New preventive drugs for migraine

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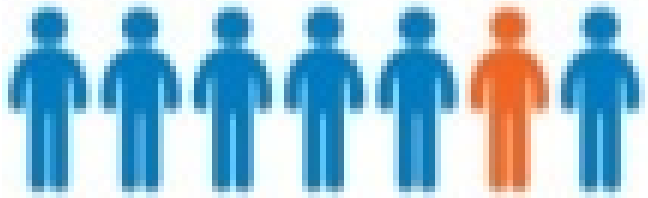
I have received fellowship grant, research grant and travel grants from International Headache Society, European Headache Federation, Candy's foundation and University of Copenhagen.

Objectives

- ✓ Explain Issues with Available Therapies for Migraine
- ✓ Explain the potential role of CGRP in migraine pathophysiology
- ✓Differentiate between small molecules (the Gepants) and monoclonal antibodies in treatment of migraine.
- ✓monoclonal antibodies and their efficacy, safety and tolerability in the prevention of migraine.

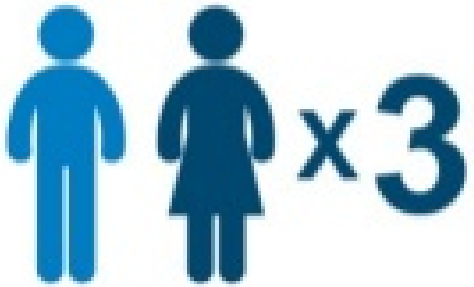
What is migraine?

1 in every 7 people suffers from migraine

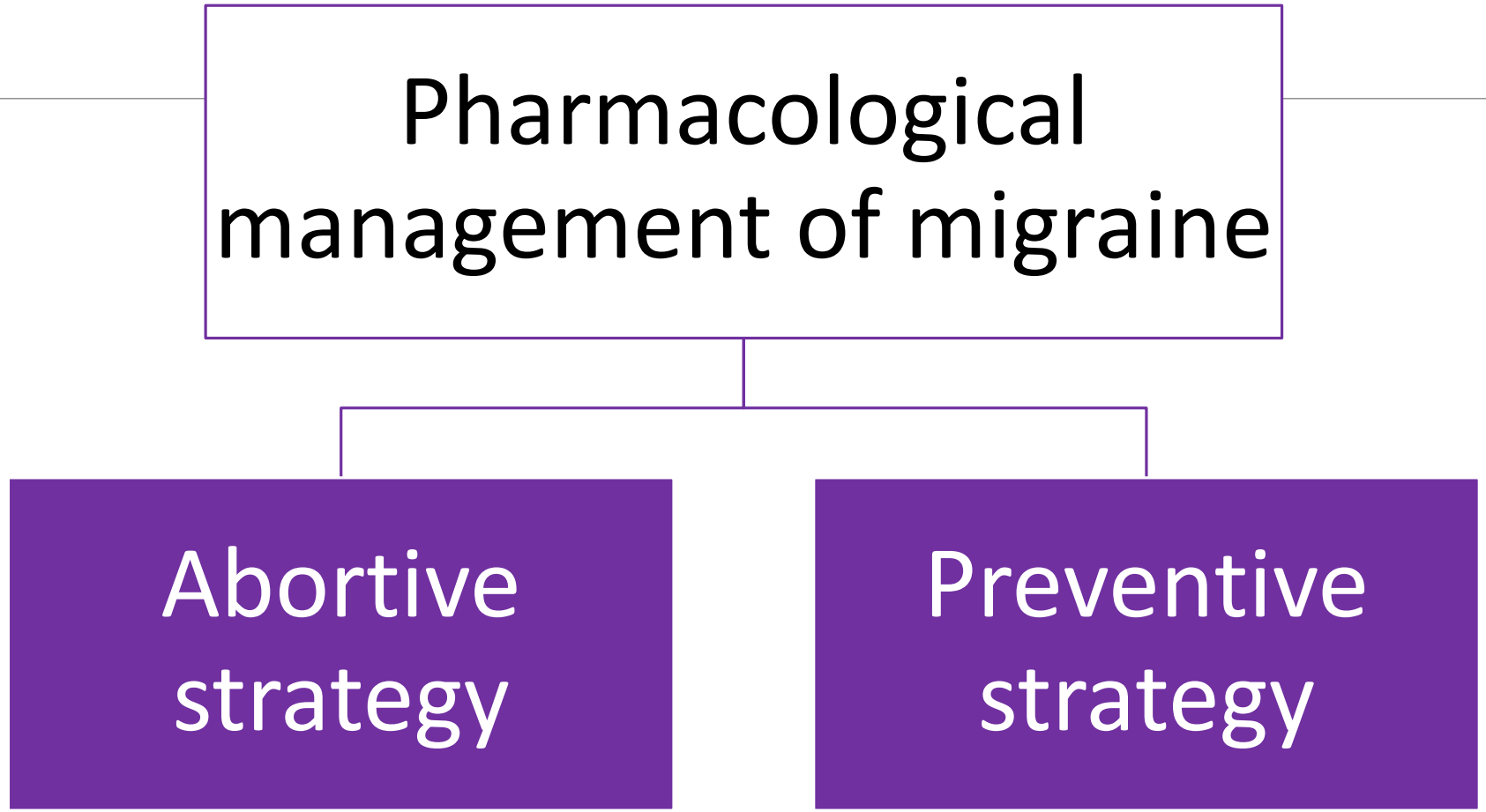


2nd most disabling disease in the world

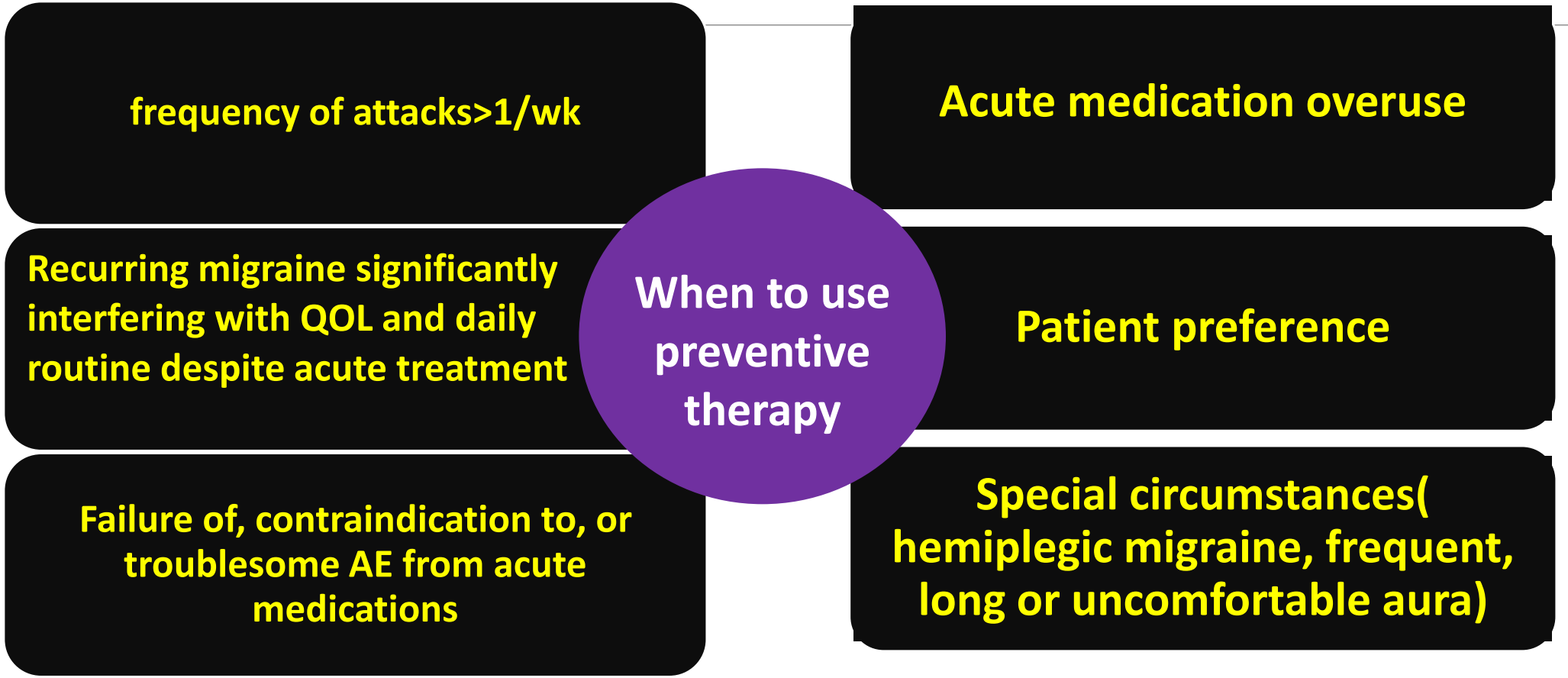
Women are 3 times more likely to get migraine compared with men



STEINER ET AL. GBD 2018, THE LANCET
YOUNGER DS ET AL. EPIDEMIOLOGY OF MIGRAINE, NEUROL CLINIC, 2016


Pharmacological management of migraine
Abortive strategy
Preventive strategy

Indications for Preventive Therapy in Patients With Migraine



Current evidence-based Migraine Prevention Treatments: EFNS Guidelines

Drugs of first choice

Level A: Medications with established efficacy and should be offered for migraine prevention

- Propranolol
- Metoprolol
- Valproic acid
- Topiramate
- Flunarizine

Drugs of second choice

Level B: Medications are probably effective and should be considered for migraine prevention

- Amitriptyline
- Venlafaxine
- Bisoprolol
- Naproxen
- Petasites

Drugs of third choice

Level C: Medications are possibly effective and may be considered for migraine prevention

- Lisinopril
- Candesartan
- Gabapentin
- Aspirin
- Coenzyme Q10
- Magnesium
- Riboflavin
- Tanacetum parthenium
- Methysergide

First choice agents recommended for Chronic Migraine:

Topiramate
Onabotulinium toxin

Issues with Available Preventive Therapies for Migraine

- ✓Non of the available preventive therapies was developed specifically for migraine.
- ✓There are efficacy, safety, adherence and drug-drug interaction issues for a substantial proportion of migraine patients.
- ✓No pharmacologic treatments hold compelling evidence of efficacy in CM refractory patients.

Emerging drugs for migraine treatment

✓ Fortunately, new and promising drugs are developed for acute and preventive migraine-specific treatment

Novel **acute** treatments:

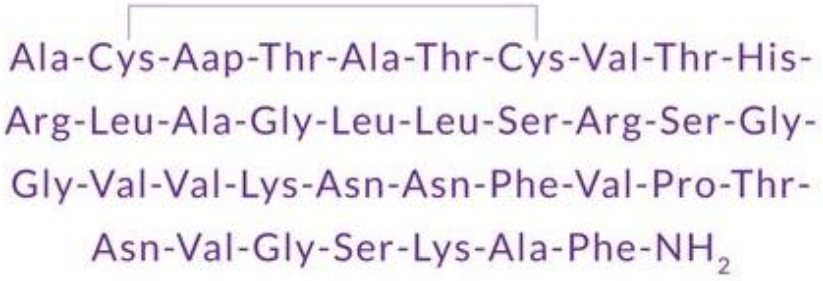
- Gepants (target CGRP pathway)

Novel **preventive** treatments:

- CGRP monoclonal antibodies

What is Calcitonin Gene-Related Peptide(CGRP)?

CGRP is a 37-amino acid neuropeptide functions as a messenger in nerve cells as a vasodilator.



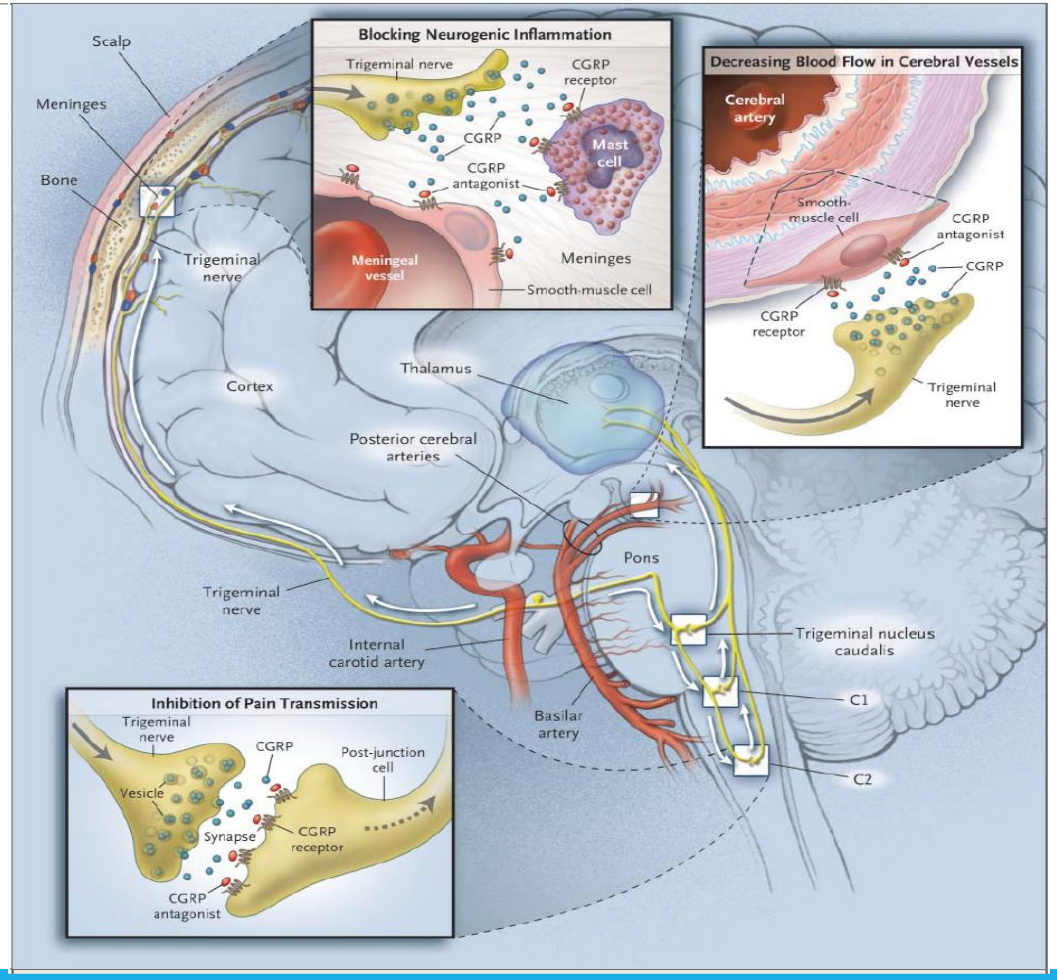
CGRP exist in two forms in humans:

α CGRP is expressed in primary sensory neurons of the dorsal root ganglia, trigeminal ganglia and vagal ganglia.

β CGRP is found in enteric neurons system. This differs in 3 amino acids.

CGRP in the Trigeminovascular System

- Main sensory neuropeptide released by activated trigeminal neurons
- Physiological actions: vasodilation, mast cell degranulation, sensory transmission



Calcitonin Gene-Related Peptide in Migraine; The Evidence

- ✓Released during migraine attacks
- ✓Persistent elevation in chronic migraine
- ✓CGRP infusion triggers migraine
- ✓Headache relief after sumatriptan coincides with normalization of CGRP levels
- ✓ CGRP blockade at key sites (TNC, PAG, thalamus) effective in preclinical models of cephalic pain

GOADSBY PJ, ET AL ANN NEUROL 1988 FEB;23(2):193-6.
LASSEN LH, ET AL. CEPHALALGIA 2002 FEB;22(1):54-61
JUHASZ G, ET AL. CEPHALALGIA 2005 MAR;25(3):179-83.
DURHAM, P. NEJM *2004;* 350(11): 1073-1075

Drugs directed at modulating CGRP activity in migraine:

- CGRP receptor antagonist (the Gepants)

- Therapeutic monoclonal antibodies
  - Monoclonal antibodies to the CGRP receptor
    - Erenumab
  - Monoclonal antibodies to the CGRP ligand:
    - Fremanezumab, Galcanezumab, Eptinezumab

Small Molecules (Gepants) vs mAbs

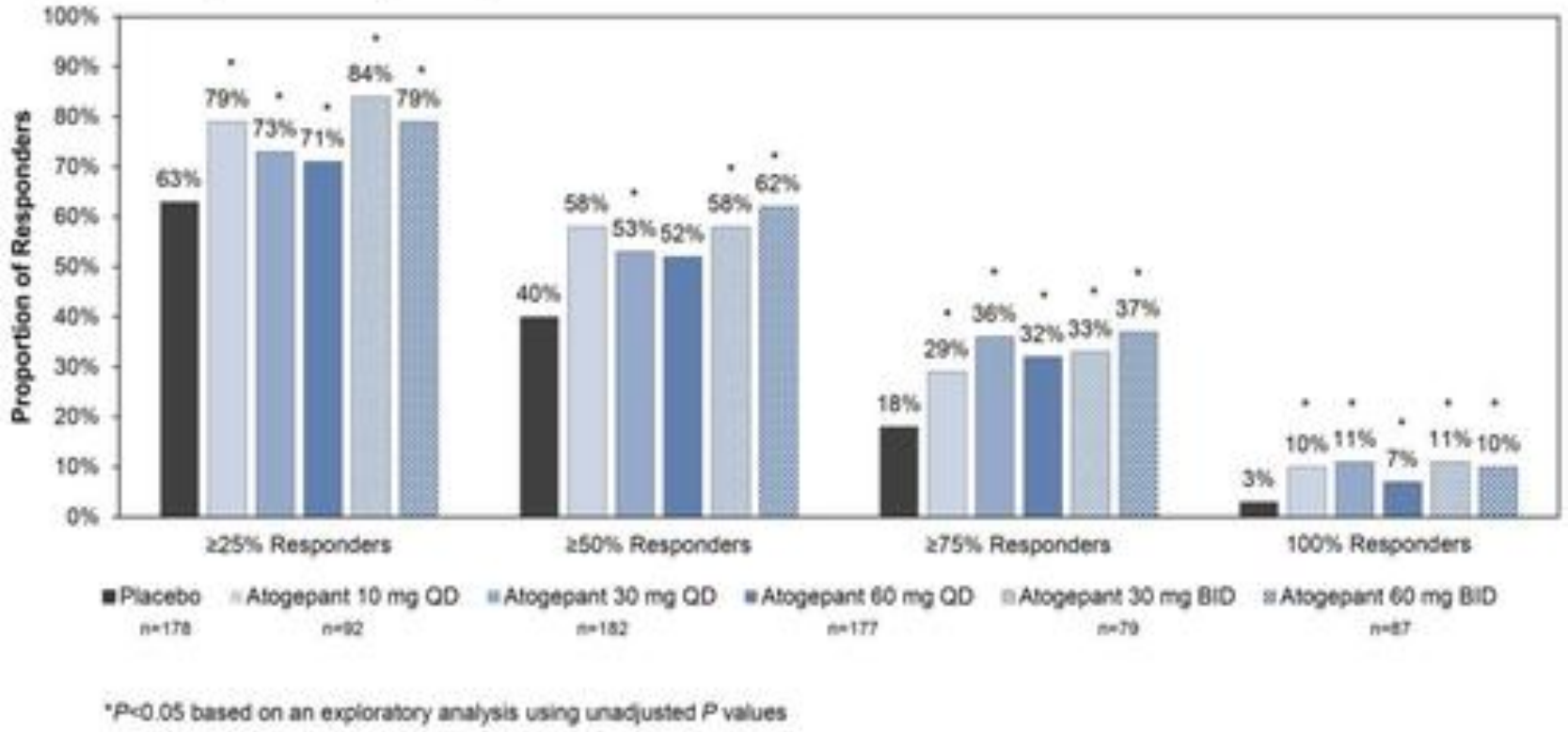
	Small Molecules (Gepants)	mAbs
Size, kDa	< 1	~150
Route of administration	Oral	Parenteral
Cross the BBB	Yes/no	No
Half-life	Minutes to hours	1 to 4 wk
Manufactured	Chemically	In tissue culture
Binding site	CGRP receptor	CGRP or its receptor
Metabolism	Renal or hepatic	Reticuloendothelium system

Edvisson L. *Br J Pharmacol*. 2008;155:967-969.

CGRP receptor antagonist(Gepants)

Atogepant

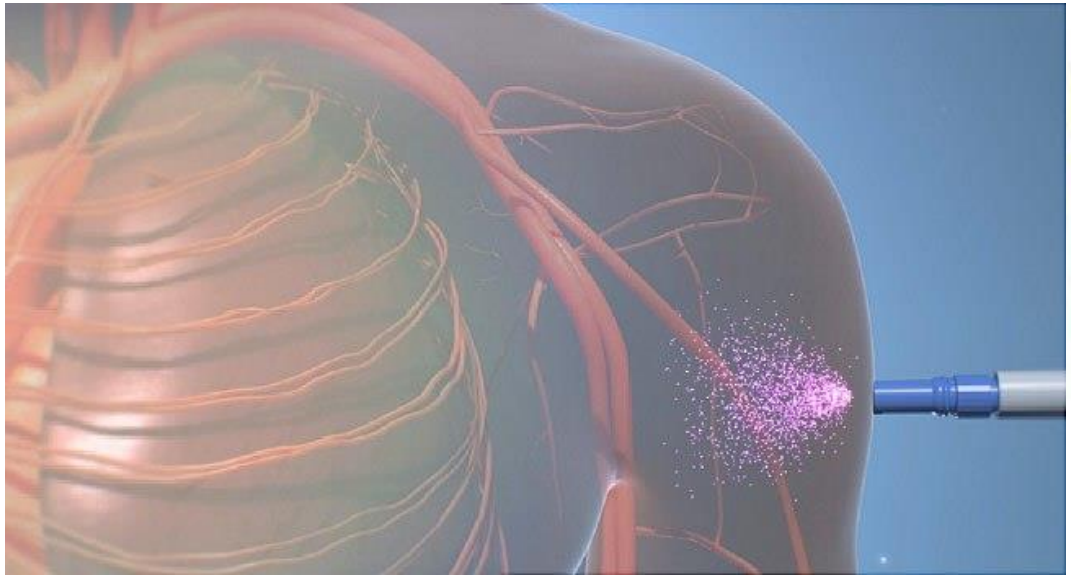
Figure. Migraine Day Responder Rates Across 12-Week Treatment Period



*P<0.05 based on an exploratory analysis using unadjusted P values

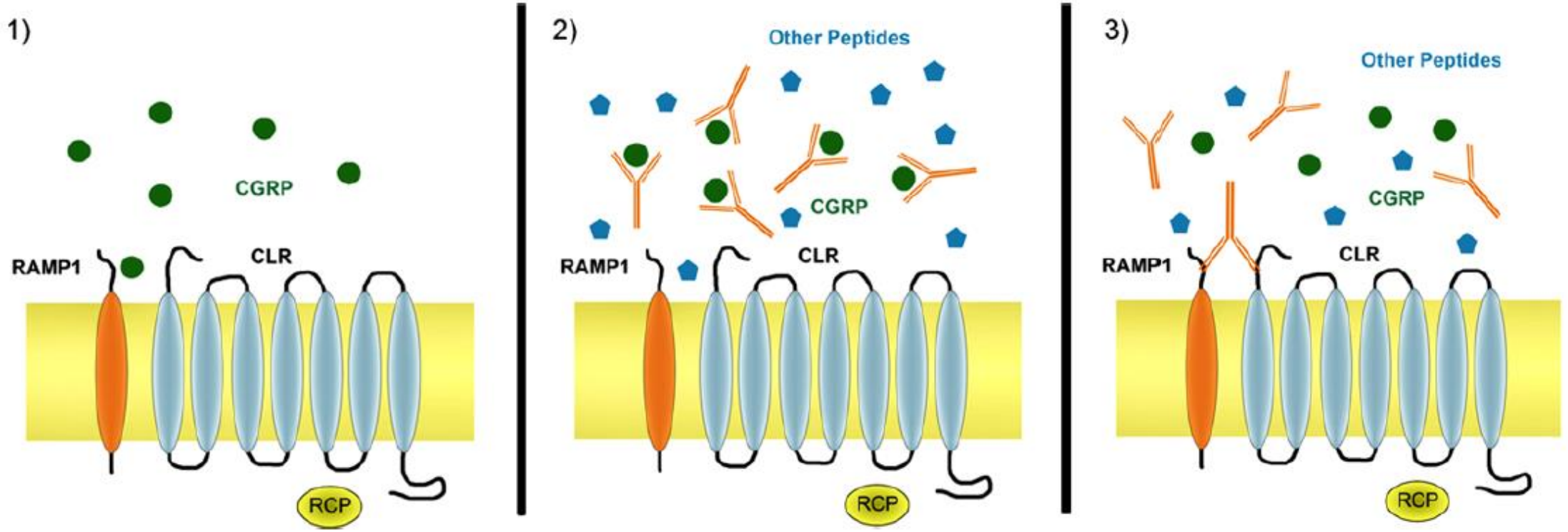
•the most common adverse events being nausea, fatigue, constipation, nasopharyngitis, and urinary tract infection.

• The liver safety profile for atogepant was similar to placebo.



Anti-CGRP and anti-CGRP receptor monoclonal antibodies

CGRP activity in the absence and/or in the presence of anti-CGRP mAbs



Emerging a-CGRP monoclonal antibodies

	Eptinezumab	Erenumab	Galcanezumab	Fremanezumab
Antibody-IgG	1	2	4	2a
Type	Humanized	Human	Humanized	Humanized
Target	CGRP	CLR/RAMP1	CGRP	CGRP
Bioavailability	100%	40-74%	40%	?
$T_{1/2}$ (days)	28	21	25–30	45
Production cell line	Yeast	Mammalian (Chinese hamster ovary)	Mammalian (Chinese hamster ovary)	Mammalian (Chinese hamster ovary)
Route frequency	IV/quarterly	SQ/monthly	SQ/monthly	SQ/monthly or quarterly

Efficacy outcomes in clinical trials using mAbs anti-CGRP for the prevention of episodic migraine.

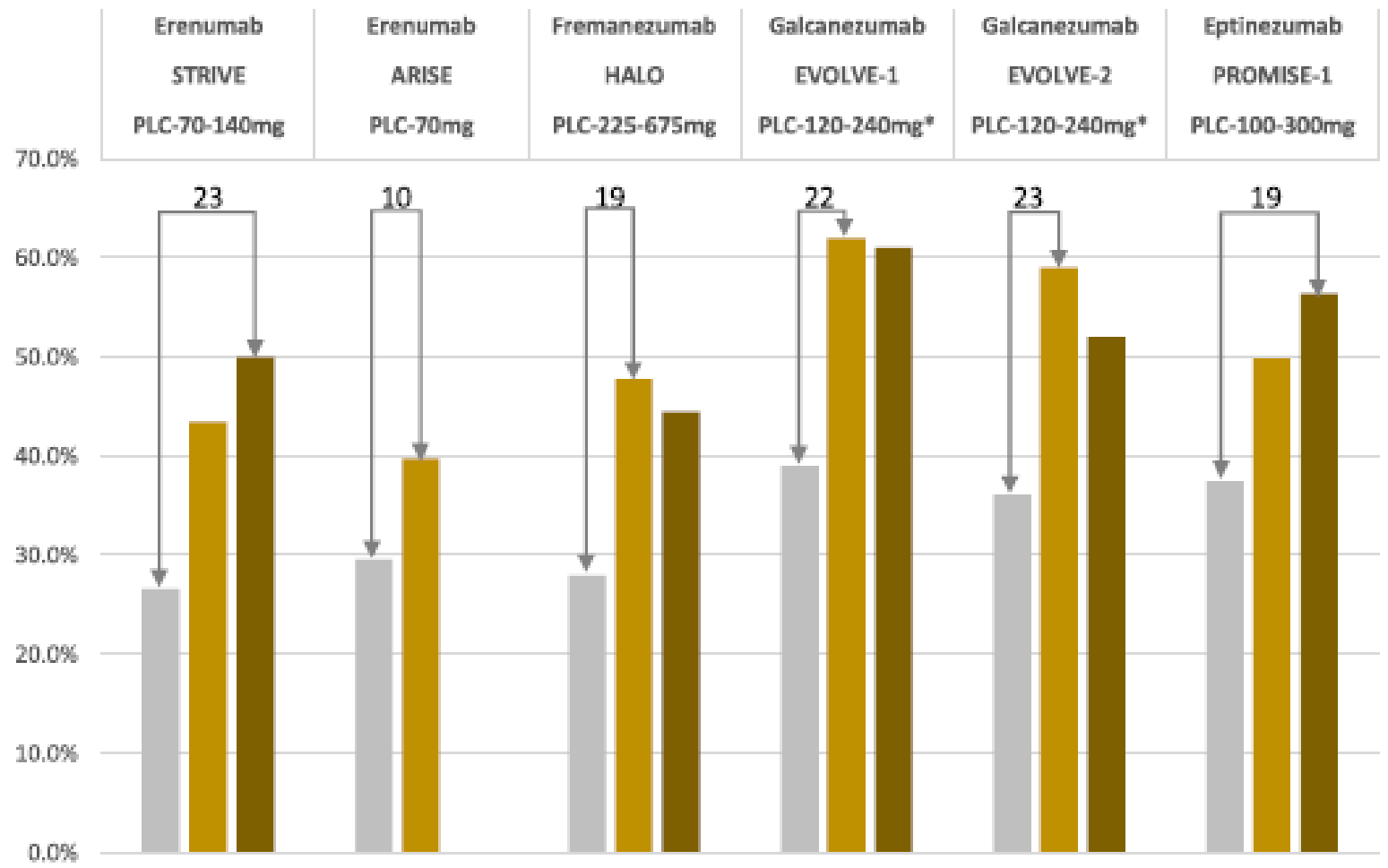


Fig. 1 50% responder rates for the prevention of episodic migraine. The numbers on top of the columns reflect therapeutic gain (verum minis placebo)

DIENER ET AL, 2020

Efficacy outcomes in clinical trials using mAbs anti-CGRP for the prevention of chronic migraine

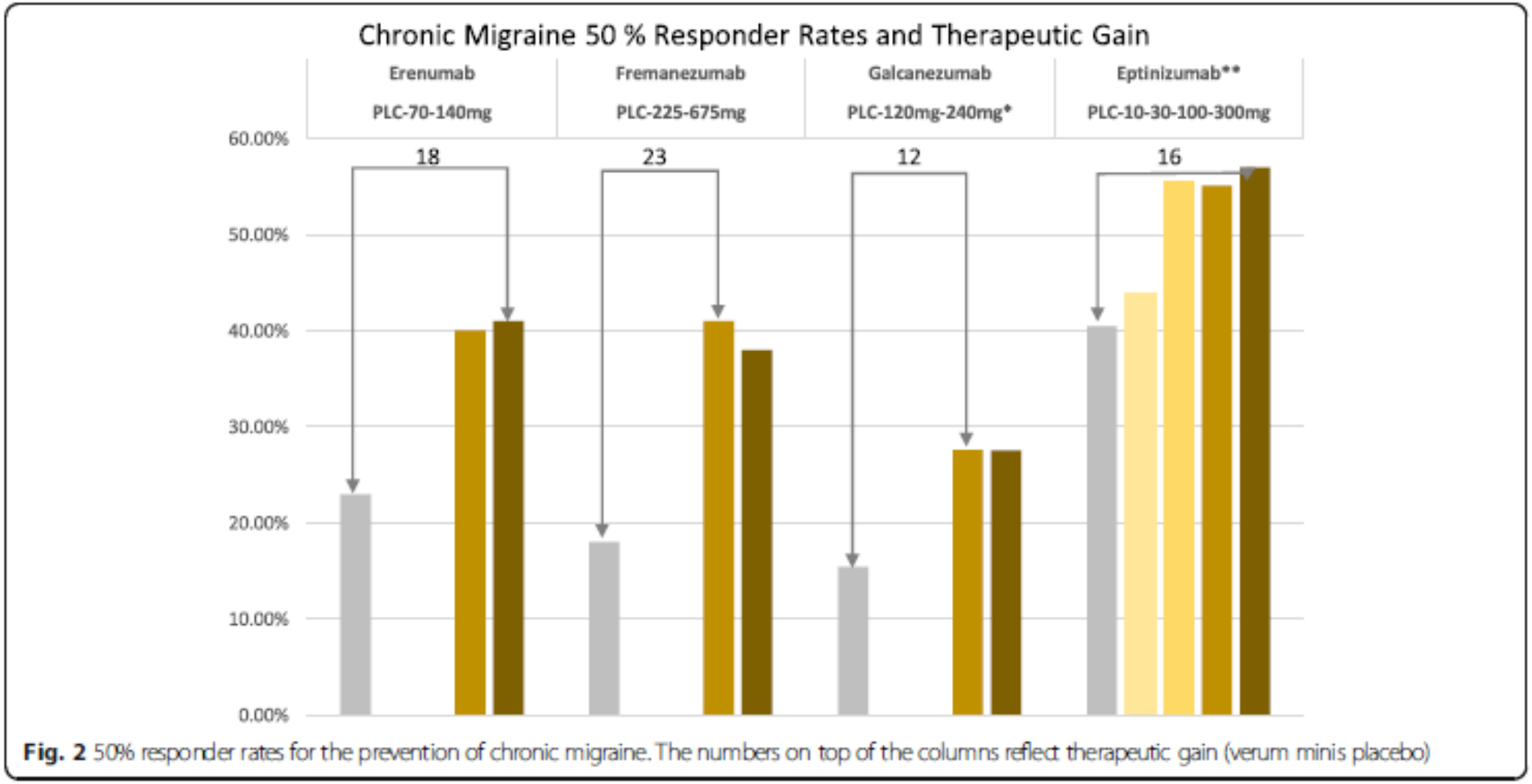


Fig. 2 50% responder rates for the prevention of chronic migraine. The numbers on top of the columns reflect therapeutic gain (verum minis placebo)

DIENER ET AL, 2020

Side effects

Monoclonal antibody	Adverse events
Erenumab (AMG 334)	Injection-site pain, upper respiratory infection, nasopharyngitis, influenza, fatigue, nausea, joint pain, back pain, and headache.
Galcanezumab (LY 2951742)	Injection-site pain, erythema, respiratory infection, nasopharyngitis, abdominal pain, nausea, and dysmenorrhoea.
Eptinezumab (ALD 403)	Respiratory infection, sinusitis, urinary infection, fatigue, dizziness, nausea, vomiting, back pain, joint pain, dry mouth, and ECG changes.
Fremanezumab (TEV 48125)	Injection-site pain, erythema, pruritus, sinusitis, urinary infection, dizziness, back pain, dry mouth, ECG changes, and tooth abscess.

FDA approved anti-CGRP monoclonal antibodies

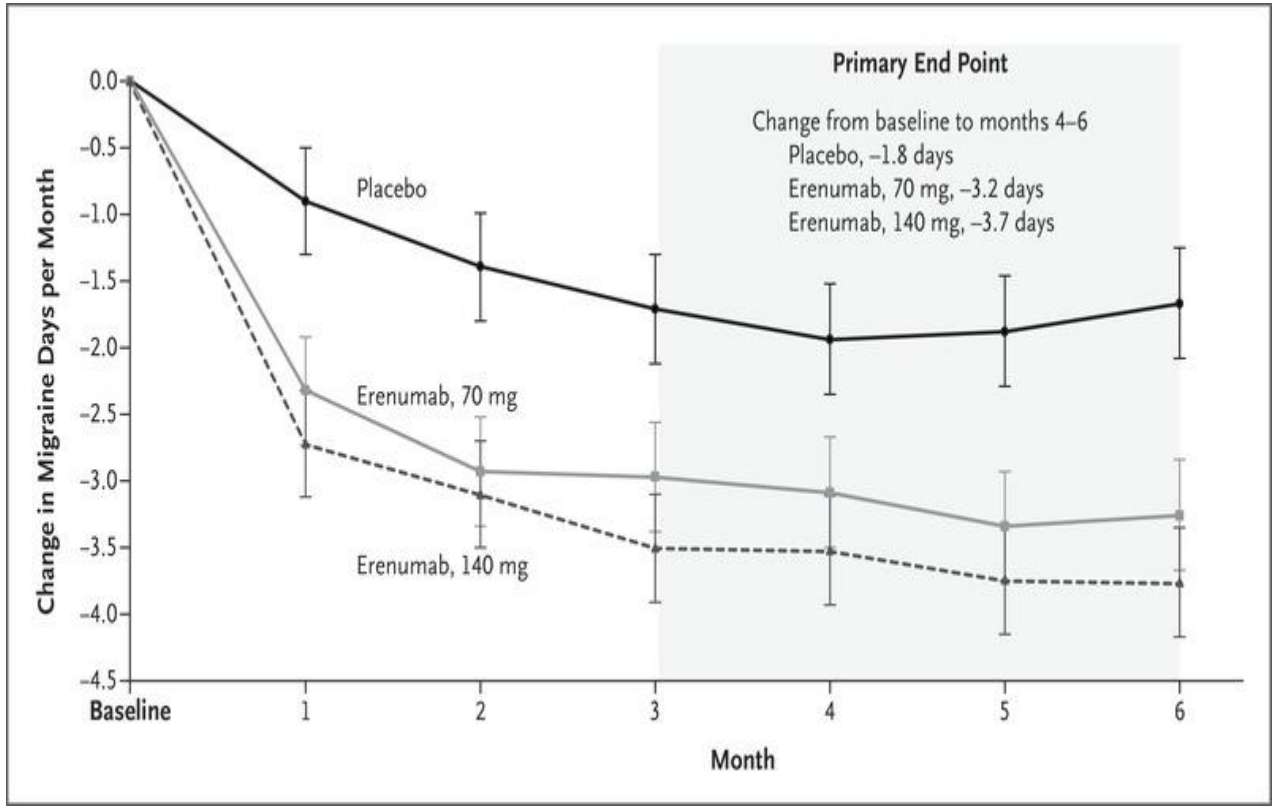
-Erenumab, 70 mg, SQ, monthly (May 2018)

-Galcanezumab, 120 mg, SQ, monthly (Sep 2018)

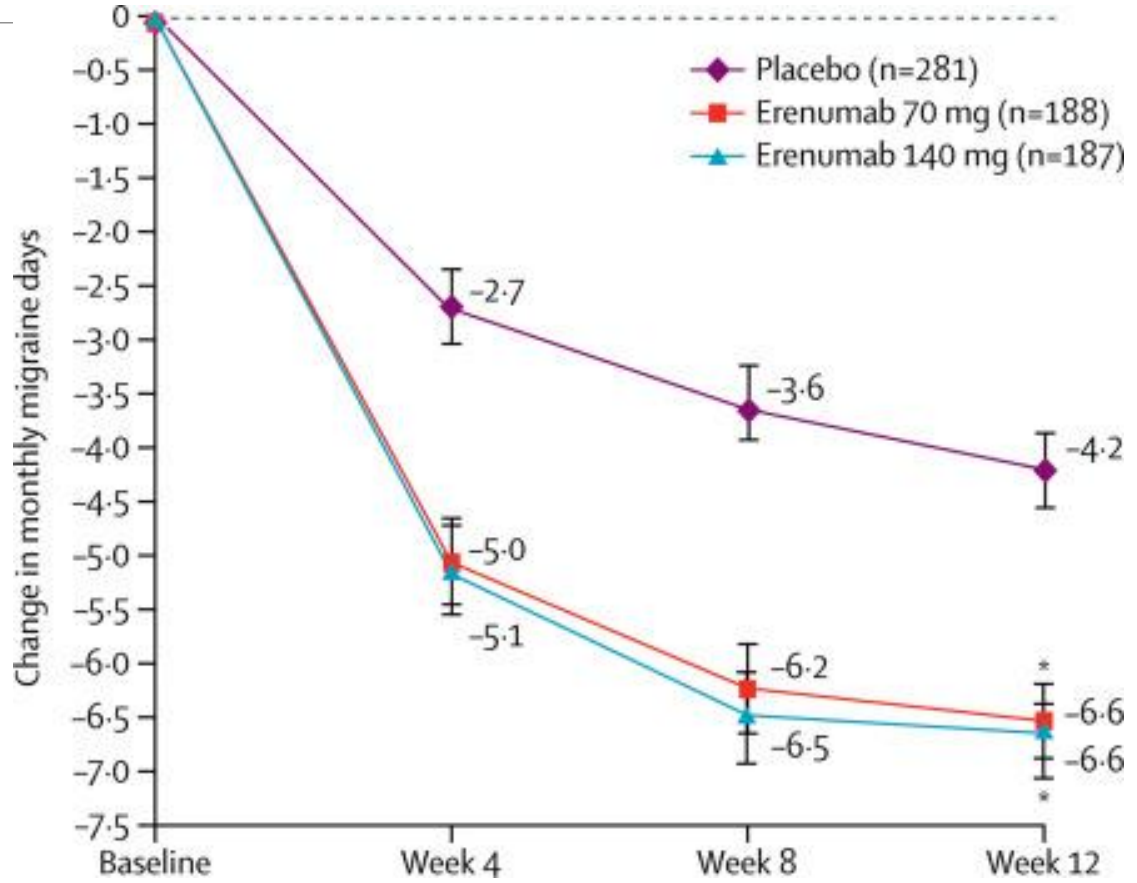
- Fremanezumab 225 mg, SQ, monthly (Sep 2018)

- Eptinezumab 100 mg, IV, quarterly (Feb 2020)

Efficacy of Erenumab in episodic and chronic migraine (Phase II study results)



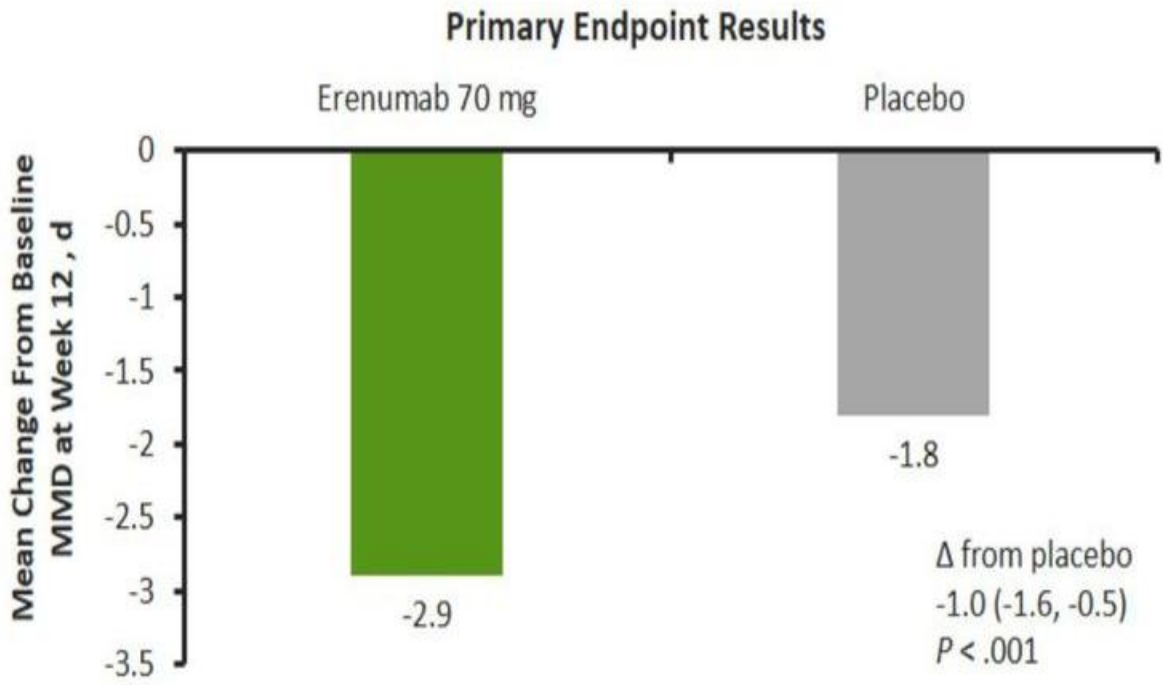
Erenumab in preventive treatment of episodic migraine (STRIVE TRIAL)



Erenumab in preventive treatment of chronic migraine

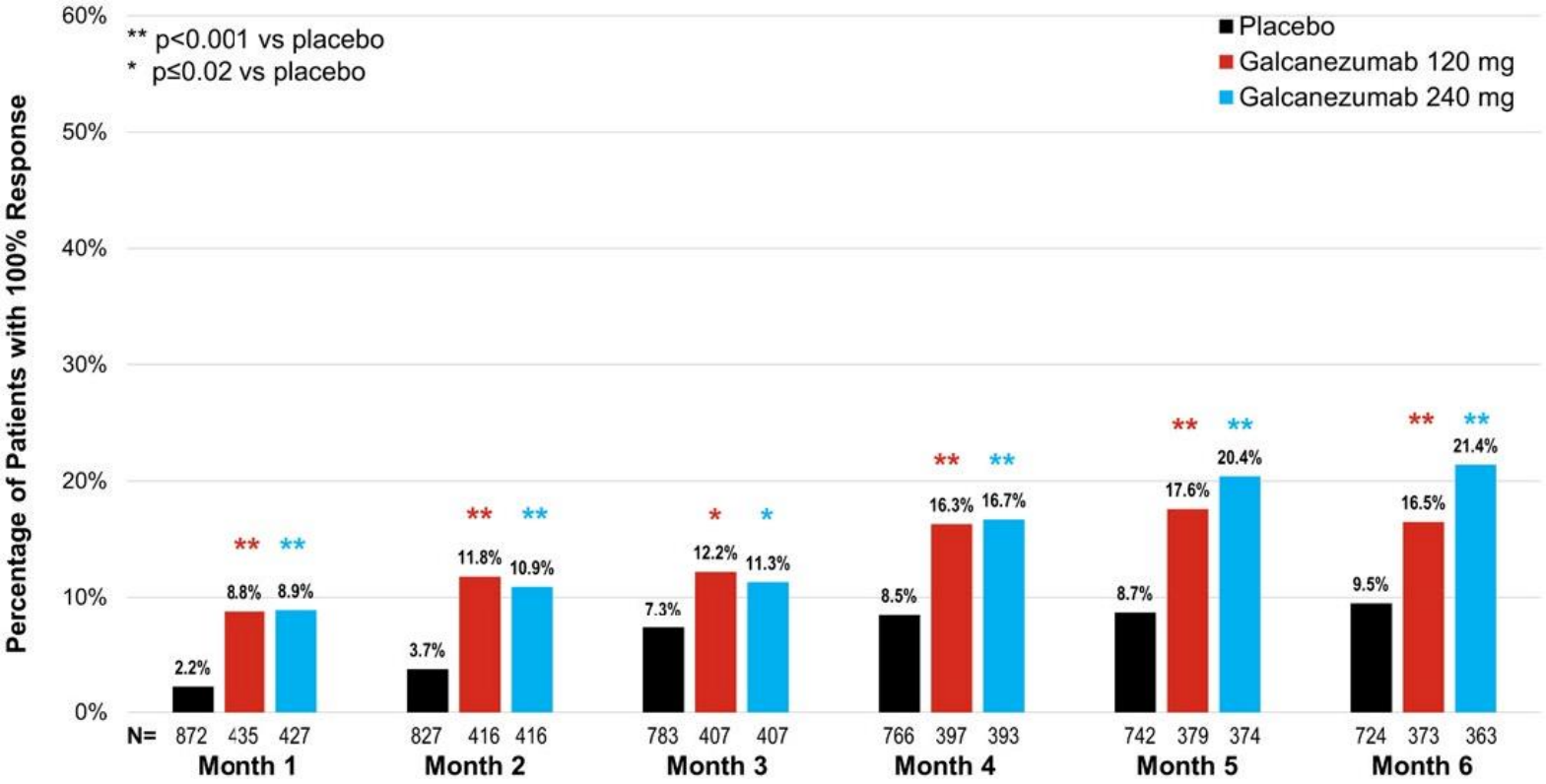
GOADSBY ET AL, 2017
TEPPER ET AL. 2017

Efficacy of Erenumab in episodic migraine (ARISE trial Phase III study results)

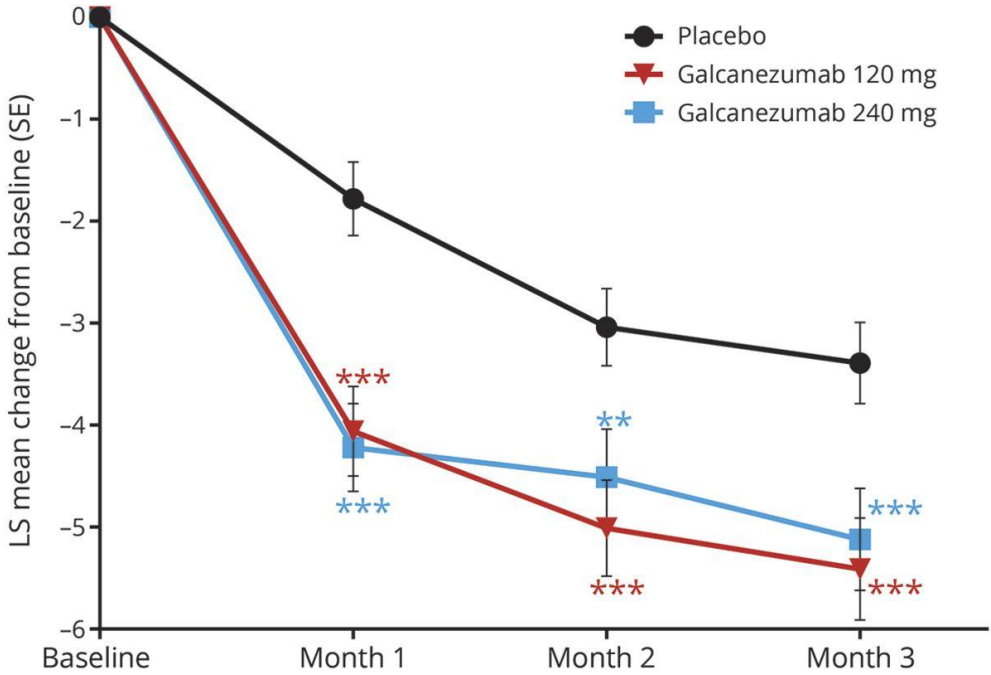


Dodick D, et al. Presented at AAN 2017. Emerging Science Abstract 001.

Efficacy of Galcanezumab in episodic and chronic migraine (Phase III study results)



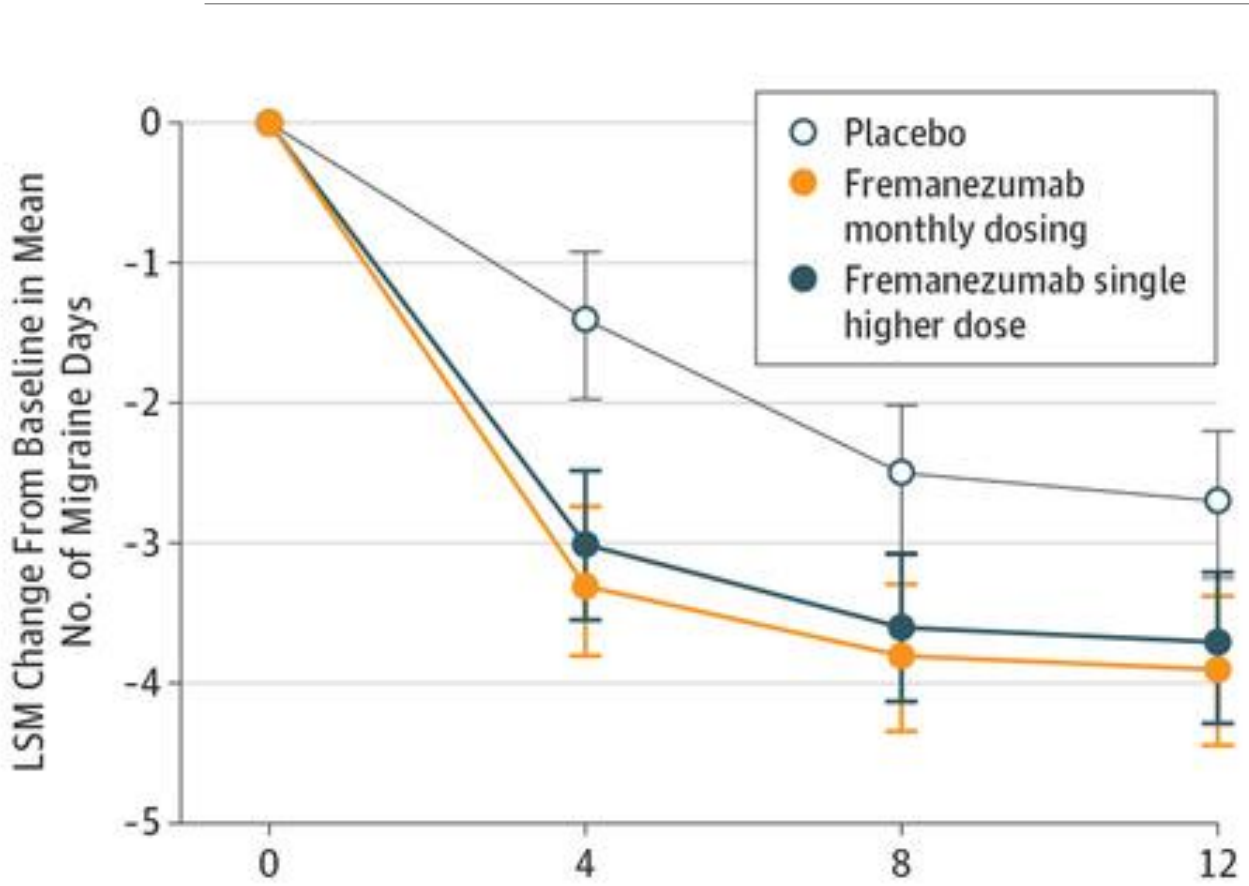
Galcanezumab in preventive treatment of episodic migraine (EVOLVE 1&2 TRIALs)



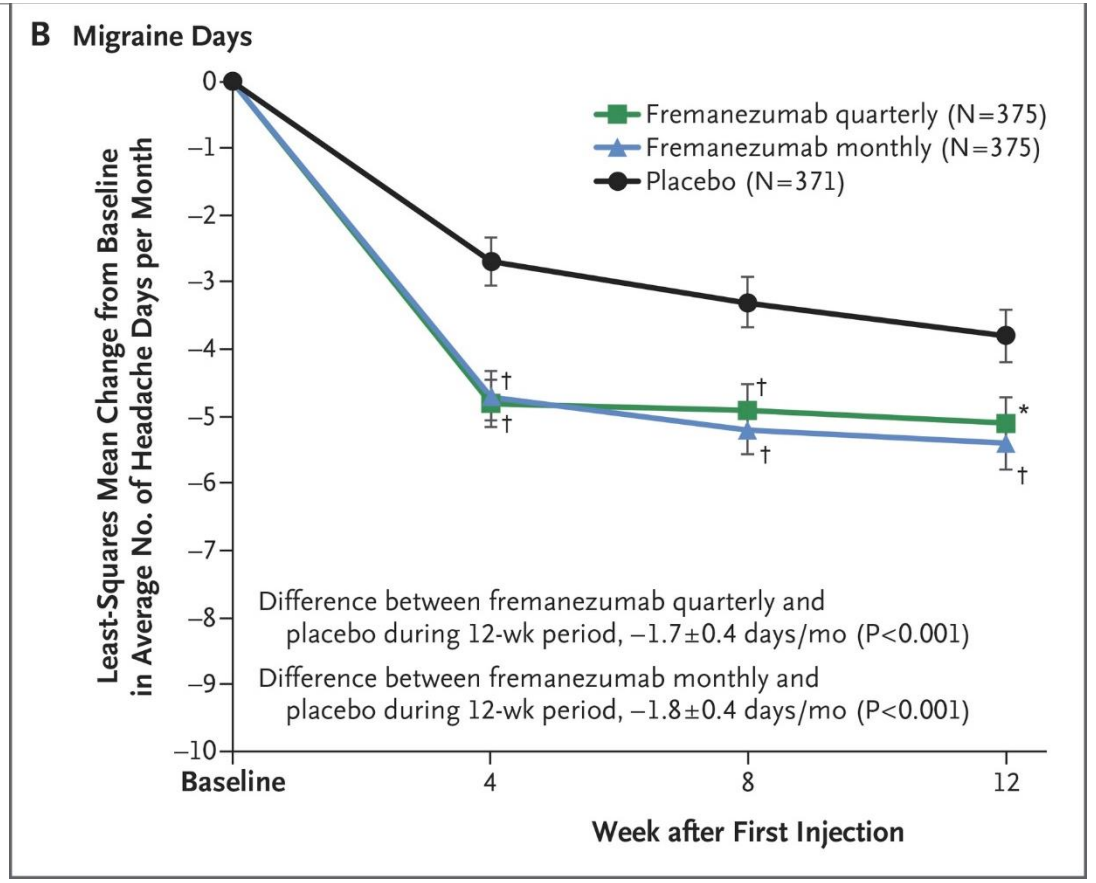
Galcanezumab in preventive treatment o chronic migraine (REGAIN study)

Skljarevsky et al. 2018, Stauffer et al. 2018, Detke et al. 2018

Efficacy of Fremanezumab in episodic and chronic migraine (Phase III study results)



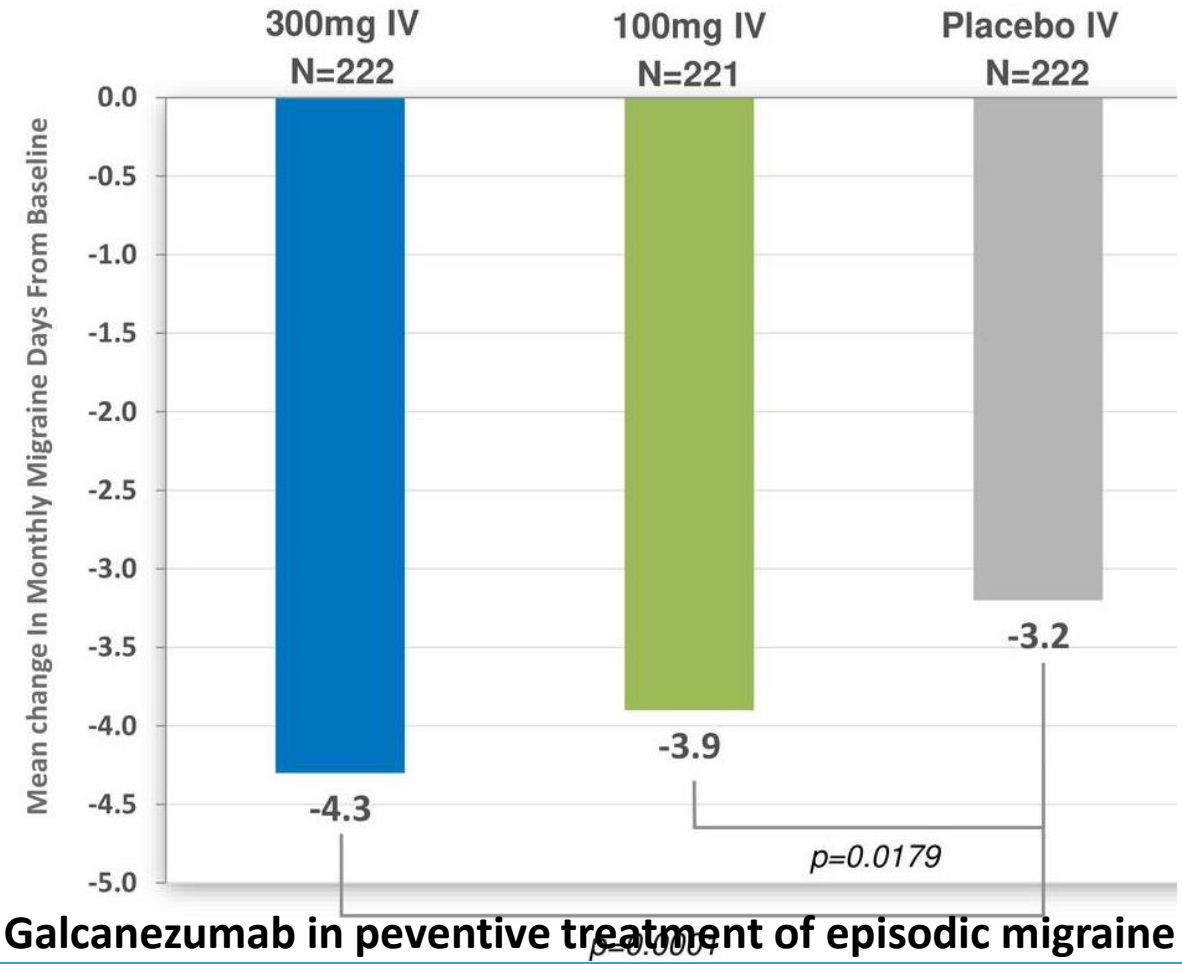
Fremanezumab in preventive treatment of episodic migraine



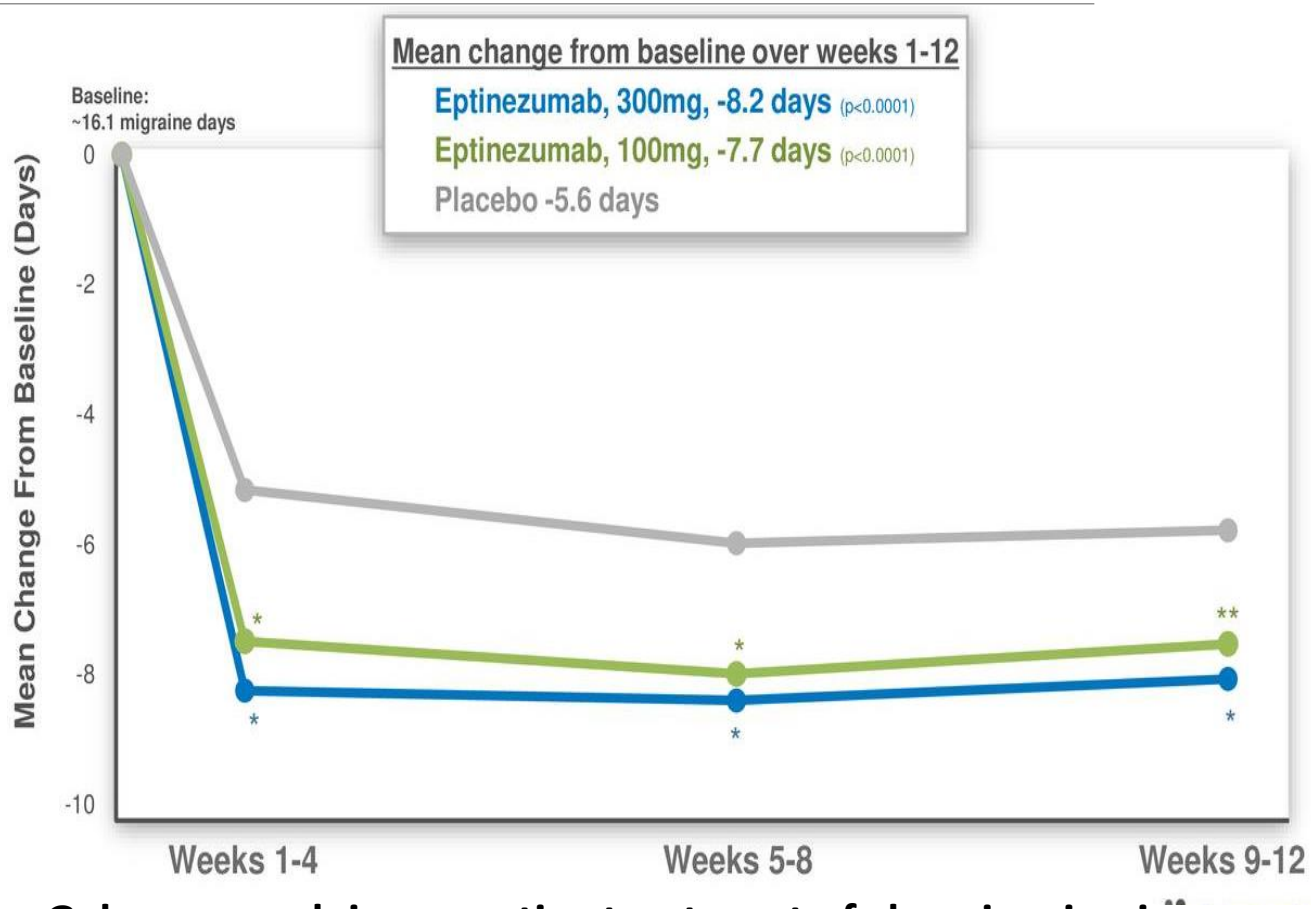
Fremanezumab in preventive treatment of episodic migraine

Dodick et al. 2018, Silberstein et al. 2017

Efficacy of Galcanezumab in episodic and chronic migraine (Phase III study results)



Galcanezumab in peventive treatment of episodic migraine (PROMISE 1 study)



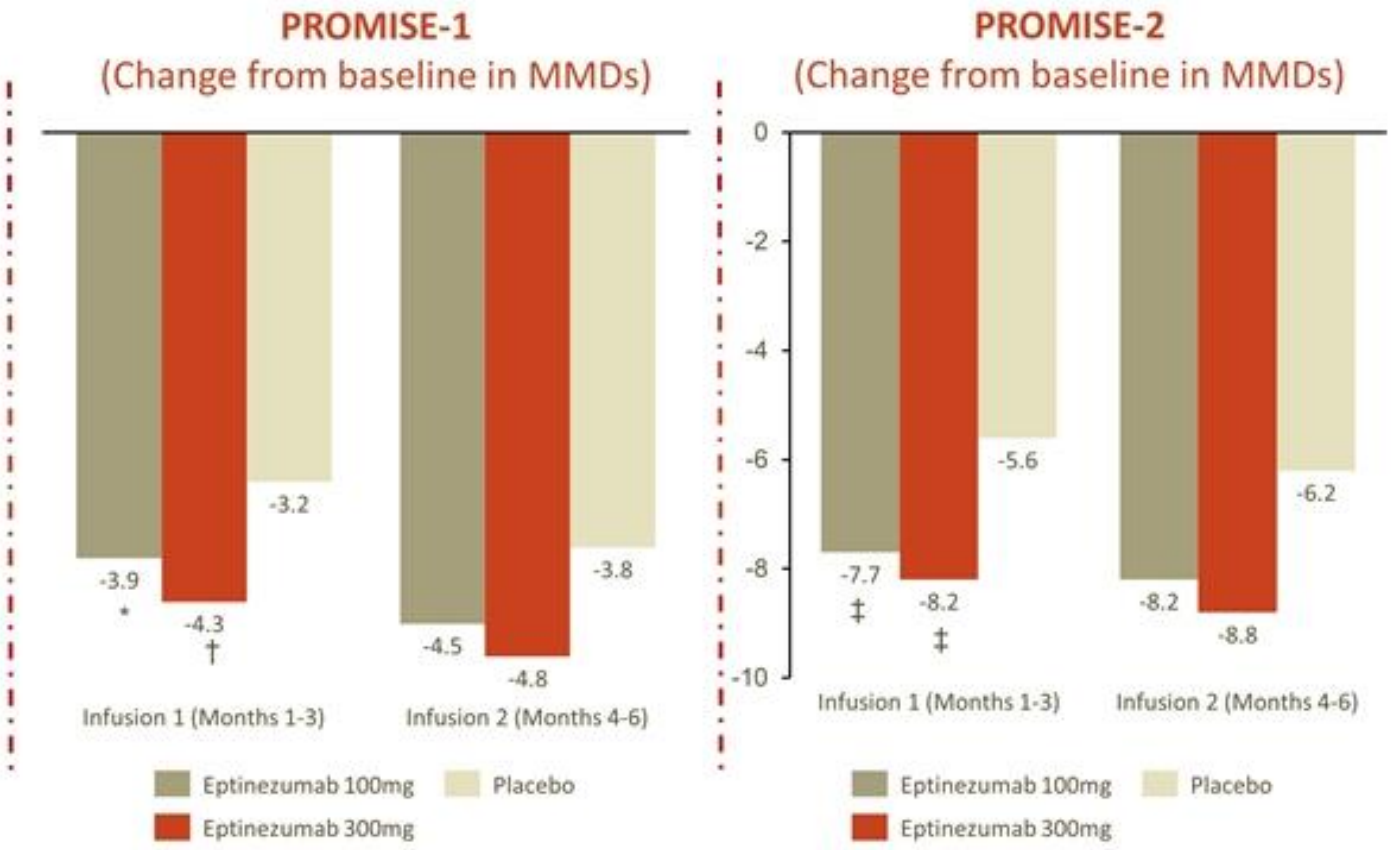
Galcanezumab in peventive treatment of chronic migraine (PROMISE 2 study)

Lipton et al. 2017, Dodick et al. 2018

Significant reduction in monthly migraine days (MMDs) with eptinezumab at both 100mg and 300 mg

Eptinezumab has shown high response rates, especially in adult patients experiencing frequent, chronic migraine

- ~60% of patients had ≥50% reduction in migraine days
- ~40% of patients had ≥75% reduction in migraine days
- Patients that experienced no migraines for at least half of the study period (≥3 mth):
  - 100mg: 14.0%
  - 300mg: 19.1%
  - Placebo: 4.9%



*p=0.0182; †p=0.0001; ‡p<0.0001 vs placebo. Months 4–6 were not included in the prespecified statistical algorithms.

Eptinezumab demonstrated rapid onset from Day 1

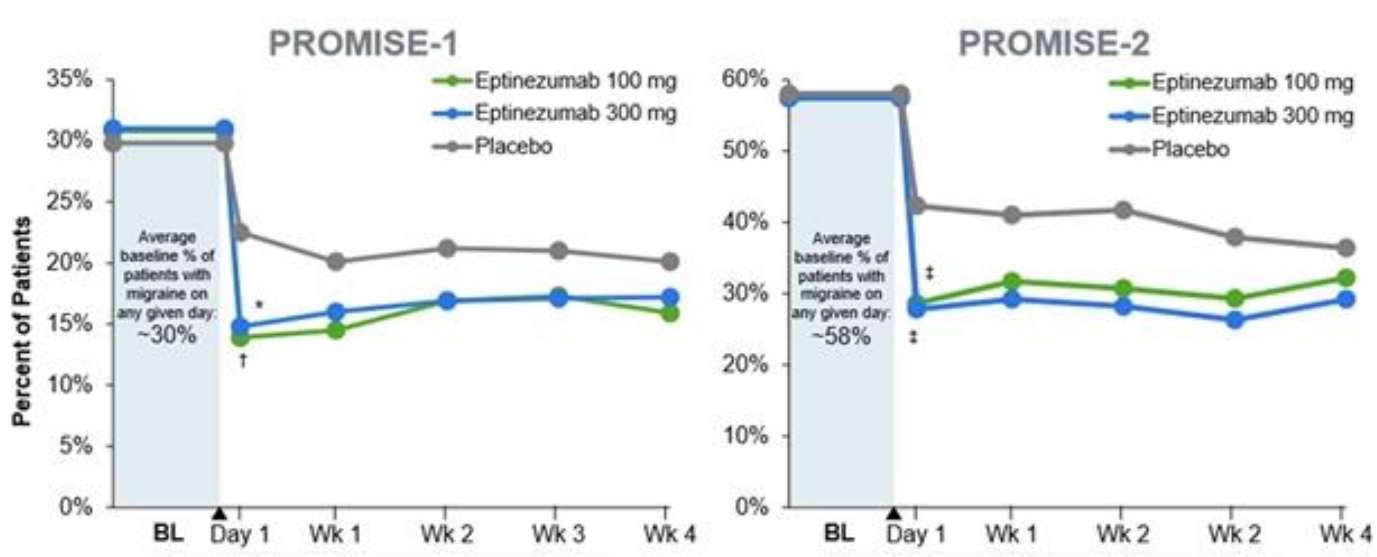
Key secondary endpoint: Percentage reduction on Day 1

PROMISE 1:

- Eptinezumab 100mg: 52.3%
- Eptinezumab 300mg: 54.9%
- Placebo: 24.5%

PROMISE 2:

- Eptinezumab 100mg: 50.3%
- Eptinezumab 300mg: 51.6%
- Placebo: 27.1%



*p=0.0159 vs placebo, unadjusted; †p=0.0312 vs placebo, unadjusted; ‡p<0.0001 vs placebo.

1. Saper J, Wilks K, Chakhava G, et al. Eptinezumab for the Prevention of Episodic Migraine Through 1 Year: Results from the Phase 3 PROMISE-1 (Prevention of Migraine via Intravenous Eptinezumab Safety and Efficacy–1) Trial. Presented at: 2019 American Academy of Neurology Annual Meeting: Philadelphia, PA; May 4-10, 2019. S38.003 2. Kudrow D, Lipton R, Silberstein S, et al. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Infusions in the Phase 3 PROMISE-2 (Prevention of Migraine via Intravenous Eptinezumab Safety and Efficacy–2) Trial. Presented at: 2019 American Academy of Neurology Annual Meeting: Philadelphia, PA; May 4-10, 2019. P2.10-006

anti-CGRP monoclonal antibodies(erenumab, fremanezumab, or galcanezumab) **indications:**

- Patients with episodic migraine(EM) or chronic migraine(CM) who
  - ✓ have failed at least two of the available medical treatments
  - ✓ cannot use other preventive treatments because of comorbidities, side effects or poor compliance

CONSENSUS ARTICLE Open Access

European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention

Simona Sacco[1*], Lars Bendtsen[2], Messoud Ashina[2], Uwe Reuter[3], Gisela Terwindt[4], Dimos-Dimitrios Mitsikostas[5†] and Paolo Martelletti[6†]

- ✓ Managing other preventive treatments when using anti-CGRP monoclonal antibodies :
  - EM: stop oral preventive drugs unless the patient had a previous history of chronic migraine before prevention.
  - CM: add anti CGRP mAb and consider later withdrawal of the oral drug
  - CM on onabotulinumtoxin A with inadequate response: stop onabotulinumtoxin A
  - CM on treatment with CGRP mAb and may benefit from additional prevention: add oral preventive drugs

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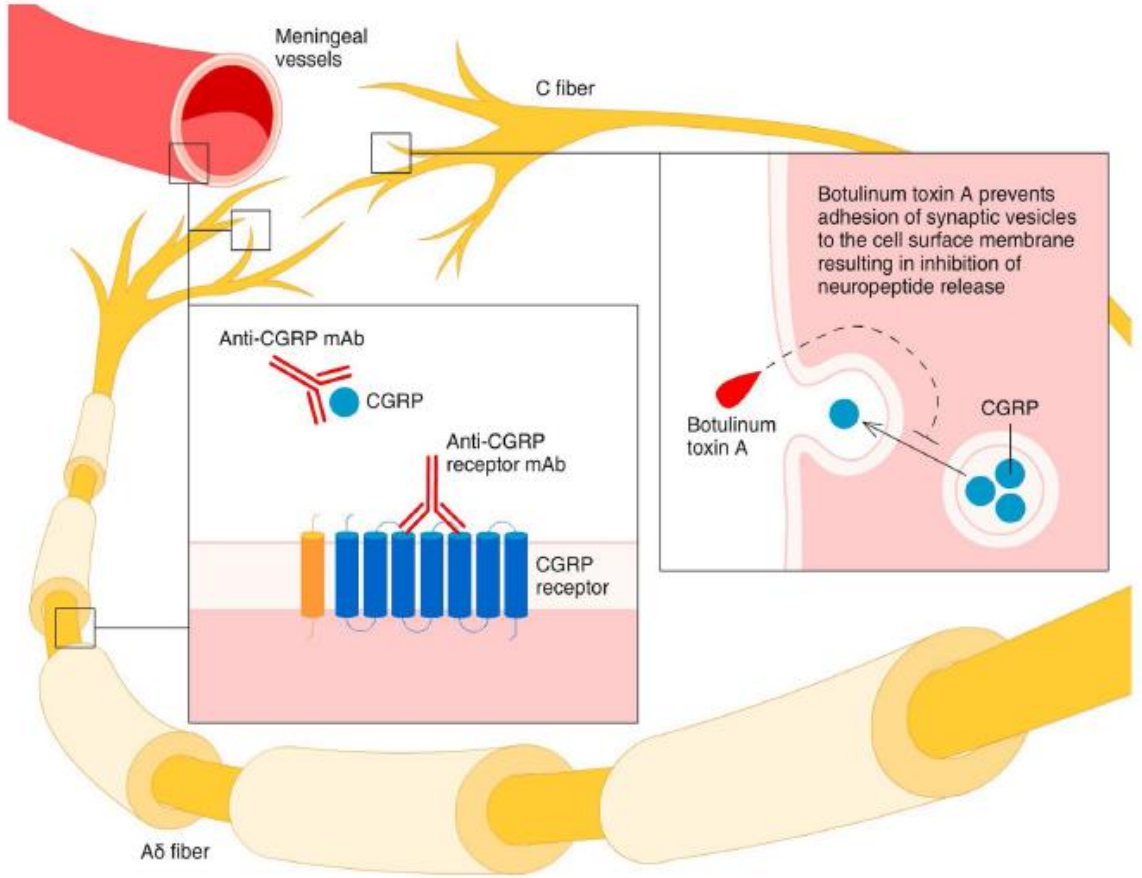
- In patients with chronic migraine and medication overuse, use anti-CGRP monoclonal antibodies before or after withdrawal of acute medications.
- Stop anti-CGRP monoclonal antibodies after 6–12 months of treatments
- Contraindications for anti-CGRP monoclonal antibodies :
  - pregnant or nursing women,
  - individuals with alcohol or drug abuse
  - cardio and cerebrovascular diseases
  - severe mental disorders

Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale?

Lanfranco Pellesi, MD ; Thien P. Do, MD; Håkan Ashina, MD; Messoud Ashina, MD, PhD, DMSc ; Rami Burstein, PhD

- ✓ **BTX-A acts by inhibiting the release of CGRP from thin unmyelinated C fiber meningeal nociceptors in the dura, thus preventing a CGRP-dependent activation of meningeal vessels and thick myelinated Aδ nociceptors.**
- ✓ **anti-CGRP mAbs prevent the interaction between the CGRP and its receptor within the meningeal vessel walls and along the fibers in at the nodes of Ranvier of the Aδ nociceptors.**
- ✓ **Concomitant use of medications blocking the activation of meningeal C-fibres may provide a synergistic effect on the trigeminal nociceptive pathway.**




It's just the beginning