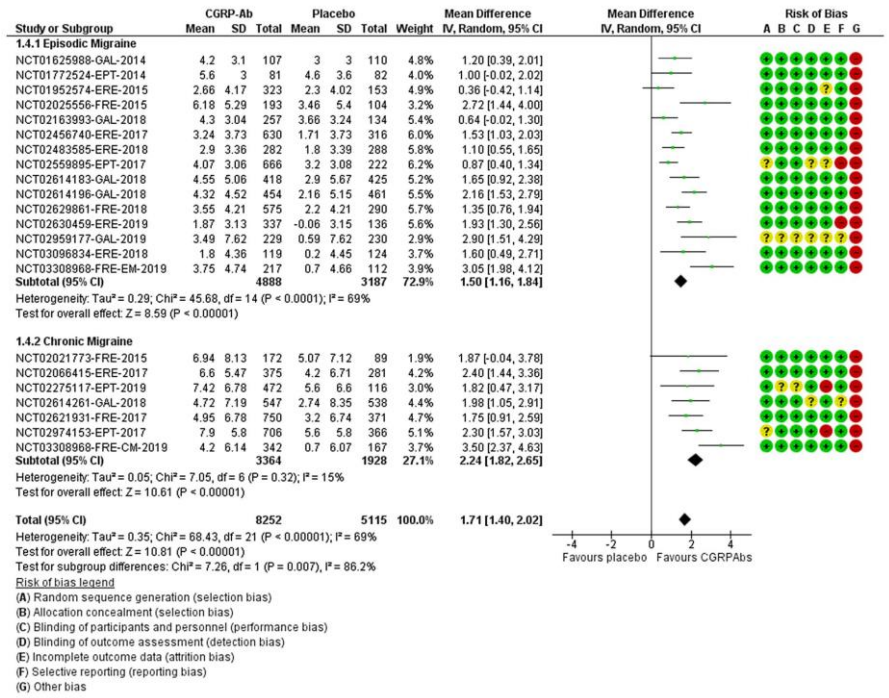
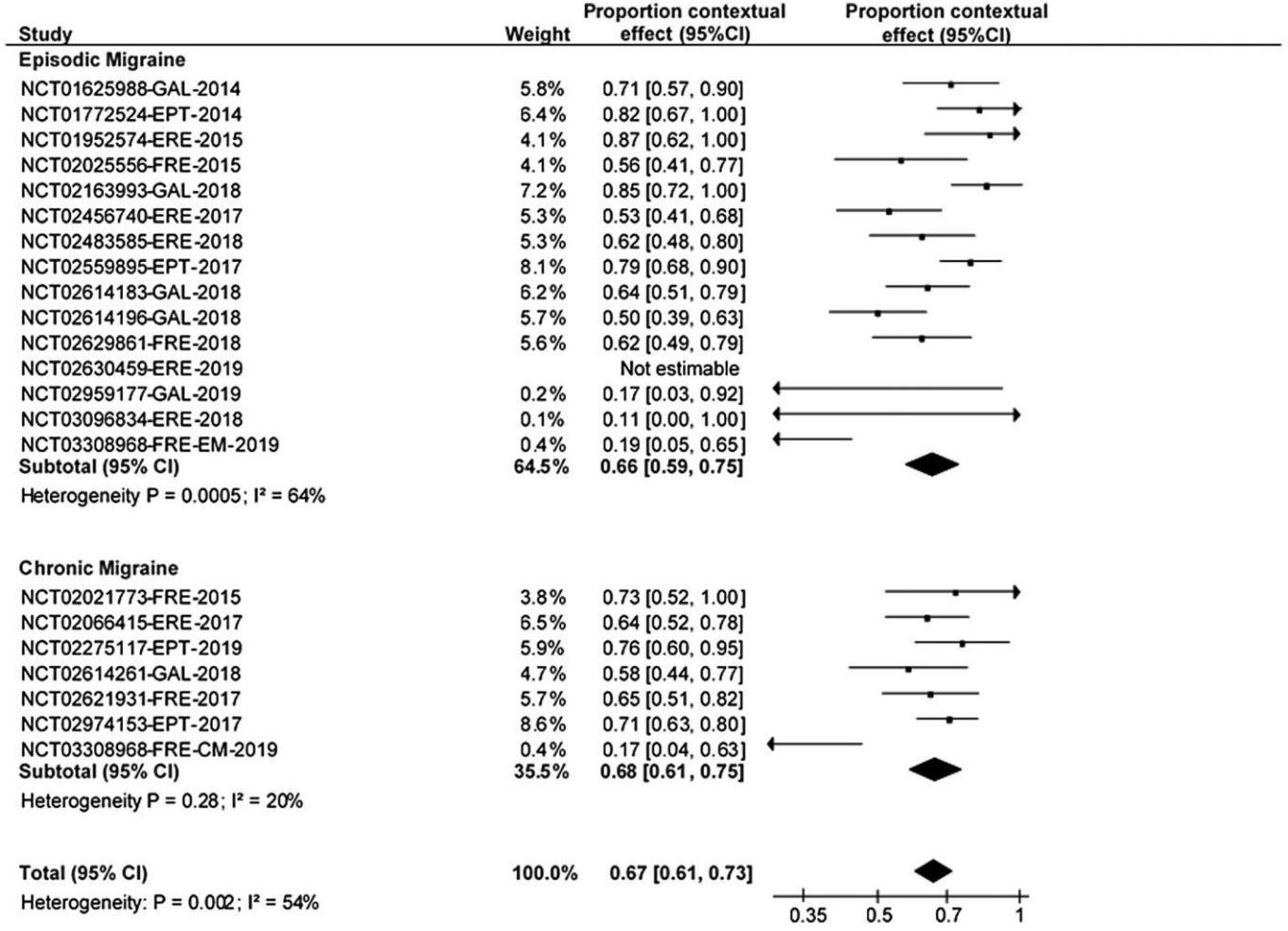
Contextual effects in episodic and chronic migraine





Forbes RB, et al. Efficacy and Contextual (Placebo) Effects of CGRP Antibodies for Migraine: Systematic Review and Meta-analysis. Headache. 2020 Sep;60(8):1542-1557.

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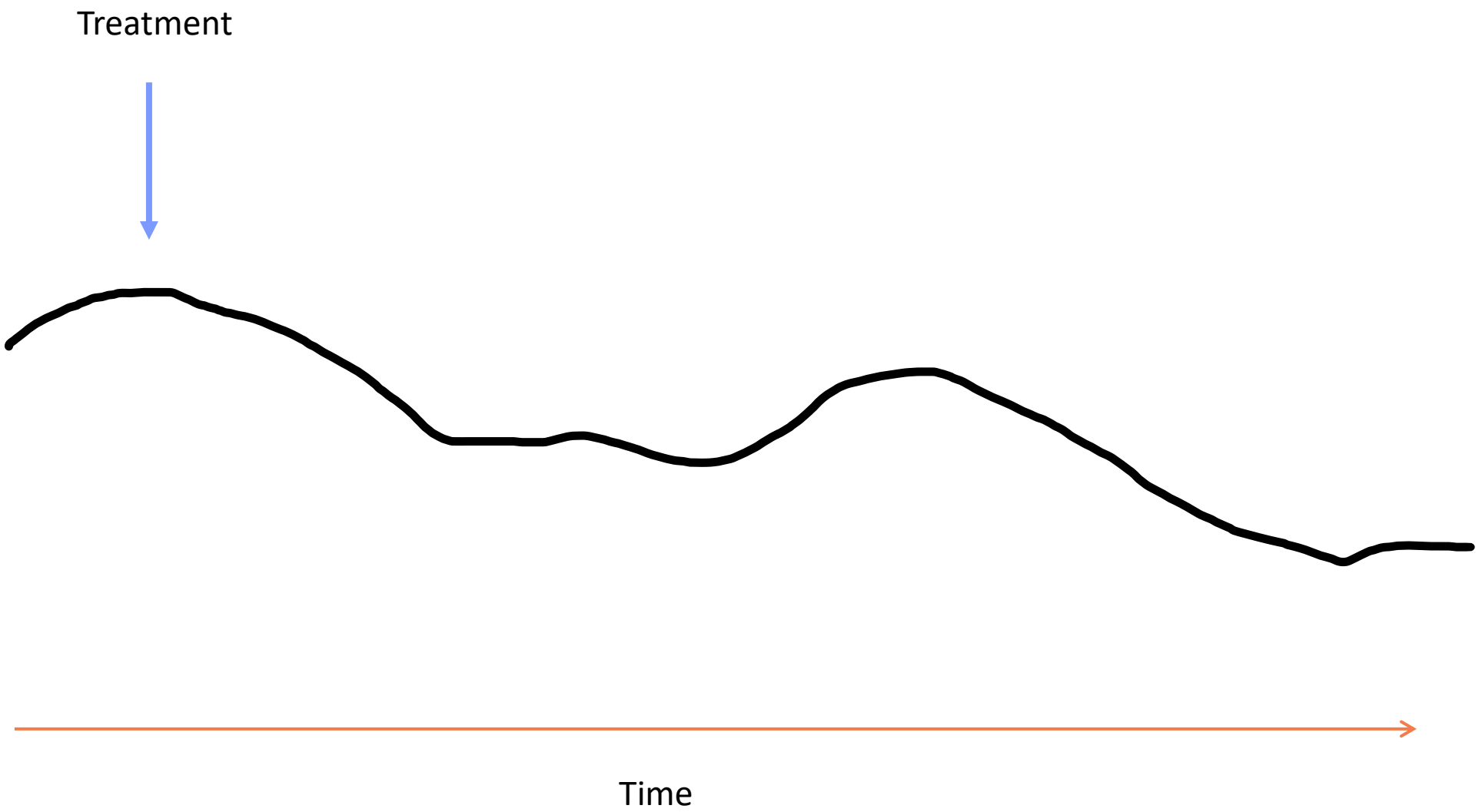

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Variables to consider when evaluating efficacy

1. Number of headache days (mild, moderate and severe)
2. Duration of attacks
3. Change in response to acute medication
5. Change in aura frequency (if relevant)
6. Change in postdromal symptoms (severity and duration) and interictal symptoms
7. Frequency reduction in month 3 compared to baseline
8. HIT-6
9. PGIC (7 item patient global impression of change)

clinical craftsmanship

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Thank You !

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