THE NEW MIGRAINE PARADIGM

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Calcitonin Gene-Related Peptide: CGRP

Present at all migraine pathogenesis sites

The most potent endogenous vasodilator and causes neurogenic inflammation

Migraine Preventative Treatment Targets

OnabotulinumtoxinA prevents CGRP release

Anti-CGRP receptor MAB: erenumab

CGRP receptor antagonists (gepants): Ubrogepant, Rimegepant, Atogepant, Vazegepant

Anti-CGRP ligand MABs: fremanezumab, galcanezumab, eptinezumab

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

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

4 FDA Approved Injectable mAbs To CGRP Or Its Receptor
Three Major MAB Questions

- Are they safe?
- Are they different than 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
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
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
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
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

Kuca et al. Neurology. 2018;91(24):e2222-e2232.3
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
The Gepants: 2 Hour Pain Free vs Placebo, Phase 3 Trials

- 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 photophobia, phonophobia, or nausea, at 2h versus placebo

**Ubrogepant 2h Pain Free**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N1=456)</th>
<th>Ubrogepant 50 mg (N1=422)</th>
<th>Ubrogepant 100 mg (N1=448)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h Pain Free (%)</td>
<td>11.8</td>
<td>19.2</td>
<td>21.2</td>
</tr>
<tr>
<td>Nominal P-value</td>
<td>0.0017</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted P-value</td>
<td>0.0023</td>
<td>1.83</td>
<td>2.04</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>1.26 (1.66)</td>
<td>2.04 (1.94)</td>
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</table>

**Rimegepant 75 mg 2h Pain Free**

- *P= 0.002
- **P<0.001

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<tr>
<th></th>
<th>Rimegepant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h Pain Free (%)</td>
<td>21.2</td>
<td>10.9</td>
</tr>
<tr>
<td>*P&lt;0.001</td>
<td></td>
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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

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
Neuromodulation For Acute Migraine Treatment
Noninvasive Neurostimulators for Migraine

**FDA CLEARED:**

**ACUTE & PREVENTATIVE**

- External Trigeminal Stimulation (eTNS)
  - CEFALY

- Single Pulse Transcranial Magnetic Stimulation (sTMS)

**FDA CLEARED: ACUTE ONLY**

- Remote Electrical Neuromodulation (REN)
  - NERIVIO

**IN DEVELOPMENT:**

**ACUTE ONLY**

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

How Do Neuromodulation Devices Work?

• Most modulate with peripheral access to central pathways
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