Faculty of Health and Medical Sciences

Choosing a preventive treatment for migraine

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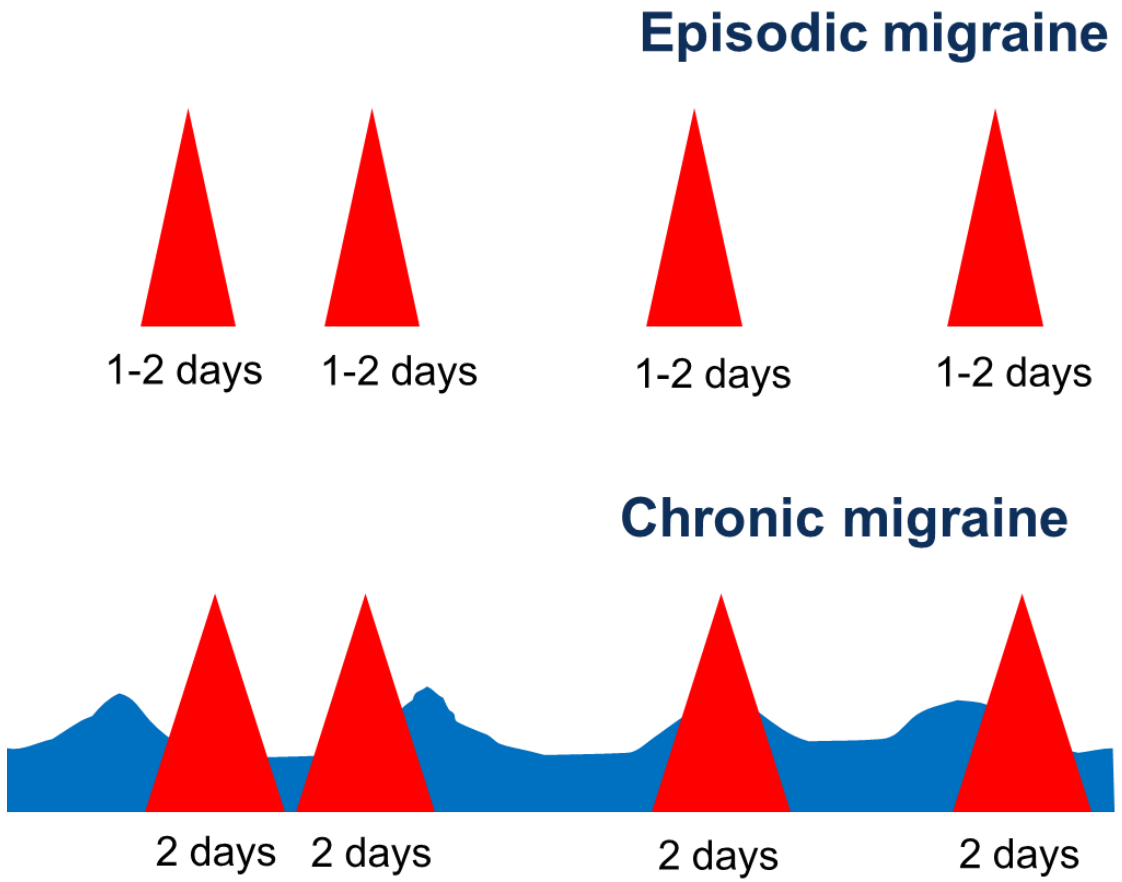
The aim is to reduce the frequency, duration, or severity of migraine attacks *rather* than to cure the migraine



Who should be treated?

- 2–3 severe attacks *per month* in spite of:
  - optimal pharmacological acute treatment

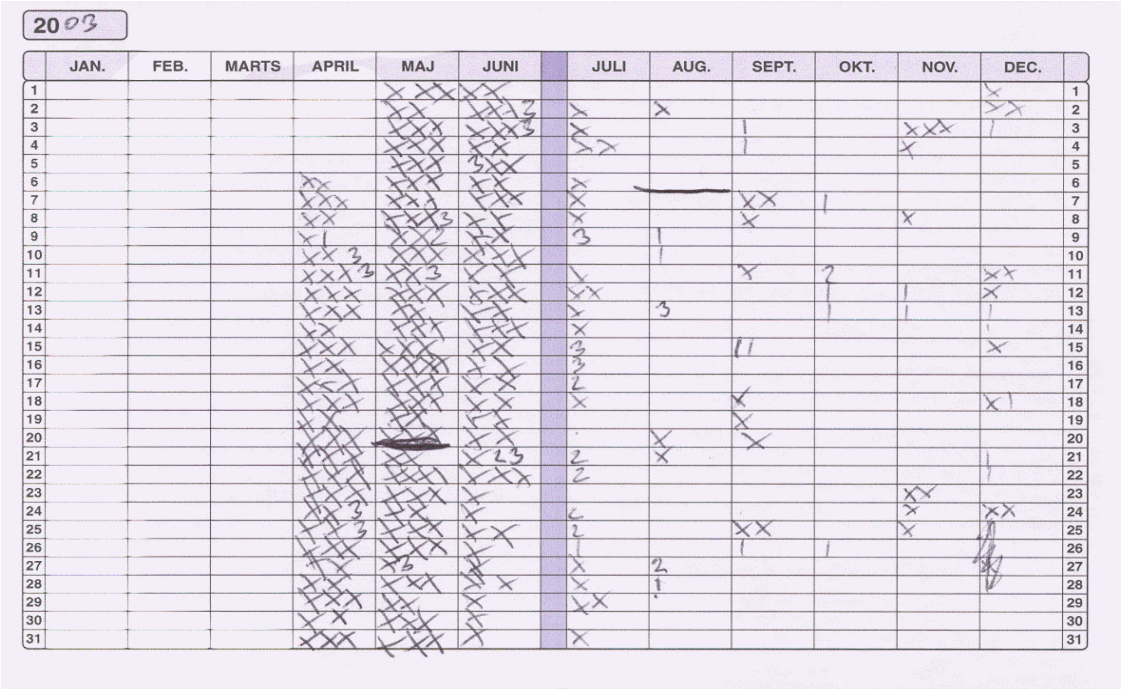
EFNS Guidelines 2006 – prophylactic drug treatment when:

- quality of life, business duties or school attendance are severely impaired
- frequency of attacks per month is two or higher
- attacks do not respond to acute drug treatment
- frequent, very long or uncomfortable auras occur

Evers S, *et al. Eur J Neurol* 2006; 13:560–572.

When is prophylactic treatment a success?

- Frequency or intensity reduced by at least 50%
- Acceptable adverse effects
- Monitor with calendar



Which drugs to choose?

- Previous treatments
  - sufficient dose?
  - sufficient duration?
  - concomitant medication overuse?
- Consider comorbidity
  - e.g. depression, overweight, cardiac problems

Preventive treatments: present and future

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
Magnesium 360 mg
Riboflavin 400 mg
Pizotifen 1.5-3 mg

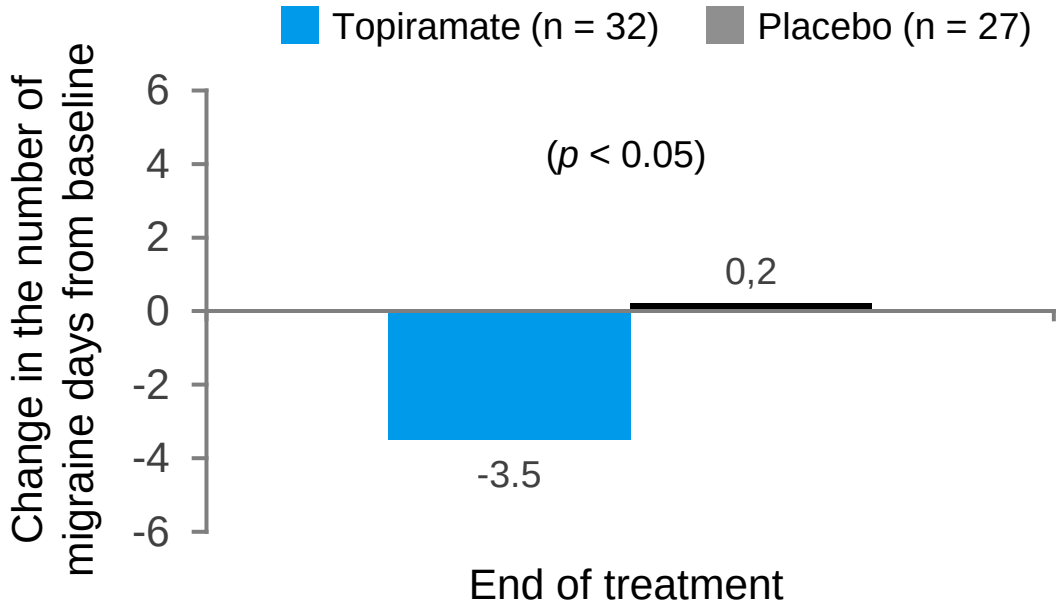
Botulinum toxin type A 155U
Indication: Chronic migraine

Anti CGRP or its receptors monoclonal antibodies

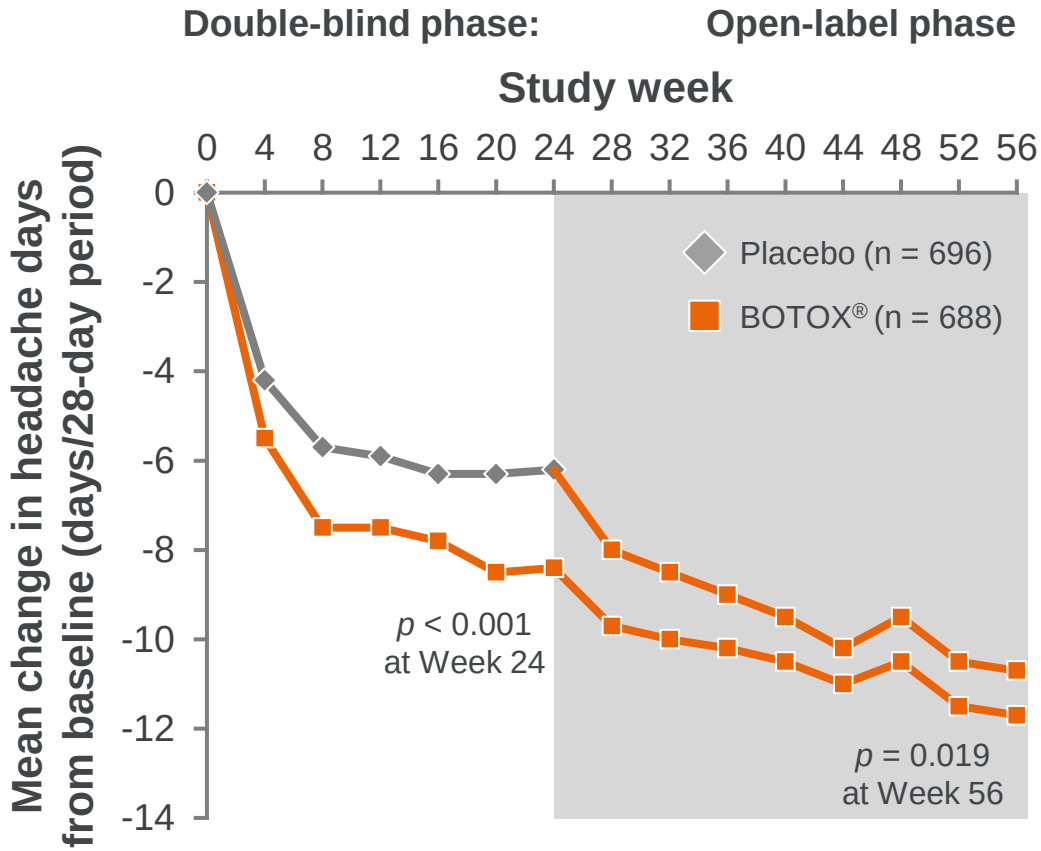
Erenumab	Fremanezumab	Galcanezumab	Eptinezumab

Chronic Migraine: Topiramate and Botox

Baseline migraine days/month: topiramate, 15.5; placebo, 16.4.



Diener HC, *et al*. Cephalalgia 2007;

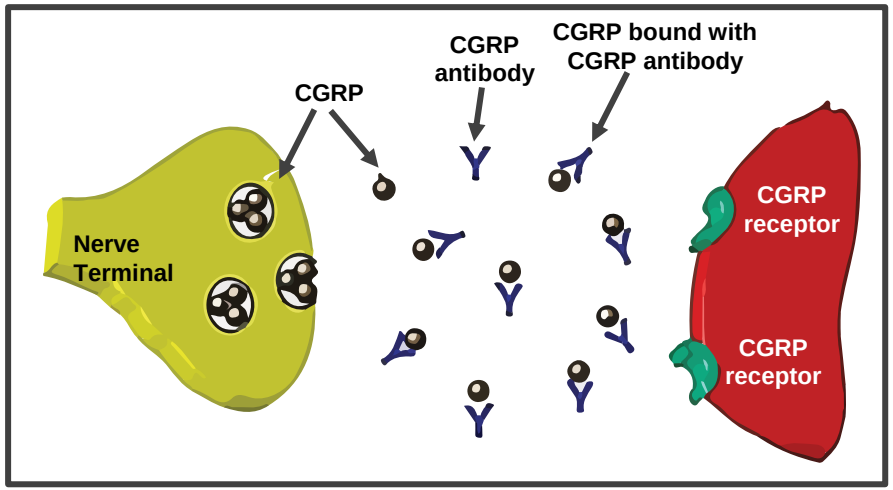


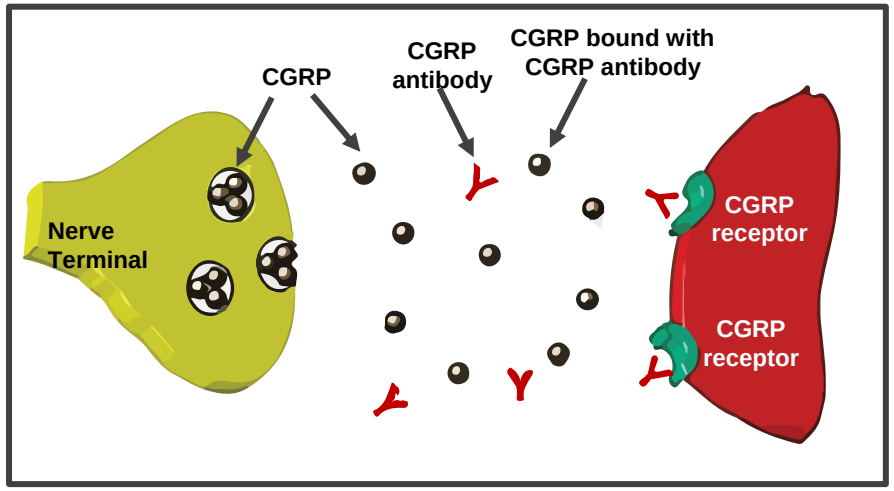
Adapted from Aurora SK, *et al*. 2011.

Anti-CGRP Therapeutic Antibodies

- **CGRP antibodies**
  - Eptinezumab (ALD403)
  - Galcanezumab (LY2951742)
  - Fremanezumab (TEV-48125)

- **CGRP receptor blockers**
  - Erenumab (AMG 334)

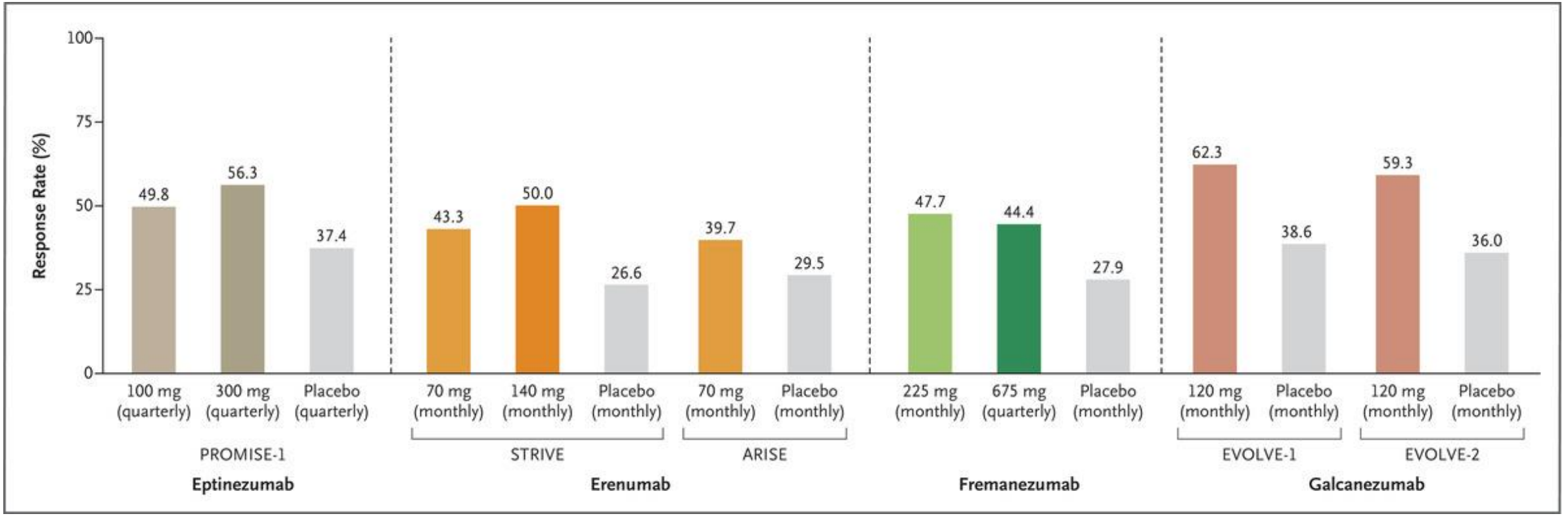




Episodic	Phase 3 studies	Primary endpoint	1º EP timeline
Erenumab	ARISE[1]	Monthly migraine days	Weeks 9–12
	STRIVE[2]		Months 4–6
Fremanezumab	HALO[3]		Months 1–3
Galcanezumab	EVOLVE-1[4]		Months 1–6
	EVOLVE-2[5]		Months 1–6
Eptinezumab	PROMISE-1[6]		Months 1–3
Chronic	**Phase 3 studies**	**Primary endpoint**	**1º EP timeline**
Fremanezumab	HALO[7]	Headache days (at least moderate severity)	Months 1–3
Galcanezumab	REGAIN[9]	Monthly migraine days	
Eptinezumab	PROMISE-2[10]		
Episodic and chronic	**Phase 3 studies**	**Primary endpoint**	**1º EP timeline**
Fremanezumab	FOCUS[8]	Monthly migraine days	Months 1–3

1. Dodick DW et al. *Cephalalgia* 2018;38(6):1026-37; 2. Goadsby PJ et al. *N Engl J Med* 2017;377(22):2123-32; 3. Dodick DW et al. *JAMA* 2018;319(19):5–14; 4. Stauffer VL et al. *JAMA Neurol* 2018;75(9):1080-8; 5. Skljarevski V et al. *Cephalalgia* 2018;38(8):1442-54; 6. Ashina M et al. *Cephalalgia* 2020; 7. Silberstein SD et al. *N Engl J Med* 2017;377(22):2113-22; 8. Ferrari MD et al. *Lancet* 2019;394(10203):1030-40; 9. Detke HC et al. *Neurol* 2018;91(24):e2211-21; 10. Lipton RB et al. *Neurol* 2020

Response Rates in Phase 3 Randomized Trials of Monoclonal Antibodies against CGRP or Its Receptor for Prevention of Episodic Migraine



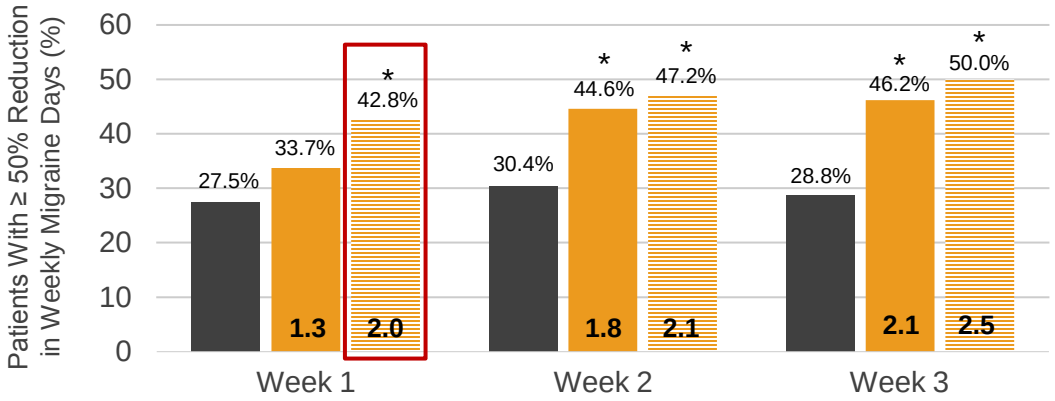
M Ashina. *N Engl J Med* 2020

CGRP mAbs: Episodic Migraine Early Onset of Efficacy

There are no head-to-head trials; results cannot be compared because of different trial designs and patient populations

Erenumab

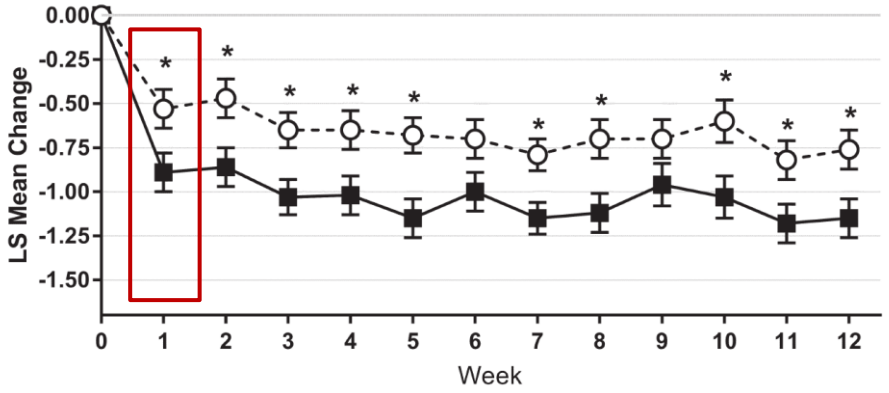
Schwedt T et al. *J Headache Pain* 2018;19(1):92



*P<0.001 vs placebo

Galcanezumab

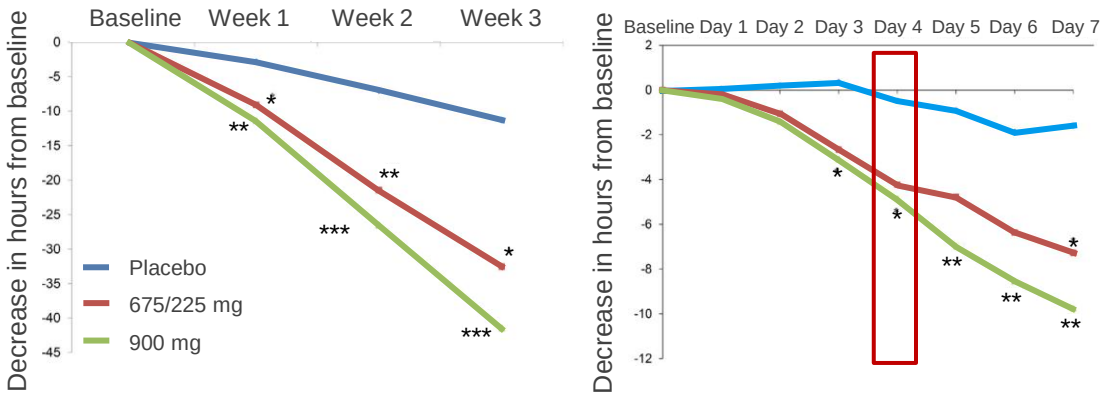
Goadsby P et al. *J Neurol Neurosurg Psychiatry* 2019;90(8):939–944



*P<0.05

Fremanezumab

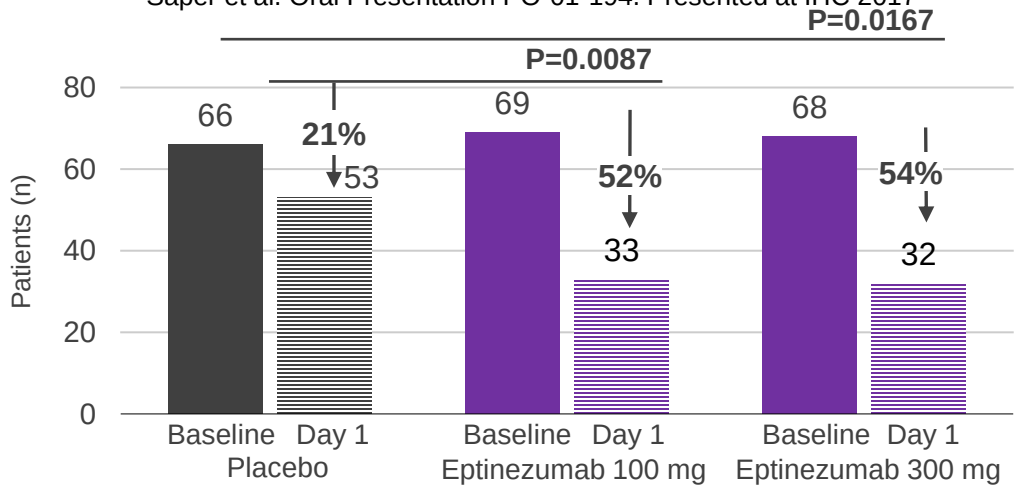
Bigal ME et al. *Neurology* 2016;87(1):41-48



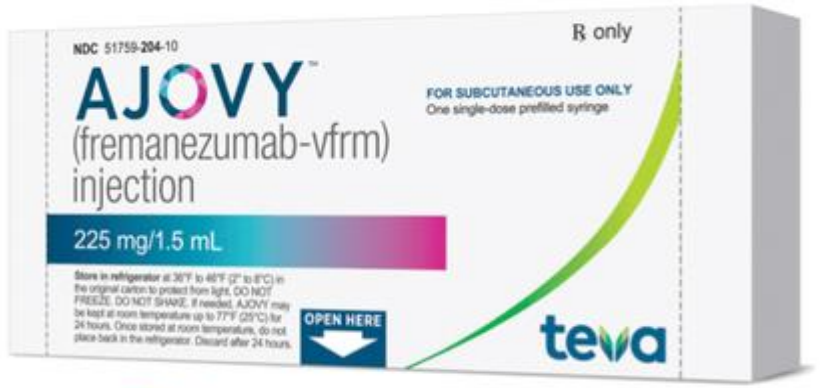
*P<0.05, **P<0.01, ***P<0.001.

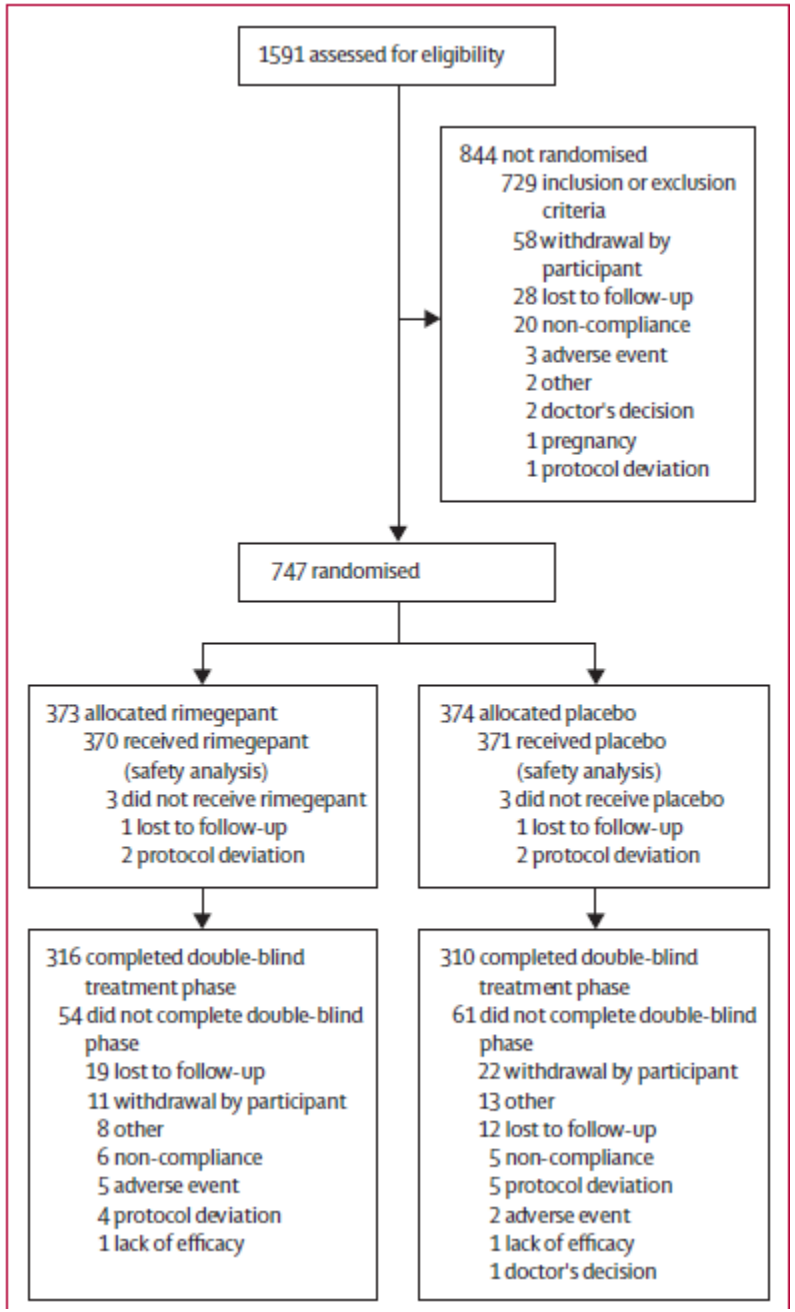
Eptinezumab

Saper et al. Oral Presentation PO-01-194. Presented at IHC 2017



Monoclonal Antibodies to CGRP or Its Receptor for Migraine Prevention





Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial

	Rimegepant (n=348)		Placebo (n=347)		Least squares mean difference between groups (95% CI)	p value
	n	Point estimate (95% CI)	n	Point estimate (95% CI)		
Change in mean number of migraine days per month during weeks 9–12, days (primary efficacy outcome)†	348	−4·3 (−4·8 to −3·9)	347	−3·5 (−4·0 to −3·0)	−0·8 (−1·5 to −0·2)	0·0099
≥50% reduction in mean number of moderate or severe migraine days per month during weeks 9–12	171	49% (44 to 54)	144	41% (36 to 47)	8% (0 to 15)	0·044
Change in mean number of total migraine days per month during weeks 1–12, days†	348	−3·6 (−4·0 to −3·2)	347	−2·7 (−3·1 to −2·3)	−0·8 (−1·3 to −0·3)	0·0017
Rescue medication days per month during weeks 9–12, days†	348	3·7 (3·3 to 4·2)	347	4·0 (3·5 to 4·4)	−0·2 (−0·8 to 0·3)	0·39‡
Change in mean number of total migraine days per month during weeks 1–4, days†	348	−2·9 (−3·3 to −2·5)	347	−1·7 (−2·2 to −1·3)	−1·2 (−1·7 to −0·6)	<0·0001‡
Change in MSQ role function (restrictive domain score) at week 12†§	269	18·0 (15·5 to 20·6)	266	14·6 (12·1 to 17·1)	3·5 (0·2 to 6·7)	0·036‡
Change in MIDAS total score at week 12†§	269	−11·8 (−15·4 to −8·2)	266	−11·7 (−15·3 to −8·1)	−0·1 (−4·7 to 4·5)	0·96‡

MSQ=Migraine-Specific Quality-of-Life Questionnaire. MIDAS=Migraine Disability Assessment. *Evaluable participants had ≥14 days of electronic diary efficacy data (not necessarily consecutive) in the 4-week observation period and data for at least 1 month (4-week interval) in the 12-week double-blind treatment phase. To control the type I statistical error rate at 0·05, a preplanned hierarchical testing procedure was applied; endpoints are presented in the sequence in which they were evaluated. †Analysed using a generalised linear mixed-effects model with treatment group, preventive migraine medication use at randomisation, study month, and month-by-treatment group interaction as fixed effects and participant as random effect. ‡Nominal p value in hierarchical testing. §Analysis only included participants who completed the MIDAS or MSQ questionnaire within the prespecified efficacy analysis window (weeks 10–13).

Table 2: **Efficacy outcomes assessed in the efficacy-evaluable population***

Croop R et al. *Lancet*. 2021 Jan 2;397(10268):51-60.

Preventive treatments: present and future

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

Topiramate 100 (200) mg
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Flunarizine 5-10 mg
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Pizotifen 1.5-3 mg

Botulinum toxin type A 155U
Indication: Chronic migraine

Anti CGRP or its receptors monoclonal antibodies

Erenumab	Fremanezumab	Galcanezumab	Eptinezumab

Future treatment: Oral CGRP-receptor antagonists

Atogepant	Rimegepant

Preventive Treatment of Migraine