# THE NEW MIGRAINE PARADIGM



Diamond Headache Clinic

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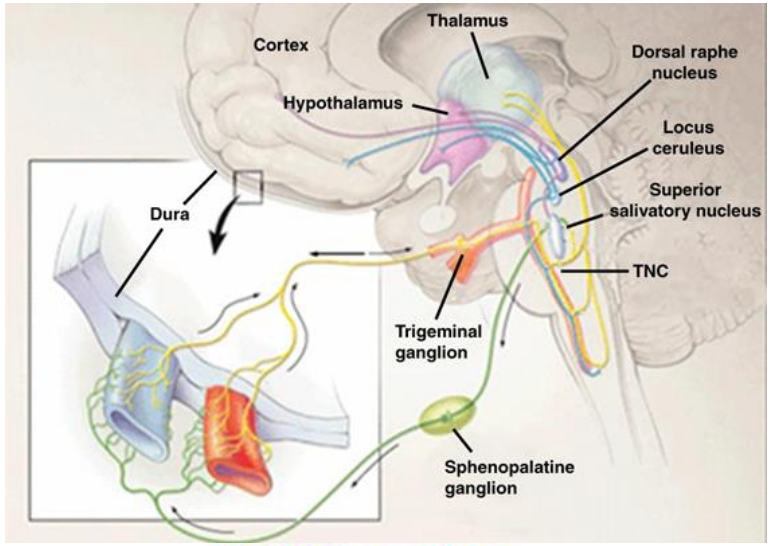
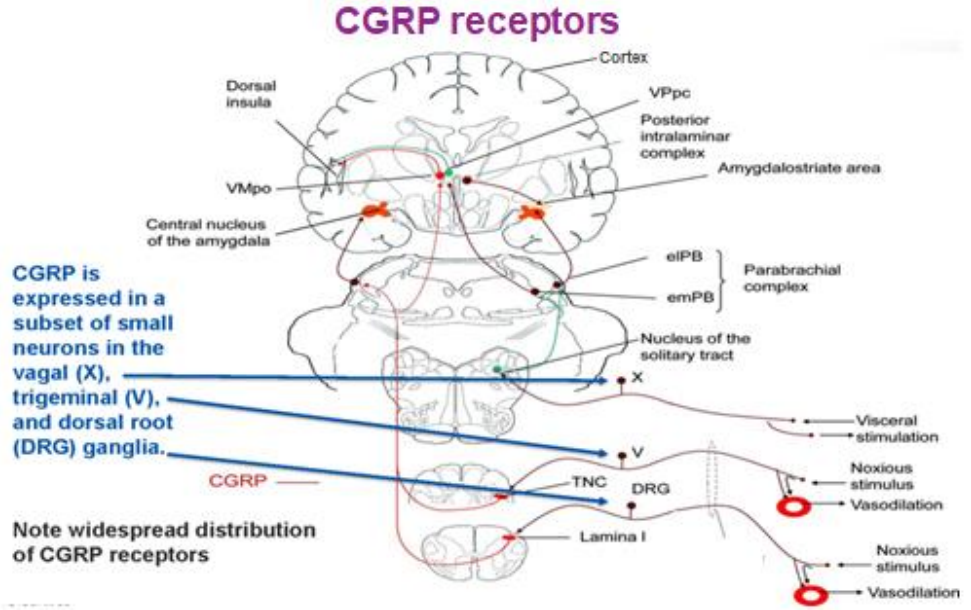
# Calcitonin Gene-Related Peptide: CGRP

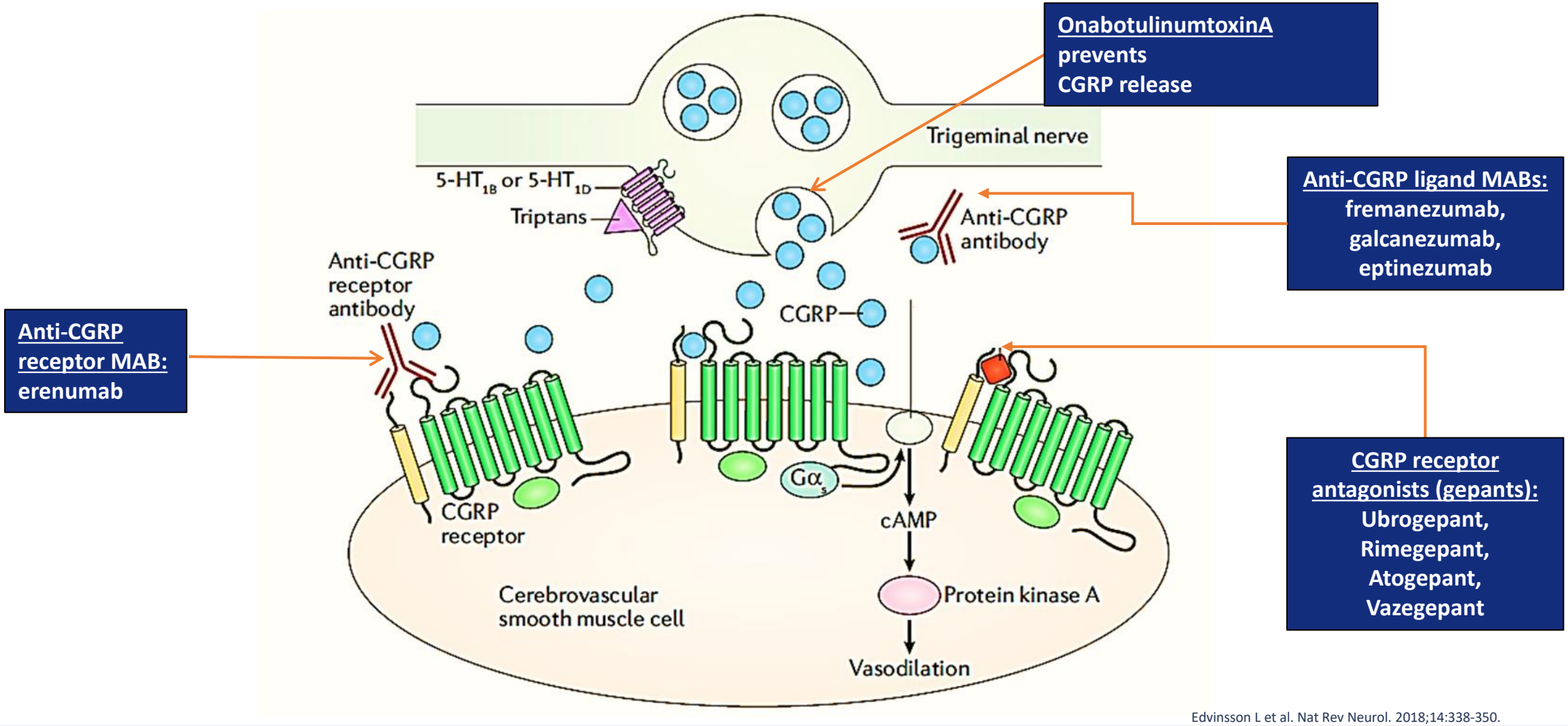
Present at all migraine pathogenesis sites

The most potent endogenous vasodilator and causes neurogenic inflammation

Goadsby et al. N Engl J Med.2002;346:257–270.
Naot and Cornish. Bone. 2008;43:813-818.
Benarroch. Neurology. 2011;77:281-287.






Edvinsson L et al. Nat Rev Neurol. 2018;14:338-350.

# Migraine Preventative Treatment Targets

# How To Target CGRP If Gepants Are Liver Toxic?

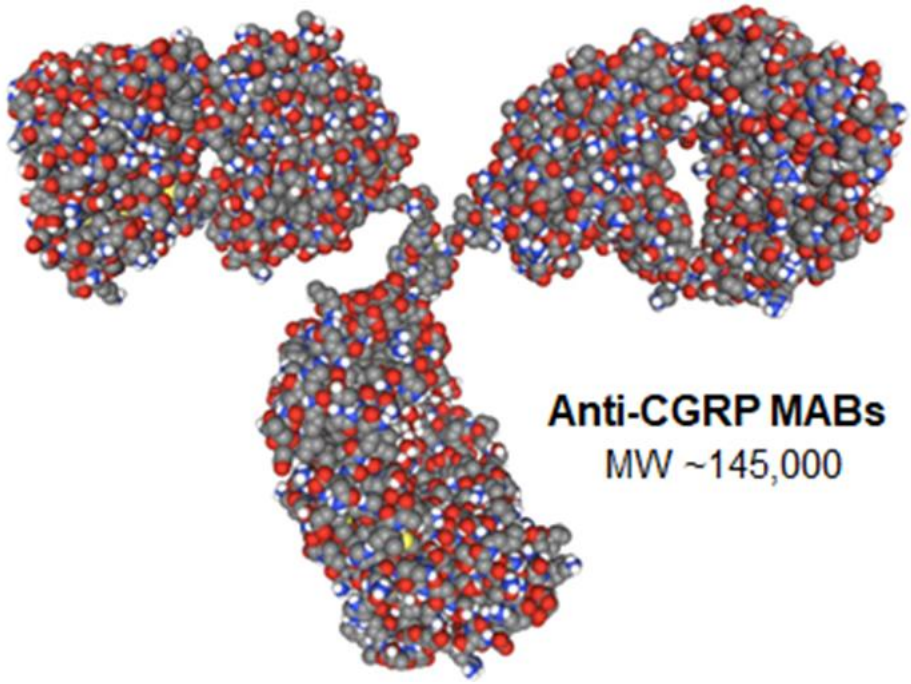
Monoclonal antibodies (MABs) are large molecules that do not pass into the brain

They are removed by the reticuloendothelial system, so no liver toxicity

They work peripherally to prevent migraine

SIZE DIFFERENCE:

MAB-truck; Gepant - grain of rice



**Gepants**
MW ~530

| | **Erenumab-aooe**<br>AIMOVIG | **Fremanezumab-vfrm**<br>AJOVY | **Galcanezumab-gnlm**<br>EMGALITY | **Eptinezumab-jjmr**<br>VYEPTI |
|---|---|---|---|---|
| **Route and Dosing** | Monthly SC<br>70, 140 mg | Monthly or quarterly<br>SC; 225 mg monthly,<br>or 675 mg Q3 months | Monthly SC; For migraine:<br>240 mg loading dose,<br>then 120 mg SC monthly thereafter.<br>For eCH: 300 mg monthly<br>SC to end of cycle | 100 mg and 300 mg<br>Q3 months IV |
| **Target** | CGRP receptor | CGRP peptide<br>or ligand | CGRP peptide<br>or ligand | CGRP peptide<br>or ligand |
| **Regulatory status** | *FDA-approved*<br>*5/17/18 for*<br>*migraine prevention* | *FDA-approved*<br>*9/14/18 for*<br>*migraine prevention* | *FDA-approved*<br>*9/26/18 for migraine prevention and*<br>*6/4/19*<br>*for treatment of eCH* | *FDA approved 2/22/20*<br>*for migraine prevention* |

eCH=episodic cluster headache. cCH=chronic cluster headache. SC=subcutaneous. BLA=biologics license application.


1.Tepper SJ. Headache 2018;58 (suppl 3):238–275.

2. Tepper SJ. Headache. 2018;58 (supp 3):276–290.

3. Edvinsson L. Headache 2018;58 (suppl 1):33-47.

4. Lilly press release. March 5, 2019 https://investor.lilly.com/news-releases/news-release-details/lilly-receives-fda-priority-review-designation-emgalityrAccessed April 5, 2019.

5. Alder press release. February 22, 2019. https://www.globenewswire.com/news-release/2019/02/22/1740250/0/en/Alder-BioPharmaceuticals-Submits-Biologics-License-Application-to-the-U-S-Food-and-Drug-Administration-for-Eptinezumab.html Accessed April 5, 2019.


# 4 FDA Approved Injectable mAbs To CGRP Or Its Receptor

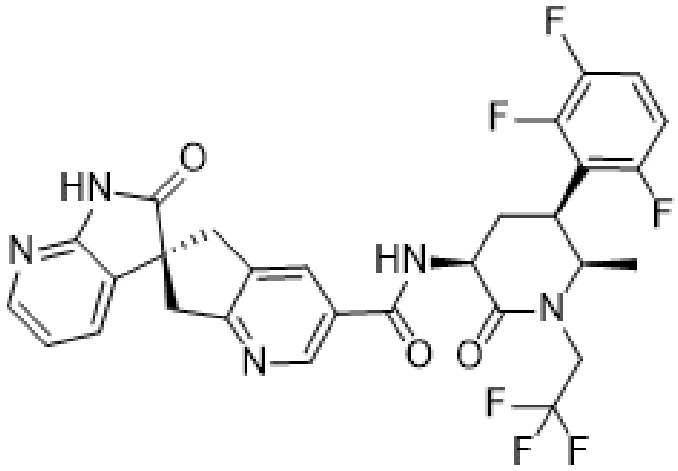
# Three Major MAB Questions

- ARE THEY SAFE?
- ARE THEY DIFFERENT THAT WHAT WE HAVE NOW?
- ARE THEY AN IMPROVEMENT?

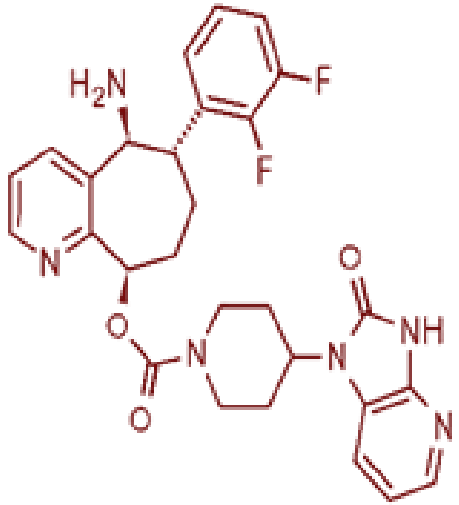
# Highlights Of MAB Efficacy

- All reduce mean monthly migraine days
- All separate from placebo in the studies in less than a week
- All show meaningful clinical benefit by one month in the studies
- All show unprecedented ≥75% responder rates
- All work in patients with ≥ 1-4 previous preventative medication class failures
- When treated, the majority of patients convert from chronic to episodic migraine and from acute medication overuse to non-overuse
- All show continued improvement over years of use with no new safety or tolerability concerns

MILES FOR MIGRAINE




Atogepant



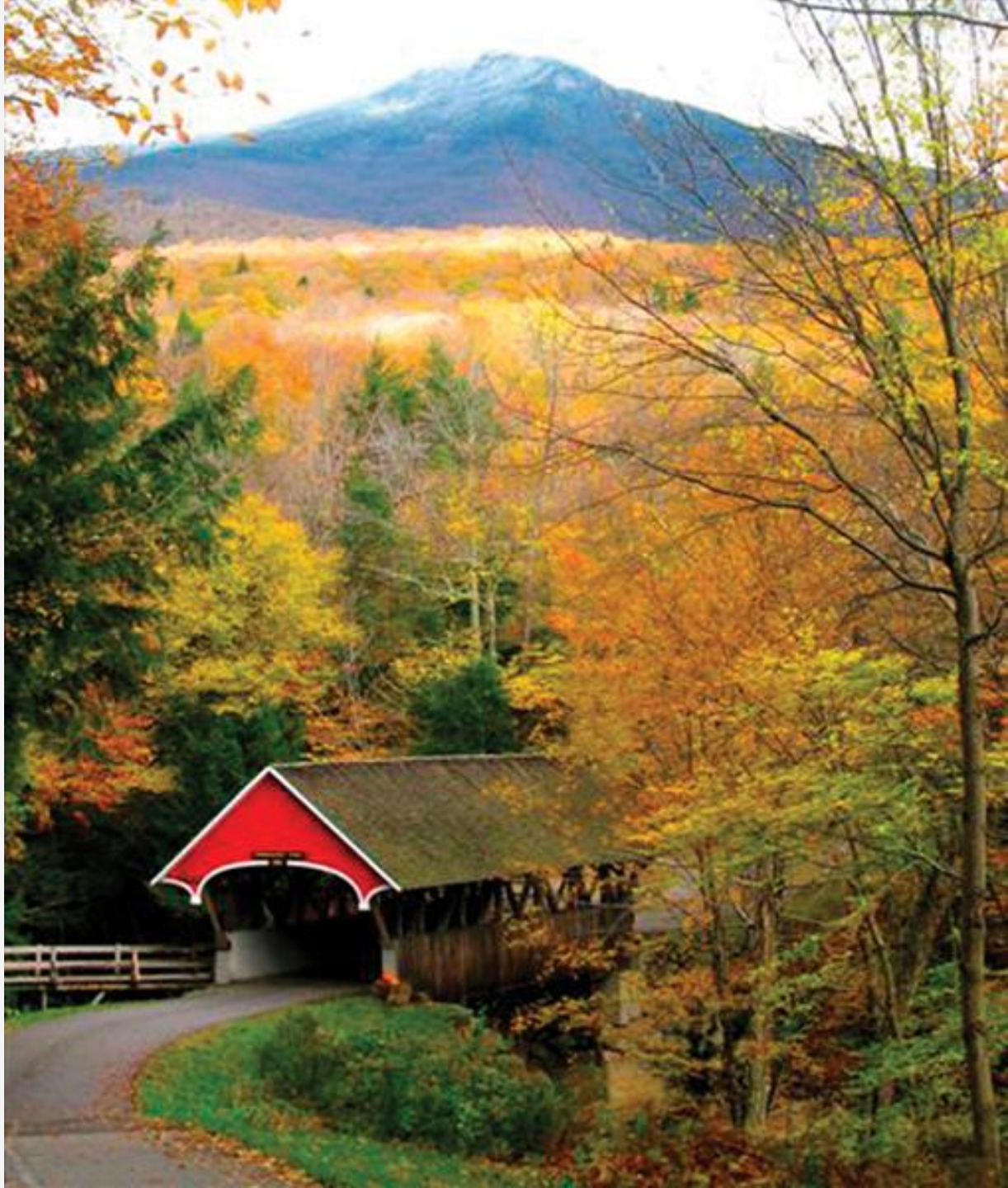

Rimegepant

# The Small Molecule CGRP Receptor Antagonists: The Gepants for Prevention in Development

*PREVENTIVE Treatment of Migraine*

- In open label trials, the more the gepants were taken for acute treatment, the fewer the migraine attacks
- Atogepant vs placebo: Daily dosing positive Phase 2 randomized controlled trial (RCT) for Episodic Migraine prevention study; now in Phase 3
  - Magnitude of decreased mean monthly migraine days similar to MABs
- Rimegepant vs placebo: QOD RCT dosing positive for migraine prevention Phase 2/3; submitted for prevention
- This would be the first medication approved for both acute and preventive migraine treatment

# New Acute Formulations and Combinations



# New Acute Migraine Formulations

## FDA Approved and Available

### ONZETRA

Sumatriptan breath powered nasal powder

22 mg

### ZEMBRACE

Sumatriptan 3 mg autoinjector

### TOSYMRA

Sumatriptan nasal spray with permeation enhancer 10 mg

MILES FOR MIGRAINE

# New Acute Migraine Formulations

## In Development

### QTRYPTA

Zolmitriptan microneedle array skin patch - submitted to FDA

### DHE NASAL SPRAY

with HFA propellant

### DHE NASAL SPRAY

Powder

MILES FOR MIGRAINE

# Acute Migraine Combinations

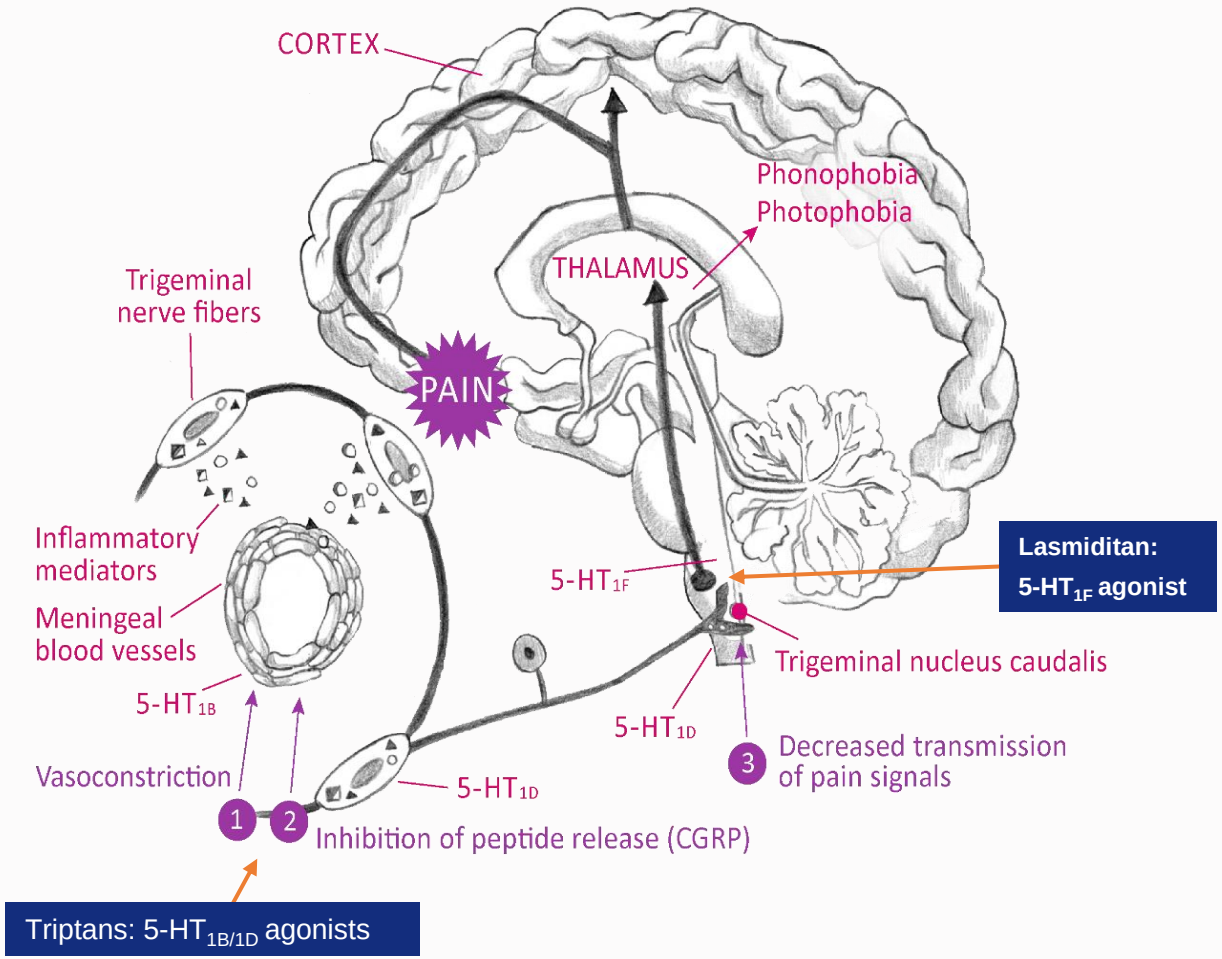
## FDA APPROVED

- Sumatriptan 85 mg
  - Naproxen sodium 500 mg TREXIMET

## IN DEVELOPMENT

- MOSEIC Meloxicam 20 mg
  - Rizatriptan 10 mg: Positive regulatory trials
- Promethazine - sumatriptan

MILES FOR MIGRAINE




# Lasmiditan

Lasmiditan (REYVOW) FDA-approved October 11, 2019 for acute treatment of migraine, w/wo aura, in adults

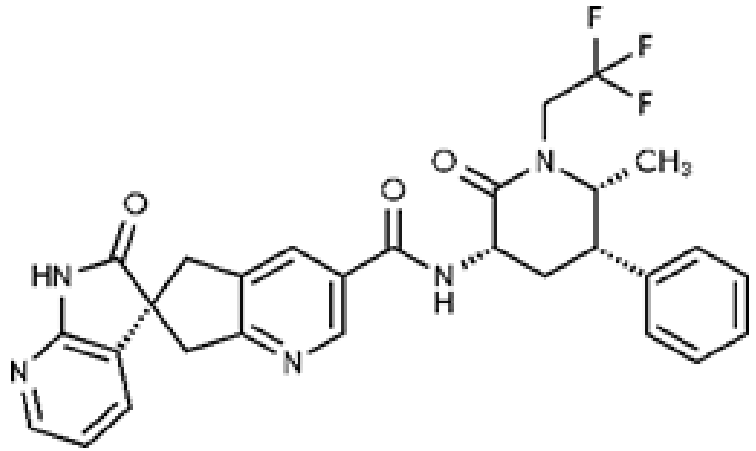
- Peripherally, 5=HT1F action inhibits CGRP release
- Centrally acting 5-HT1F agonist
- Lacks vasoconstrictive activity; appropriate for patients with vascular disease
- 2-hour pain freedom:
  - 100 mg, 28.2-31.4%
  - 200 mg, 32.2-38.8%
  - Placebo, 15.3-21.3%
- Most common were dizziness, paresthesia, and somnolence
- Patients advised not to drive/operate machinery for 8 hours after dosing even if no CNS adverse events (somnolence, dizziness)
- Controlled substance Class V, same as pregabalin

Adapted from Hargreaves et al. Can J Neurol Sci. 1999;26(suppl 3):S12-S19.
Kuca et al. Neurology. 2018;91(24):e2222-e2232.3
Goadsby et al. Brain. 2019;142:1894-1904.
Oswald et al. J Pain Res. 2018;11:2221-2227.

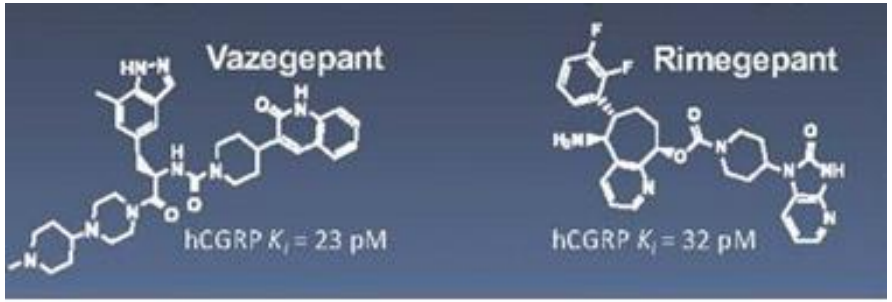
# The Small Molecule CGRP Receptor Antagonists: The Gepants

ACUTE Treatment of Migraine

- 7 gepants have demonstrated efficacy in acute migraine treatment
- Early gepants were liver toxic; development halted, then resumed with four newer gepants
- Ubrogepant tablets approved Dec 23, 2019 for acute migraine treatment
- Rimegepant orally dissolvable tablets approved Feb 28, 2020 for acute migraine treatment
- 2-hour pain freedom for both ≈20%
- Vazegepant reported positive Phase 2 as a nasal gepant for acute migraine treatment
- Do not cause blood vessels to constrict; so, unlike triptans, should be safe in people with vascular disease




**Ubrogepant (UBRELVY)**

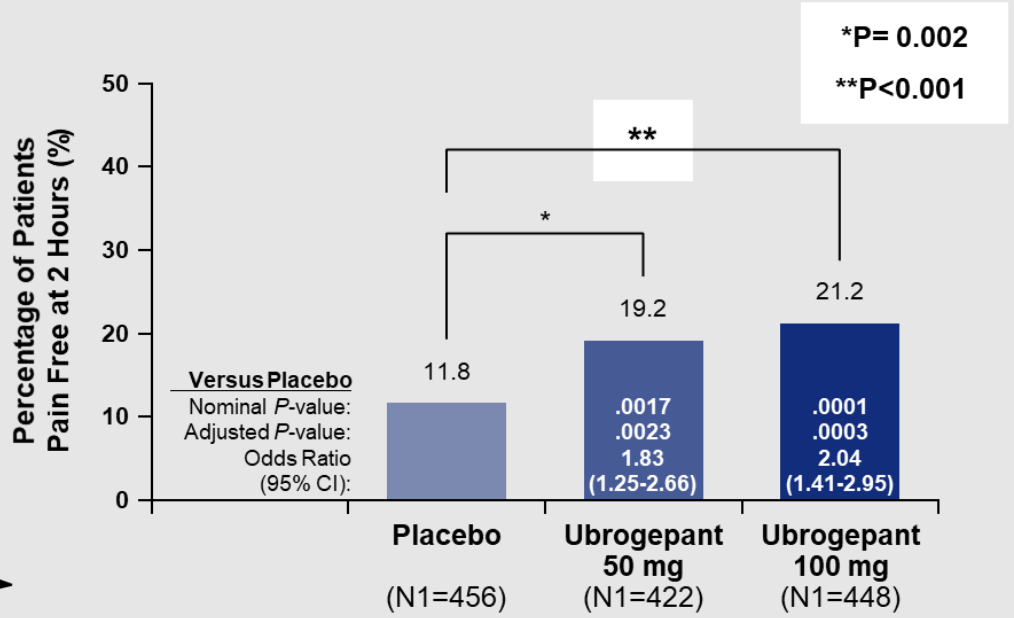



**Rimegepant (NURTEC)**

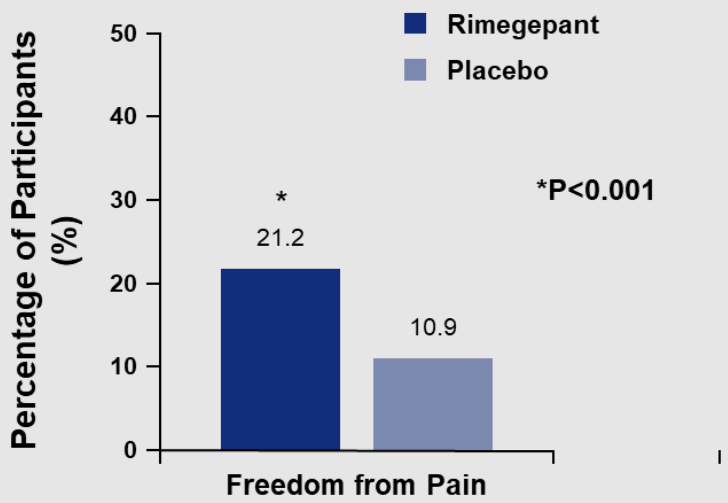
Tepper SJ. Headache. 2018;58(Suppl 3):238-275.
Tepper SJ. Headache. 2018;58(Suppl 3):276-290.

# The Gepants: 2 Hour Pain Free vs Placebo, Phase 3 Trials

## Ubrogepant 2h Pain Free[1]




## Rimegepant 75 mg 2h Pain Free[2] ODT




- Vazegepant nasal spray 10 mg also resulted in 2h pain free of 22.5% in Phase 2/3 study
- All gepants studied for acute treatment also achieved the other FDA mandated co-primary endpoint, relief of most bothersome symptom (MBS), patient chosen from photohobia, phonophobia, or nausea, at 2h versus placebo

Dodick et al. N Engl J Med. 2019;381:2230-2241. 2. Croop R, et al. Lancet. 2019;394(10200):737-745. https://www.biohavenpharma.com/investors/news-events/press-releases/12-17-2019

# Safety and Tolerability of the Gepants

- Both gepants are metabolized in the liver by CYP3A4
- The gepants are remarkably well tolerated and appear very safe

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## Ubrogepant

- AEs<5%: Nausea, somnolence, dizziness, dry mouth
- Prospective trial of ubrogepant QOD to assess liver with no clinically relevant signal of hepatotoxicity

>>

## Rimegepant

- Nausea 0.7-2% over placebo
- No liver signal

Lipton et al. JAMA. 2019;322:1887-1898.
Dodick et al. NEJM. 2019;381:2230-2241.
Goadsby et al. Cephalalgia 2019;39:1753-1761.
Croop et al. Lancet.2019;394(10200):737-745.
Lipton et al. NEJM. 2019;381:142-149.

# Neuromodulation For Acute Migraine Treatment

# Noninvasive Neurostimulators for Migraine

Tepper SJ, Tepper DE. Practical Neurology. 2018;17:42-45. | Yarnitsky et al. Headache. 2019;59:1240-1252. | Rapoport AM and Tepper SJ. Headache. 2020;60:229-234.

## FDA CLEARED: ACUTE & PREVENTATIVE

External Trigeminal Stimulation (eTNS)
CEFALY

Single Pulse Transcranial Magnetic Stimulation (sTMS)

Noninvasive Vagal Nerve Stimulation (nVNS) GAMMACORE

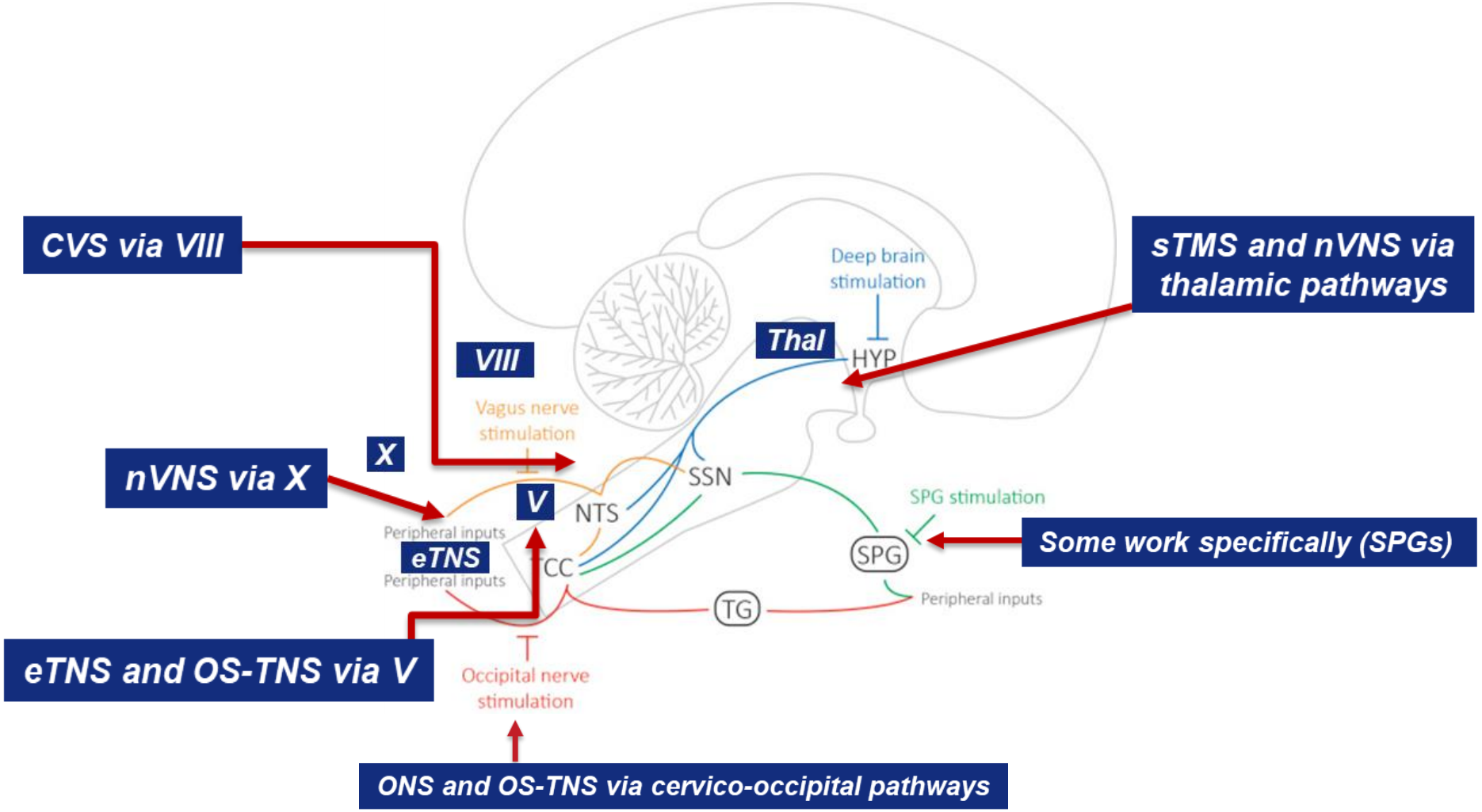
## FDA CLEARED: ACUTE ONLY

Remote Electrical Neuromodulation (REN)
NERIVIO

## IN DEVELOPMENT: ACUTE ONLY

Combined occipital & supraorbital transcutaneous nerve stimulation (OS-TNS)
RELIVION

MILES FOR MIGRAINE




- Most modulate with peripheral access to central pathways

# How Do Neuromodulation Devices Work?

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Diamond Headache Clinic

# Follow Us

MILES FOR MIGRAINE

THANK YOU!

# Get In Touch With Us

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