New treatments for migraine

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outline

ACUTE

PREVENTION

What is happening in the brain during migraine?

Activation of trigeminal system

Cortical spreading depression

Explains aura

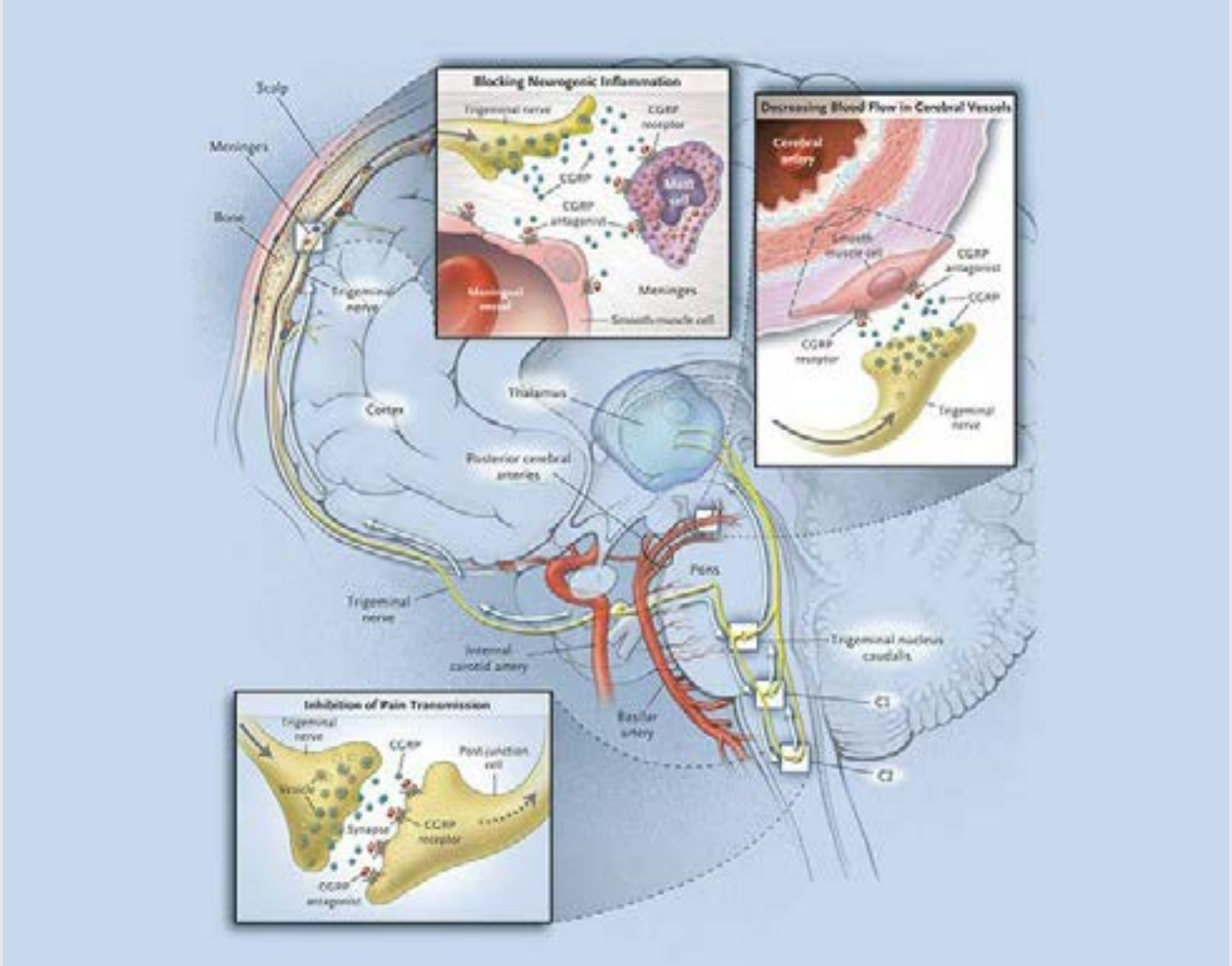
Vasodilation

Activation of trigeminal ganglion leads to increase in extracerebral blood flow

Local release of CGRP and substance P

Inflammatory response

Mast cell degranulation/release of histamine, changes in post capillary venules, platelet aggregation



20 years from the laboratory bench to bedside

Drugs that block CGRP

- Monoclonal antibodies (mAbs)
- Small molecules (“gepants”)

NEW ACUTE TREATMENTS for Migraine

"Gepants"

"Ditans"

What does a patient that is having a migraine want?

- Complete freedom from pain
- FAST!
- Minimal or NO side effects
- No headache recurrence
- Rapid return to normal function

“Gepants”

small molecules that block the CGRP receptor

Ubrogepant (*Ubrelvy*)

50 & 100 mg tablet

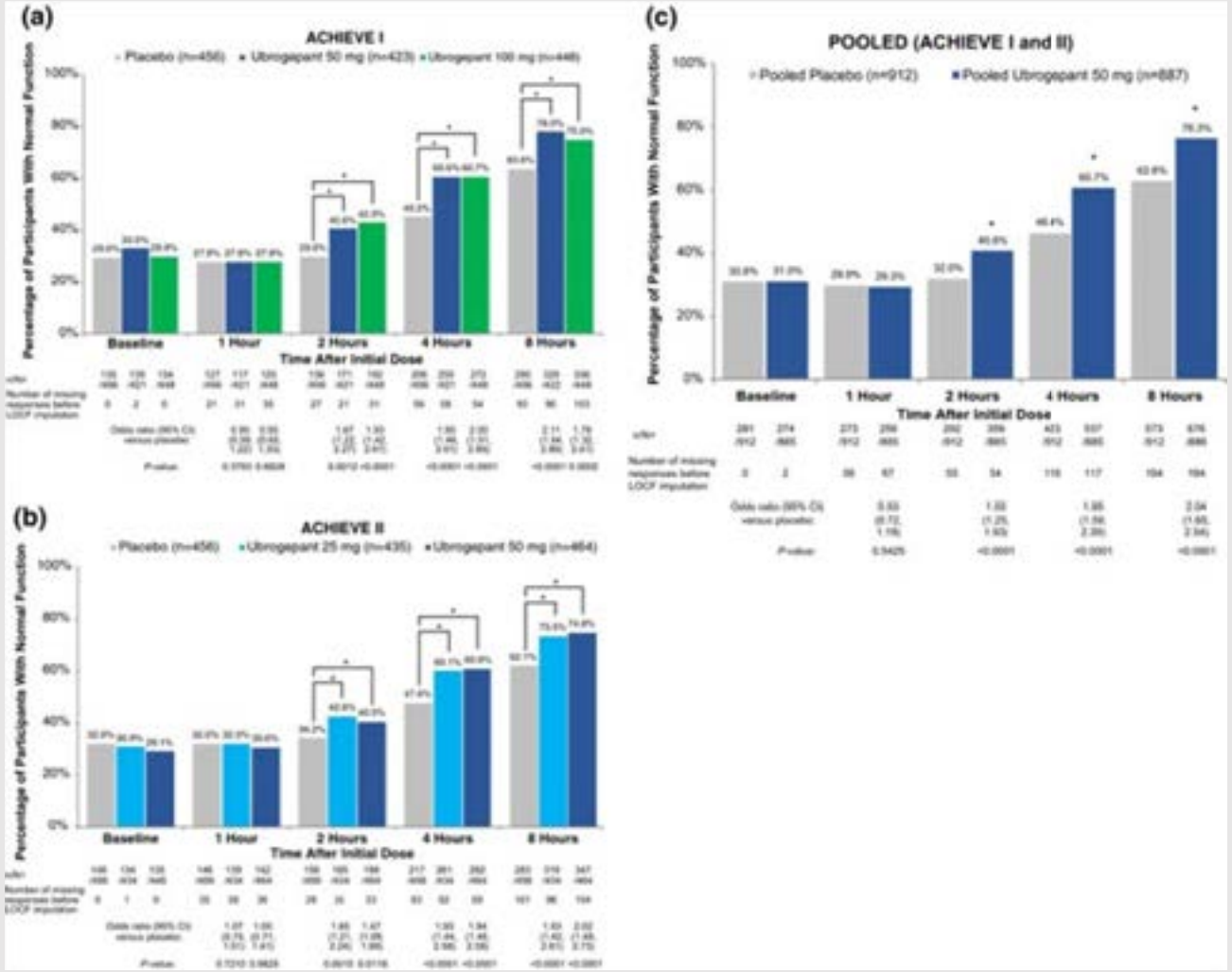
Rimegepant (*Nurtec ODT*)

75 mg orally disintegrating tablet

Ubrogepant (*Ubrelvy*)

- At 2 hrs, odds of reporting return to normal function were 2X as high in patients treated with either 50/100 mg Ubrelvy vs placebo

- At 24 hrs, patient reported satisfaction and improved change was 61% treated vs 37% placebo



Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant, an Acute Treatment for Migraine, Improved Patient-Reported Functional Disability and Satisfaction in 2 Single-Attack Phase 3 Randomized Trials, ACHIEVE I and II. *Headache*. 2020;60(4):686-700.

Rimegepant (*Nurtec ODT*)

Pain freedom at 2 hrs

21% vs 11% placebo

Free most bothersome symptom

35% vs 27% placebo

Both parameters sustained through 48 hours

86% pts treated with Nurtec did not use any rescue medication 24 hrs post-dose

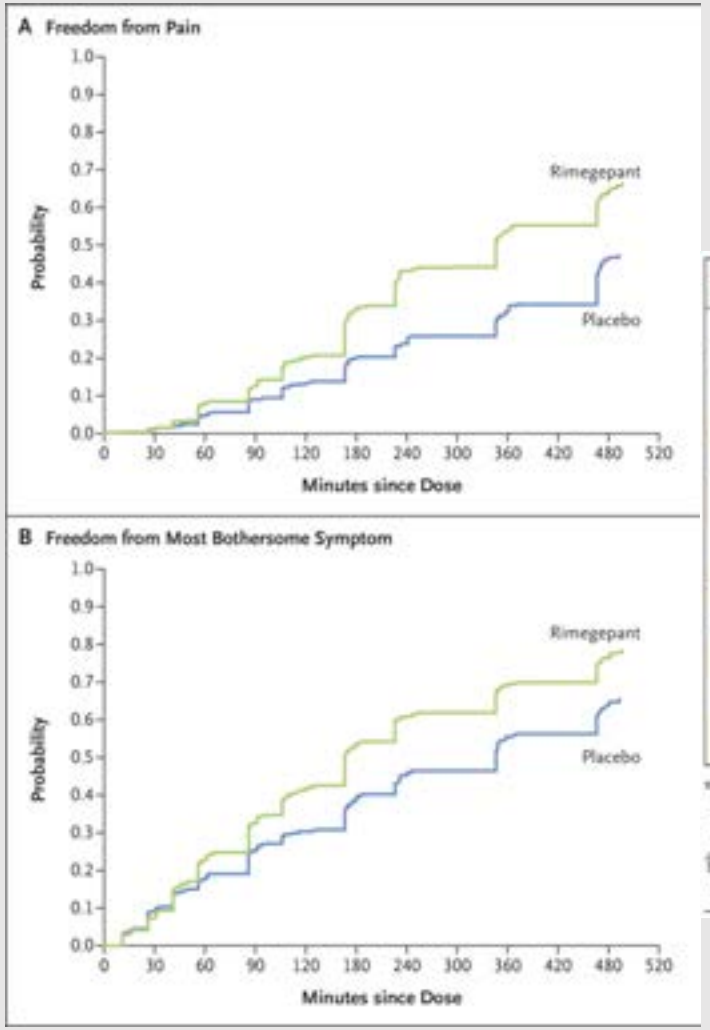


Table 3. Adverse Events and Liver-Function Test Findings in the Safety Population.*

Variable	Rimegepant (N = 543)	Placebo (N = 543)
	number of patients (percent)	
Any adverse event	93 (17.1)	77 (14.2)
Adverse events reported in ≥1% of patients in either treatment group		
Nausea	10 (1.8)	6 (1.1)
Urinary tract infection	8 (1.5)	6 (1.1)
Serious adverse event†	1 (0.2)	2 (0.4)
Liver-function tests		
Serum AST or ALT above ULN	13 (2.4)	12 (2.2)
Serum AST or ALT >3× ULN	0	0
Total bilirubin >2× ULN	0	0

* The safety population included all patients who underwent randomization and took a dose of rimegepant or placebo. Patients could have had more than one adverse event. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† The serious adverse event reported in the rimegepant group was back pain, and the serious adverse events reported in the placebo group were chest pain (1 patient) and urinary tract infection (1 patient).

Lipton RB, Croop R, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine.
N Engl J Med 2019; 381:142-149

“Ditans”

Lasmiditan (*Reyvow*)

- 5-HT1F serotonin receptor agonist
- receptor activation is linked to the inhibition of CGRP release
- NOT vasoconstrictive

Lasmiditan (*Reyvow*)

Data from 100 mg dose

Pain freedom at 2 hrs

25% vs 11% placebo (UP)

31% vs 20% placebo (NUP)

Free most bothersome symptom

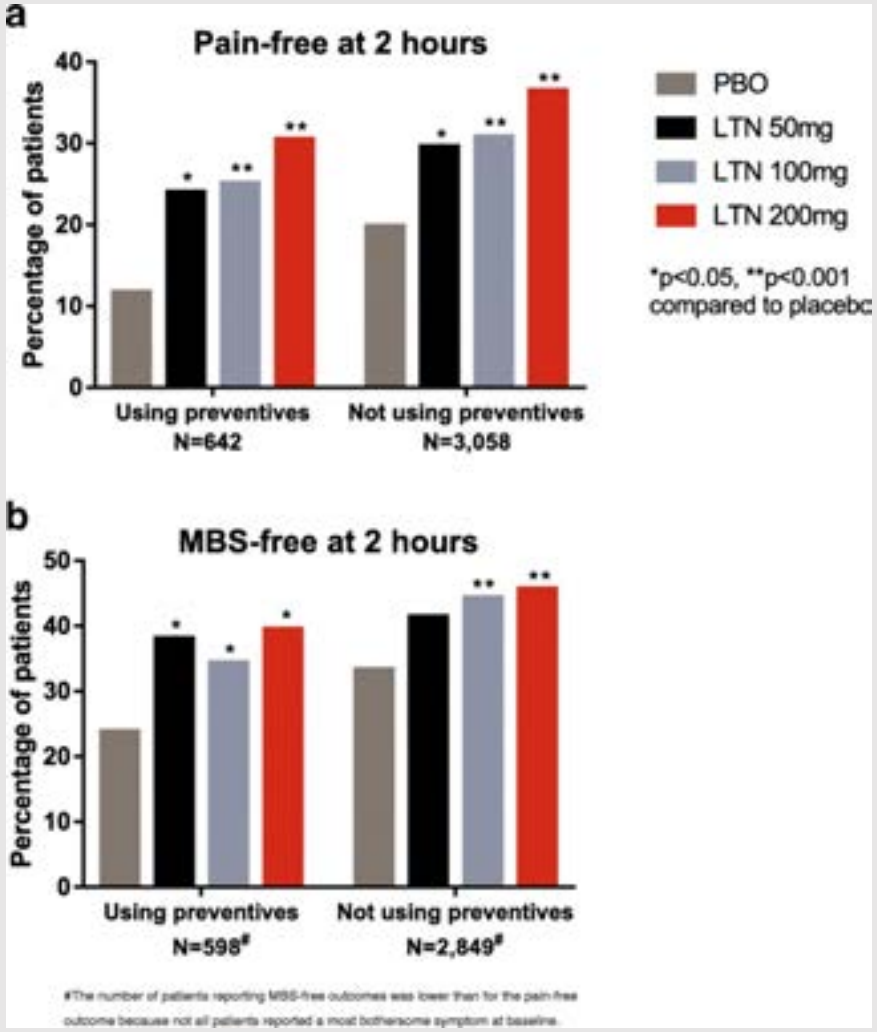
34% vs 24% placebo (UP)

33% vs 44% placebo (NUP)

Sustained pain freedom at 24 hours

14/17 % vs 5.6% placebo

Patient perceived outcomes +



Loo LS, Ailani J, Schim J, et al. Efficacy and safety of lasmiditan in patients using concomitant migraine preventive medications: findings from SAMURAI and SPARTAN, two randomized phase 3 trials. *J Headache Pain*. 2019;20(1):84. Published 2019 Jul 24.

NEW PREVENTIVE TREATMENTS for Migraine

CGRP monoclonal Antibodies

-link to CGRP receptor

-link to CGRP peptide

Erenumab (*Aimovig*)

Galcanezumab (*Emgality*)

Fremanezumab *(Ajovy*)

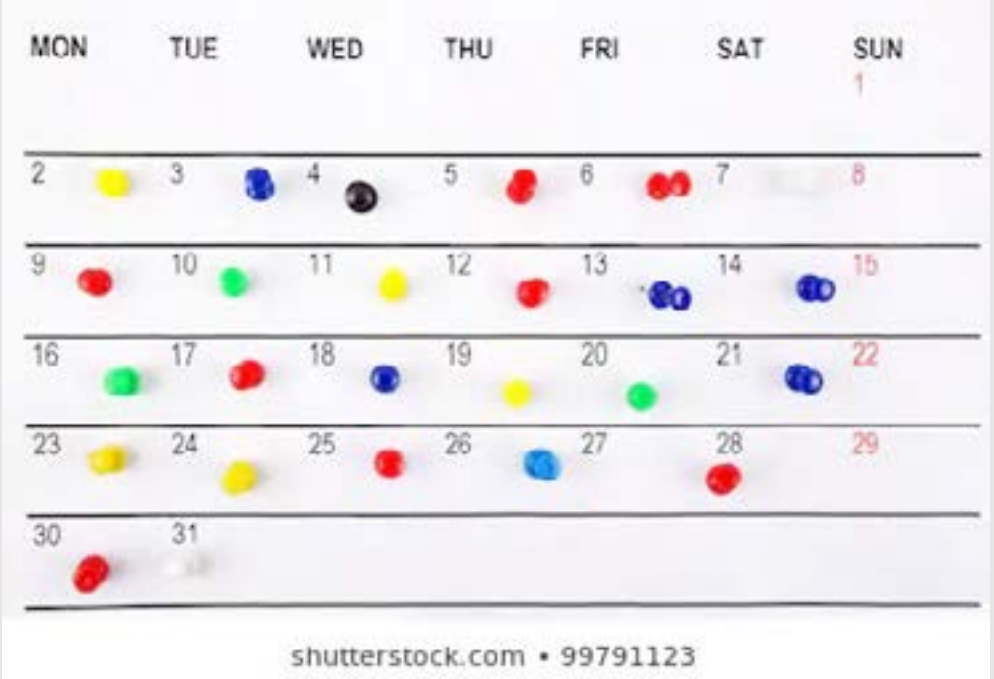
Eptinezumab (*Vyepti*)

MILES FOR MIGRAINE

Who benefits from starting a CGRP preventive?

- > 1-2 migraines a week
- Long disabling duration of attacks
- Intolerance or contraindication to oral preventive drugs
- Not planning pregnancy, not breastfeeding

Headache Calendar May 2020



Headache free days

Disabling migraine days

How to decide which CGRP mAb to choose?

- Fast onset of effect
- High efficacy in all
- **1/3 of patients achieve >75% reduction in frequency of migraines in first 1-3 months**
- Well tolerated and minimal side effects

Facts to keep in mind when making a choice…

- mode
  - …3 are self-injections
  - …1 is an intravenous infusion
- counteract potential side effects
  - constipation and muscle spasms would make Erenumab less favored
- coverage/cost
  - likely limiting factor, depends if included in your insurance's formulary and their pre-authorization requirements

Frequently asked questions…

- How long is an adequate trial?
  - 4-6 months
- If a patient does not respond to 1 CGRP mAb, will another work?
  - probably
- Will the CGRP mAb stop working?
  - low risk
- Will the CGRP mAb work if there is medication overuse headache (MOH)?
  - Yes they can
- Do CGRP mAbs help in chronic migraine?
  - All 4 have evidence
- Can you take CGRP mAbs and "gepants"?
  - Yes, but would like more studies

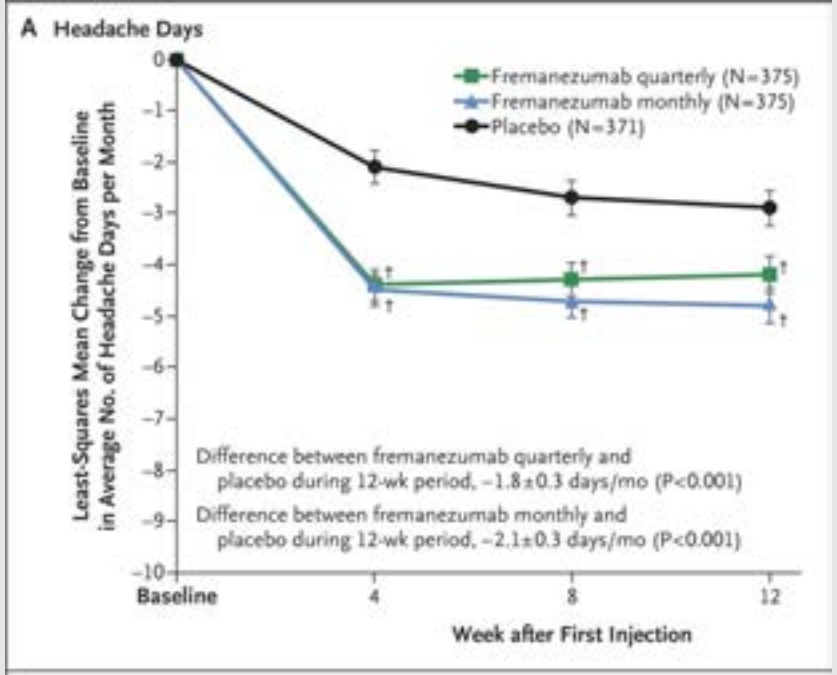
Do CGRP mAbs help Chronic Migraine (CM)?

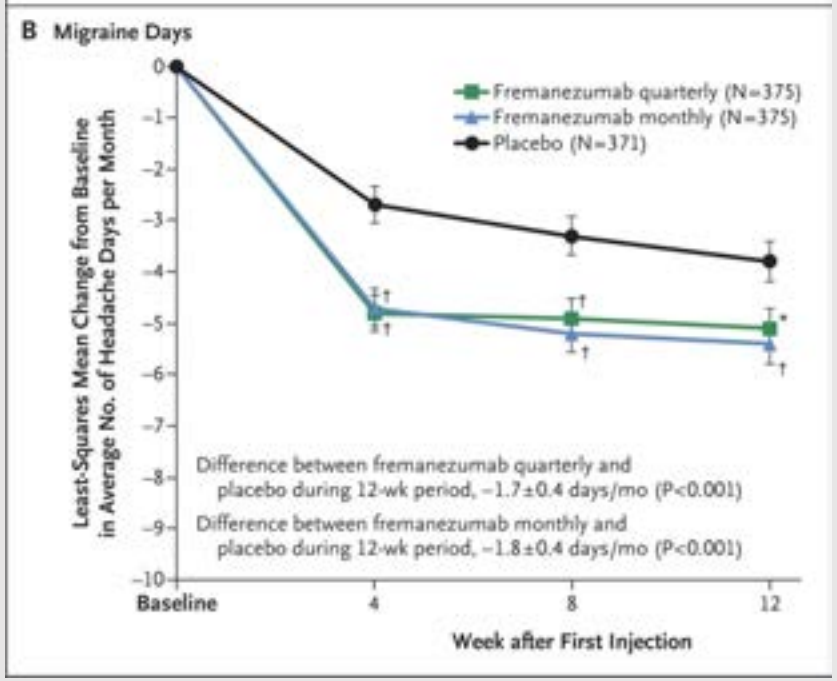
Botulinum toxin injection treatments every 3 months had been the only FDA approved treatment in CM from 2010 to 2017

Data from the clinical trial Fremanezumab (*Ajovy*)

50% reduction in average of headache days per month

- 38% pts quarterly use
- 41% pts monthly use
- 18% pts placebo

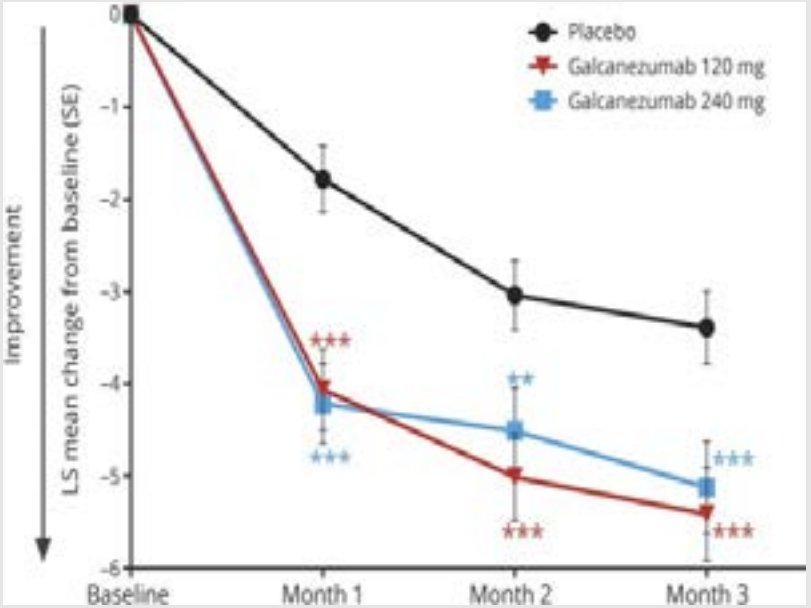




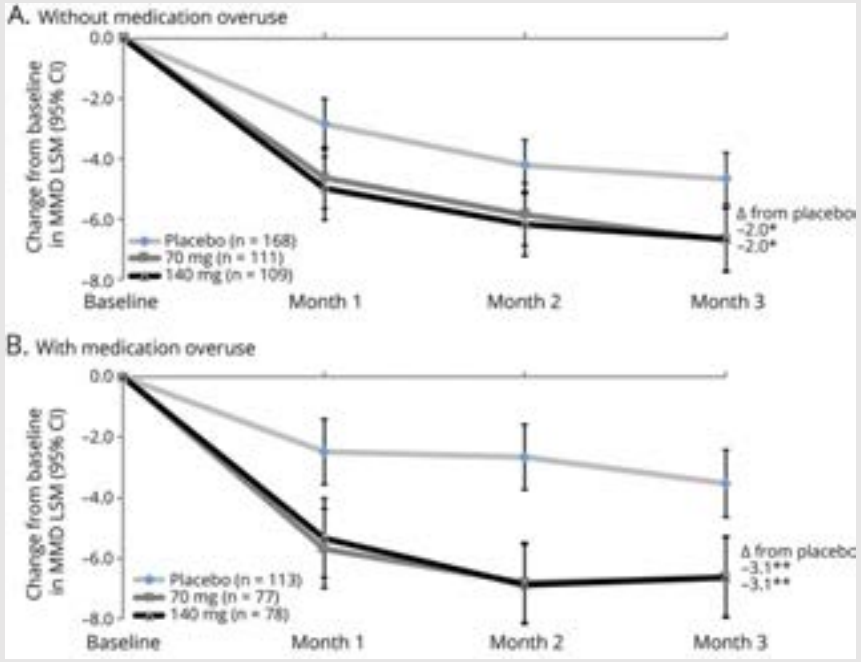
Fremanezumab for the Preventive Treatment of Chronic Migraine
List of authors.Stephen D. Silberstein, M.D., David W. Dodick, et al.
November 30, 2017
N Engl J Med 2017; 377:2113-2122

Do CGRP mAbs help Chronic Migraine (CM)?

- Data from the clinical trials
  - Galcanezumab (*Emgality*)
    - Included pts with MOH
  - Erenumab (*Aimovig*)
    - Included pts with MOH



Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. **Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study**. *Neurology*. 2018;91(24):e2211-e2221.

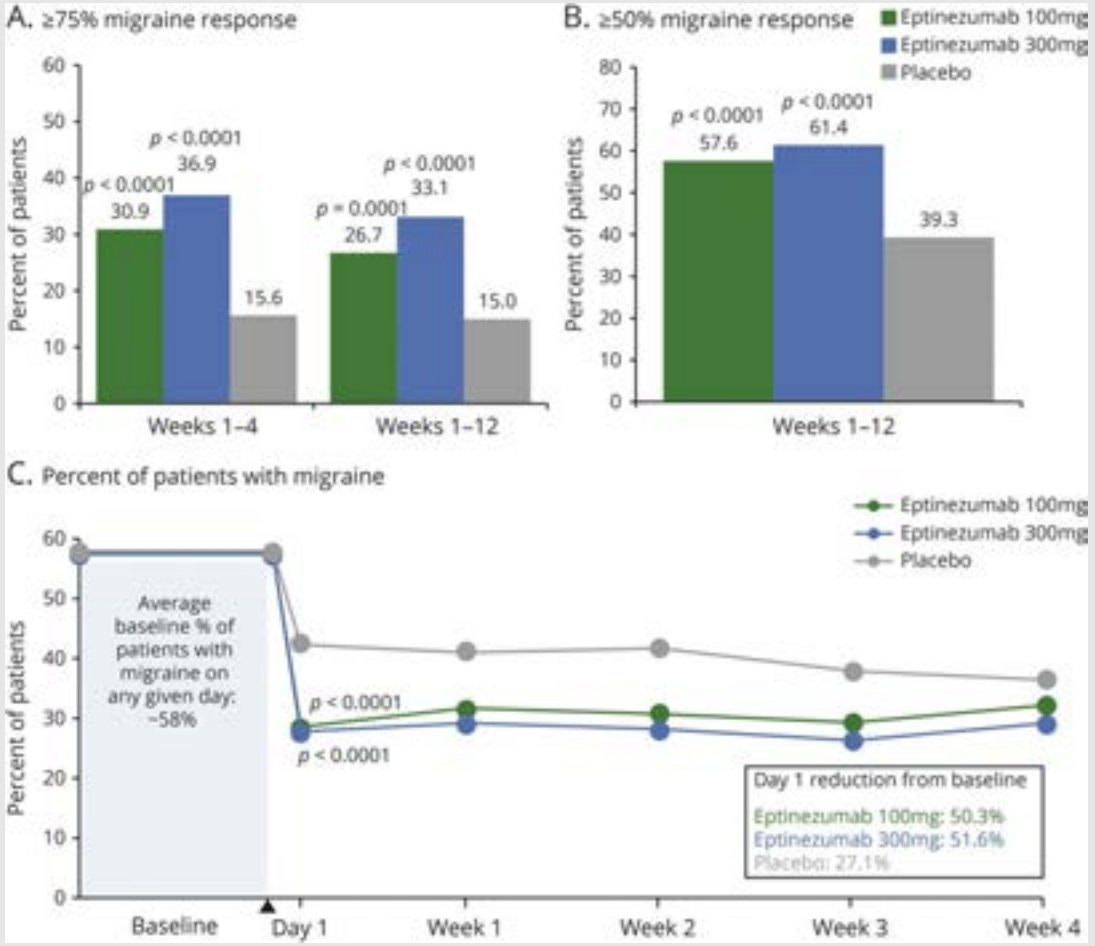


Tepper SJ, Diener HC, Ashina M, et al. **Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial**. *Neurology*. 2019;92(20):e2309-e2320.

MILES FOR MIGRAINE

Do CGRP mAbs help Chronic Migraine (CM)?

- Data from the clinical trials
  - Eptinezumab (*Vyepti*), Promise 2 trial specifically looked at CM
  - 40% pts had MOH



Efficacy and safety of eptinezumab in patients with chronic migraine PROMISE-2
Richard B. Lipton, Peter J. Goadsby, Jeff Smith, Barbara A. Schaeffler, David M. Biondi, Joe Hirman, Susan Pederson, Brent Allan, Roger Cady
Neurology Mar 2020, 94 (13) e1365-e1377

MILES FOR MIGRAINE

Treatments in the horizon…

Other "gepants"

- Atogepant- in trials for prevention of migraine
- Vazegepant- nasal spray in trial for acute treatment
- Rimegepant- completed trial for preventive use, awaiting FDA review

Other novel mechanisms…

- Pit adenyl cyclase-activating polypeptide mAb

Thank yo

MILES FOR MIGRAINE