Review: New Treatment and Prevention Agents for Migraine

2Q2020 P&T DUR Education, April 9, 2020
Presented by Shannon Lee, PharmD
Migraine Epidemiology

Migraines are estimated to affect up to 12% of the US population
- Up to 17% of adult women and 6% of adult men
- Most commonly affects those aged 30-39

Major cause of disability
- Ranked 2nd worldwide in 2016 among all diseases for years of life lived with disability
- Accounts for more than $29 billion in expenses annually in the US
  - Between $5.6 and $17.2 billion in lost work productivity

Two main classifications of migraine frequency
- Episodic: less than 15 headache days per month
- Chronic: at least 15 headache days per month
- Over 25% have more than 3 headache days per month

4/24/2020
Migraine Pathology

- Migraine is a whole nervous system disease.
- Spontaneous pain and sensory amplification.
- Trigger is unknown and likely varies between individuals.
- Neurovascular disorder caused by activation of the trigeminovascular system and cranial vasodilation.
- Mediated by release of calcitonin gene-related peptide (CGRP).
# New Agents

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Treatment Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Reyvow (lasmiditan)</td>
<td>Selective serotonin 1F receptor agonist</td>
</tr>
<tr>
<td>Ubrelvy (ubrogepant)</td>
<td>Calcitonin gene-related peptide (CGRP) receptor antagonist (peptide)</td>
</tr>
<tr>
<td>Nurtec (rimegepant)</td>
<td></td>
</tr>
<tr>
<td><strong>Prophylaxis Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Aimovig (erenumab-aooe)</td>
<td>CGRP receptor antagonist (monoclonal antibody)</td>
</tr>
<tr>
<td>Ajovy (fremanezumab-vfrm)</td>
<td></td>
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<tr>
<td>Emgality (galcenezumab-gnlm)</td>
<td></td>
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<tr>
<td>Vyepti (eptinezumab-jjmr)</td>
<td></td>
</tr>
</tbody>
</table>
Triptans are Mainstay of Acute Treatment

Utilize migraine specific agents (i.e. triptans) after failure of non-specific pain agents (APAP & NSAIDs)
- Limit to 2 treatment days per week per American Headache Society (AHS) 2018

Triptan use has many limitations
- MOA: Serotonin 1B/1D/(1F) receptor agonist
- High expression of serotonin 1B receptors in the cranial blood vessels but also present in peripheral blood vessels
  - Contraindicated in vascular disease
  - Use is consistently shown to increase blood pressure
New Acute Treatment Agents

- Three new non-triptan oral agents recently approved
- Indicated for acute treatment of migraine with or without aura in adults

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Approval Date</th>
<th>Coverage Guidelines</th>
</tr>
</thead>
</table>
| Reyvow     | October 11, 2019  | CP.PMN.218 Lasmiditan (Reyvow)  
  • Approved 1Q2020 and went into effect 4.1.2020 |
| Ubrelvy    | December 23, 2019 | CP.PMN.476 Ubrelvy (Ubrogepant)  
  • Under 2Q2020 review; will go into effect 7.1.2020 |
| Nurtec     | February 27, 2020 | In development; expect to see in 3Q2020 materials |

- All agents are currently non-formulary
Reyvow (Lasmiditan)

**FDA Approved Dosing:** 50mg, 100mg, or 200mg as needed
- Not to exceed one dose in 24 hours
- Safety of treating more than 4 migraine episodes in 30 day period is not established

**Available Strengths:** 50mg, 100mg oral tablets

**Clinically Significant Side Effects:**
- Dizziness
- Fatigue
- Paresthesia
- Sedation

**Additional Warnings and Precautions:**
- Driving impairment
- Central nervous system depression
- Serotonin syndrome
- Medication overuse headache

**Regulatory Status:** Schedule 5 controlled substance classification; may cause euphoria
SAMURAI & SPARTAN:
R, DB, PC, Phase 3 Trials

**Patient eligibility criteria:**
- Dx of migraine with or w/o aura
- ≥ 18 years of age
- H/o disabling migraine for ≥ 1 yr
- MIDAS* total score of ≥ 11
- H/o 3-8 migraine attacks/month (<15 headache days/month)

**Exclusion criteria:**
- H/o chronic migraine or chronic headache w/in the prior 12 months
- Medication-overuse headache
- Initiation/change in migraine preventive meds w/in 3 months before screening
- Increased seizure risk
- Known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension^*

**Randomization 1:1:1:1**
- Reyvow 50 mg N=544*
- Reyvow 100 mg N=523*; 498^*
- Reyvow 200 mg N=521*; 503^*
- Placebo N=534*; 515^*

**Efficacy endpoints:**
At 2 hrs post-dose
- Pain free
- Free of MBS (most bothersome symptom)
- Pain relief**

*SPARTAN only; ^SAMURAI only; #MIDAS=Migraine Disability Assessment; **defined as a reduction in migraine pain from “moderate or severe” to “mild or none”
**Conclusion**: Reyvow demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary outcome**: 7 or 8 patients must be treated with Reyvow 200 mg or 100 mg, respectively, for every one patient who achieves freedom from pain at 2 hours after study medication, relative to placebo.
- **Secondary outcomes**: 9 or 10 patients must be treated with Reyvow 100 mg or 200 mg, respectively, for every one patient who achieves freedom from their MBS at 2 hours after study medication, relative to placebo. 7 or 8 patients must be treated with Reyvow 200 mg or 100 mg, respectively, for every one patient who achieves migraine pain relief at 2 hours after study medication, relative to placebo.

**Number Needed to Harm (NNH):**
- For every 625 patients treated for acute migraines with Reyvow, one patient discontinued Reyvow due to adverse effects, relative to placebo.

### Table: SAMURAI: Results

<table>
<thead>
<tr>
<th></th>
<th>Reyvow 100mg</th>
<th>Reyvow 200mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain Free at 2 hrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>28.3</td>
<td>31.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>13</td>
<td>16.5</td>
<td>n/a</td>
</tr>
<tr>
<td>p-value (vs. Placebo)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>MBS Free at 2 hrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>41.2</td>
<td>40.7</td>
<td>29.6</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>11.6</td>
<td>11.1</td>
<td>n/a</td>
</tr>
<tr>
<td>p-value (vs. Placebo)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Pain Relief at 2 hrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>54.0</td>
<td>55.3</td>
<td>40.0</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>14.0</td>
<td>15.3</td>
<td>n/a</td>
</tr>
</tbody>
</table>
**SPARTAN: Results**

<table>
<thead>
<tr>
<th></th>
<th>Reyvow 50mg</th>
<th>Reyvow 100mg</th>
<th>Reyvow 200mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain Free at 2 hrs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>28.3</td>
<td>31.4</td>
<td>38.8</td>
<td>21.0</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>7.3</td>
<td>10.4</td>
<td>17.8</td>
<td>n/a</td>
</tr>
<tr>
<td>p-value (vs. Placebo)</td>
<td>0.006</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>MBS Free at 2 hrs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>40.8</td>
<td>44.0</td>
<td>48.7</td>
<td>33.2</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>7.6</td>
<td>10.8</td>
<td>15.5</td>
<td>n/a</td>
</tr>
<tr>
<td>p-value (vs. Placebo)</td>
<td>0.014</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>n/a</td>
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<tr>
<td><strong>Pain Relief at 2 hrs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>55.9</td>
<td>61.4</td>
<td>61.0</td>
<td>45.1</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>10.8</td>
<td>16.3</td>
<td>15.9</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Conclusion:** Reyvow demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.  

**Number Needed to Treat (NNT):**  
- **Primary outcome:** 6, 10, or 14 patients must be treated with Reyvow 200 mg, 100 mg, or Reyvow 50 mg respectively, for every one patient who achieves freedom from pain at 2 hours after study medication, relative to placebo. 7, 10, or 14 patients must be treated with Reyvow 200 mg, 100 mg, or Reyvow 50 mg respectively, for every one patient who achieves freedom from their MBS at 2 hours after study medication, relative to placebo.  
- **Secondary outcomes:** 7, 7, or 10 patients must be treated with Reyvow 200 mg, 100 mg, or Reyvow 50 mg respectively, for every one patient who achieves migraine pain relief at 2 hours after study medication, relative to placebo.  

**Number Needed to Harm (NNH):**  
- For every 384 patients treated for acute migraines with Reyvow, one patient discontinued Reyvow due to adverse effects, relative to placebo.
**FDA Approved Dosing:** 50 mg or 100 mg taken orally, as needed.

- If needed, a second dose may be administered at least 2 hours after the initial dose.
- Maximum dose in a 24-hour period is 200 mg.
- The safety of treating more than 8 migraines in a 30-day period has not been established.

**Available Strengths:** 50mg and 100mg oral tablets

**Clinically Significant Side Effects:**
- Nausea
- Somnolence
- Dry mouth

**Additional Warnings and Precautions:**
- Drug-Drug Interactions Impact Use:
  - Concomitant use with strong CYP3A4 inhibitors is **contraindicated**
  - Avoid concomitant use with strong CYP3A4 inducers
  - Dose adjustment recommended with: moderate CYP3A inhibitors; strong, moderate and weak CYP3A inducers; BCRP inhibitors; P-gp inhibitors
Dodick/Lipton et al.,
R, MC, DB, PC Phase 3 Trials

Randomization 1:1:1

Ubrelvy 25 mg (Lipton), 50 mg, 100 mg (Dodick) N=1,994
Placebo N=1,019

Patient eligibility criteria:
- Age 18 to 75
- ≥ 1-year history of migraine with onset before age 50
- History of 2-8 migraines/month with moderate to severe headache pain
- Migraines lasted between 4 and 72 hours with attacks separated by ≥ 48 hours of freedom from headache pain

Exclusion criteria:
- Chronic migraine
- Acute migraine treatment on 10 or more days/month
- Cardiovascular or cerebrovascular disease

Efficacy endpoints: assessed 2 hours after initial dose
- Co-primary: freedom from pain; absence of MBS
- Secondary: pain relief

2 hours

Primary analysis

4/24/2020
Conclusion: Ubrelvy demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

Number Needed to Treat (NNT):

- **Primary outcome:** Fourteen or 11 patients must be treated with Ubrelvy 50 mg or 100 mg, respectively, for one additional patient to achieve freedom from pain at 2 hours after study medication, relative to placebo. Ten or 11 patients must be treated with Ubrelvy 50 mg or 100 mg, respectively, for one additional patient to achieve freedom from their MBS at 2 hours after study medication, relative to placebo.
- **Secondary outcomes:** Nine patients must be treated with Ubrelvy 50 mg or 100 mg, for one additional patient to achieve migraine pain relief at 2 hours after study medication, relative to placebo.

Number Needed to Harm (NNH):

- For every 277 patients treated with Ubrelvy, one patient discontinued the study drug due to adverse effects.
### Lipton et al.: Results

<table>
<thead>
<tr>
<th></th>
<th>Ubrelvy 50mg</th>
<th>Ubrelvy 25mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain Free at 2 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>21.8</td>
<td>20.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>7.5</td>
<td>6.4</td>
<td>n/a</td>
</tr>
<tr>
<td><em>p</em>-value (vs. Placebo)</td>
<td>0.01</td>
<td>0.03</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>MBS Free at 2 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>38.9</td>
<td>34.1</td>
<td>27.4</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>11.5</td>
<td>6.7</td>
<td>n/a</td>
</tr>
<tr>
<td><em>p</em>-value (vs. Placebo)</td>
<td>0.01</td>
<td>0.07</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Pain Relief at 2 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>62.7</td>
<td>60.5</td>
<td>48.2</td>
</tr>
<tr>
<td>Difference from Placebo (%)</td>
<td>14.5</td>
<td>12.3</td>
<td>n/a</td>
</tr>
<tr>
<td><em>p</em>-value (vs. Placebo)</td>
<td>0.01</td>
<td>Not reported</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Conclusion**: Ubrelvy demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

**Number Needed to Treat (NNT):**
- **Co-primary outcomes**: Fourteen or 16 patients must be treated with Ubrelvy 50 mg or 25 mg, respectively, for one additional patient to achieve freedom from pain at 2 hours after study medication, relative to placebo. Nine or 15 patients must be treated with Ubrelvy 50 mg or 25 mg, respectively, for one additional patient to achieve freedom from their MBS at 2 hours after study medication, relative to placebo.
- **Secondary outcomes**: Seven or 9 patients must be treated with Ubrelvy 50 mg or 25 mg, respectively, for one additional patient to achieve migraine pain relief at 2 hours after study medication, relative to placebo.

**Number Needed to Harm (NNH):**
- For every 1,111 patients treated for acute migraines with Ubrelvy, one patient discontinued Ubrelvy due to adverse effects, relative to placebo.
Nurtec (rimegepant)

FDA Approved Dosing: 75 mg orally [PRN; swallowed or placed under tongue].
- Maximum dose in 24-hour period: 75 mg.
- Safety of treating > 15 migraines in 30-day period not established.

Available Strengths: 75mg ODT

Clinically Significant Side Effects:
- Nausea

Additional Warnings and Precautions:
- Drug-Drug Interactions Impact Use
  - Avoid with strong/moderate CYP3A4 inhibitors, strong/moderate CYP3A inducers, P-gp/BCRP inhibitors: avoid
Randomization 1:1

Nurtec ODT 75 mg PRN moderate/severe N=669

Placebo PRN moderate/severe N=682

Patient eligibility criteria:
- Adults, 1-year history of migraine, 2-8 moderate/severe migraines/month.
- Stable preventive medication for 3 months.

Exclusion criteria:
- Medical conditions with undue risk, recent alcohol/drug abuse, relevant allergies, ECG/lab findings that raised concerns re safety and tolerability.

Efficacy endpoints:
- Primary: 2 hours post dose: freedom from pain and most bothersome symptom – times one migraine

4/24/2020
**Croop R, et al.: Results**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Nurtec ODT 75 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Pain Free at 2 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>21.2</td>
<td>10.9</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MBS Free at 2 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>35.1</td>
<td>26.8</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*n=number of responders/N=number of patients in the treatment group

**Conclusion:** Nurtec ODT 75 mg demonstrated an effect on pain freedom and most bothersome symptom (MBS) freedom at two hours after dosing compared to placebo. Among patients who selected an MBS, the most commonly selected symptom was photophobia (54%), followed by nausea (28%), and phonophobia (15%).

**Number Needed to Treat (NNT):**
- **Primary outcome:** Ten patients must be treated with Nurtec ODT for one patient to achieve a pain freedom outcome at 2 hours after study medication (defined as a reduction of moderate or severe headache pain to no headache pain), relative to placebo.
- **Secondary outcomes:** Thirteen patients must be treated with Nurtec ODT for one patient to achieve freedom from their MBS at 2 hours after study medication (defined as the absence of the self-identified MBS (i.e., photophobia, phonophobia, or nausea)), relative to placebo.

**Number Needed to Harm (NNH):**
- Not applicable
Study Limitations:

- Long-term data needed to determine safety and tolerability
- Studies did not compare with existing acute migraine therapies (eg triptans)
  - CPAC Review: Fairly equal therapeutic outcomes anticipated with new agents and triptans however *efficacy* outcomes are better with triptans
- Reyvow study showed low frequency of likely CV treatment-emergent adverse events
  - Good option for those with CV risk factors contraindicating use of triptans

Cost is ~3x as much as generic oral triptans

New agents are appropriate after trial and failure or contraindication to triptans
Prophylaxis Treatment of Migraines

Consider prophylaxis when at least 4 migraines on average a month, or when frequency/severity significantly interferes with daily activities.
• No preference for a specific preventative medication and choice should be based on patient-specific factors

Prophylaxis Agents:
Oral Agents:
• Antiepileptics (e.g., divalproex sodium, topiramate)
• Beta-blockers (e.g., metoprolol, propranolol, timolol)
• Antidepressants (e.g., amitriptyline, venlafaxine)

Injectable Agents:
• Botox *Only indicated for chronic migraine
• CGRP antagonists (e.g., Aimovig, Ajovy, Emgality)

Menstrual Migraines: The use of hormone-based interventions to stabilize estrogen levels may eliminate or sufficiently minimize migraines when standard treatment for acute attacks is inadequate
• Note: estrogen containing contraceptive use may be limited in individuals who have migraine with aura

4/24/2020
New Prophylaxis Agents

Three Injectable Agents Approved in 2018 and another early 2020
• Indicated for preventative treatment of migraine in adults
  – Approved for use in both episodic AND chronic migraine

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Approval Date</th>
<th>Coverage Criteria in Place</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aimovig</td>
<td>May 17, 2018</td>
<td>CP.PMN.128 Erenumab-aaoe (Aimovig)</td>
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<tr>
<td>Ajovy</td>
<td>September 18, 2018</td>
<td>CP.PHAR.403/CP.PCH.17 Fremanezumab-vfrm (Ajovy)</td>
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<tr>
<td>Emgality</td>
<td>October 6, 2018</td>
<td>CP.PHAR.404/CP.PPA.344 Galcanezumab-gnlm (Emgality)</td>
</tr>
<tr>
<td>Vyepti</td>
<td>February 21, 2020</td>
<td>In development; expect to see in 3Q2020 materials</td>
</tr>
</tbody>
</table>

• Trillium OHP Preferred Agent (PA required): Aimovig
Aimovig (Erenumab)

FDA Approved Dosing: 70 mg SC once monthly.
• Dose may be increased to 140 mg SC once monthly

Dosage Forms:
• 70 mg/ml single-dose autoinjector or prefilled syringe

Clinically Significant Side Effects:
• Injection site reactions
• Constipation
STRIVE/ARISE:
(Episodic Migraine Prophylaxis)
P3, MC, R, DB, PC study

Randomization
[1:1:1]

Aimovig 70 mg SC monthly N=312*; N=282^
Aimovig 140 mg SC monthly N=318*
Placebo N=316*; N=288^  

Patient eligibility criteria:
- Age 18 to 65
- 12 month history of migraine (with or without aura)
- Episodic migraine

Exclusion criteria:
- Age >50 at migraine onset
- History of hemiplegic migraine or cluster headache
- Botulinum toxin use last 4 months; migraine prophylaxis device or procedure last 2 months
- No response to >2 migraine-preventative treatments

Efficacy endpoints:
- Primary: migraine days/month
- Secondary: ≥50% reduction in migraine days/month, number of acute migraine-specific medication use days

*STRIVE only
^ARISE only

4/24/2020
### STRIVE: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Aimovig 70 mg†</th>
<th>Aimovig 140 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.8 ± 0.2</td>
<td>-3.2 ± 0.2</td>
<td>-3.7 ± 0.2</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-1.4 (−1.9 to −0.9)</td>
<td>-1.9 (−2.3 to −1.4)</td>
</tr>
<tr>
<td>≥50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>84 (26.6)</td>
<td>135 (43.3)</td>
<td>159 (50.0)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>-</td>
<td>2.13 (1.52 to 2.98)</td>
<td>2.81 (2.01 to 3.94)</td>
</tr>
<tr>
<td>Days of use of acute migraine–specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.2 ± 0.1</td>
<td>-1.1 ± 0.1</td>
<td>-1.6 ± 0.1</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-0.9 (−1.2 to −0.6)</td>
<td>-1.4 (−1.7 to −1.1)</td>
</tr>
</tbody>
</table>

†P<0.001 for all pairwise comparisons between erenumab and placebo

**Conclusion:** Aimovig demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary outcome:** not applicable
- **Secondary outcomes:** 6 or 4 patients must be treated with Aimovig 70mg or Aimovig 140 monthly for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

**Number Needed to Harm (NNH):**
- For every 333 patients treated with either Aimovig 70mg or Aimovig 140mg, one patient discontinued the study drug due to adverse effects.

4/24/2020
## ARISE: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Aimovig 70 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td>−1.8 ± 0.2</td>
<td>−2.9 ± 0.2</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−1.8 ± 0.2</td>
<td>−2.9 ± 0.2</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>−1.0 (−1.6 to −0.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>85 (29.5)</td>
<td>112 (39.7)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>−1.59 (1.12 to 2.27)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Days of use of acute migraine–specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−0.6 ± 0.1</td>
<td>−1.2 ± 0.1</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>−0.6 (−1.0 to −0.2)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Aimovig demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary outcome:** not applicable
- **Secondary outcomes:** 10 patients must be treated with Aimovig 70mg monthly for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

**Number Needed to Harm (NNH):**
- For every 67 patients treated with either Aimovig 70mg or Aimovig 140mg, one patient discontinued the study drug due to adverse effects.

4/24/2020
Tepper S, et al.: (Chronic Migraine Prophylaxis)
Phase 2, MC, R, DB, PC study

Randomization [3:2:2]

Aimovig 70 mg SC monthly N=188
Aimovig 140 mg SC monthly N=187
Placebo N=281

4 week baseline

Patient eligibility criteria:
- Age 18 to 65
- 3 month history of migraine (with or without aura)
- Chronic migraine

Exclusion criteria:
- Age >50 at migraine onset
- History of hemiplegic migraine or cluster headache
- Botulinum toxin use last 4 months; migraine prophylaxis drugs last 2 months
- No response to >3 migraine-preventative treatments

Efficacy endpoints:
- Primary: migraine days/month
- Secondary: ≥50% reduction in migraine days/month, number of acute migraine-specific medication use days, cumulative headache days

12 weeks

Primary analysis

4/24/2020
Tepper S, et al.: Results

<table>
<thead>
<tr>
<th>Outcome†</th>
<th>Placebo</th>
<th>Aimovig 70 mg†</th>
<th>Aimovig 140 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-4.2 ± 0.4</td>
<td>-6.6 ± 0.4</td>
<td>-6.6 ± 0.4</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-2.5 (-3.5 to -1.4)</td>
<td>-2.5 (-3.5 to -1.4)</td>
</tr>
<tr>
<td>≥50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>66 (23)</td>
<td>75 (40)</td>
<td>77 (41)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>-</td>
<td>2.2 (1.5 to 3.3)</td>
<td>2.3 (1.6 to 3.5)</td>
</tr>
<tr>
<td>Days of use of acute migraine-specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.6 ± 0.2</td>
<td>-3.5 ± 0.3</td>
<td>-4.1 ± 0.3</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-1.9 (-2.6 to -1.1)</td>
<td>-2.6 (-3.3 to -1.8)</td>
</tr>
<tr>
<td>Cumulative monthly headache hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-55.2 ± 5.7</td>
<td>-64.8 ± 6.9</td>
<td>-74.5 ± 6.9</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-9.5 (-27 to 7.9)</td>
<td>-19.3 (-36.7 to -1.9)</td>
</tr>
</tbody>
</table>

†P≤0.001 for all pairwise comparisons between Aimovig and placebo, except for cumulative monthly headache hours, where only Aimovig 140 mg demonstrated a significant reduction compared to placebo (P=0.0296)

**Conclusion:** Aimovig demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary outcome:** not applicable
- **Secondary outcomes:** 6 patients must be treated with Aimovig 70mg or Aimovig 140mg monthly for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

**Number Needed to Harm (NNH):**
- **Aimovig 70mg:** not applicable. For every 333 patients treated with Aimovig 140mg, one patient discontinued the study drug due to adverse effects.

4/24/2020
**Ajovy** (Fremanezumab-vfrm)

**FDA Approved Dosing:** 225 mg SC once monthly or 675 mg SC every three months

**Dosage Forms:**
- 225 mg/1.5 mL single-dose prefilled syringe

**Clinically Significant Side Effects (≥5%):**
- Injection site reactions
Randomization [1:1:1]

Dodick, et al. (Episodic Migraine Prophylaxis): P3, MC, R, DB, PC Trial

- Ajovy 225 mg SC monthly N=290
- Ajovy 675 mg SC once N=291
- Placebo N=294

Patient eligibility criteria:
- Age 18 to 70
- 12 month history of migraine (with or without aura)
- Episodic migraine

Exclusion criteria:
- Age >50 at migraine onset
- Botulinum toxin use last 4 months; migraine prophylaxis device or procedure last 2 months
- No response to >2 migraine-preventative treatments

Efficacy endpoints:
- Primary: migraine days/month
- Secondary: ≥50% reduction in migraine days/month, number of acute migraine-specific medication use days
<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Placebo (N = 294)</th>
<th>Ajovy 225 mg (N = 290)</th>
<th>Ajovy 675 mg (N = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.2</td>
<td>-3.7</td>
<td>-3.4</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-1.5 (-2.01 to -0.93)</td>
<td>-1.3 (-1.79 to -0.72)</td>
</tr>
<tr>
<td>≥50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>81 (27.9)</td>
<td>137 (47.7)</td>
<td>128 (44.4)</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>19.8 (12 to 27.6)</td>
<td>16.5 (8.9 to 24.1)</td>
</tr>
<tr>
<td>Days of use of acute migraine–specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.6</td>
<td>-3.0</td>
<td>-2.9</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-1.4 (-1.84 to -0.89)</td>
<td>-1.3 (-1.76 to -0.82)</td>
</tr>
</tbody>
</table>

*p < 0.001 for all pairwise comparisons between Ajovy and placebo

**Conclusion:** Ajovy demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary Outcome:** not applicable
- **Secondary Outcome(s):** 6 patients must be treated with Ajovy 225 mg monthly (7 patients with Ajovy 675 mg every 3 months) for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

**Number Needed to Harm (NNH):**
- For episodic migraine prophylaxis, 99 patients treated with Ajovy 225 mg (151 patients treated with Ajovy 675 mg) to avoid one additional patient discontinuing the study drug due to adverse effects.
Silberstein, et al.  
(Chronic Migraine Prophylaxis):  
P3, MC, R, DB, PC Trial

Randomization
[1:1:1]

- Ajovy 225 mg SC monthly N=375
- Ajovy 675 mg SC once N=375
- Placebo N=371

4 week baseline

Patient eligibility criteria:
- Age 18 to 70
- 12 month history of migraine (with or without aura)
- Chronic migraine

Exclusion criteria:
- Age >50 at migraine onset
- Botulinum toxin use last 4 months; migraine prophylaxis device or procedure last 2 months
- No response to >2 migraine-preventative treatments

Efficacy endpoints:
- Primary: headache days/month
- Secondary: migraine days/month, ≥50% reduction in headache days/month, number of acute migraine-specific medication use days

12 weeks

Primary analysis

4/24/2020
<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Placebo</th>
<th>Ajovy 225 mg</th>
<th>Ajovy 675 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache days per month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−2.5 ± 0.3</td>
<td>−4.6 ± 0.3</td>
<td>−4.3 ± 0.3</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-</td>
<td>−2.1 ± 0.3</td>
<td>−1.8 ± 0.3</td>
</tr>
<tr>
<td><strong>Migraine days per month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−3.2 ± 0.4</td>
<td>−5.0 ± 0.4</td>
<td>−4.9 ± 0.4</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-</td>
<td>−1.8 ± 0.4</td>
<td>−1.7 ± 0.4</td>
</tr>
<tr>
<td><strong>≥50% Reduction from baseline in headache days per month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>67 (18)</td>
<td>153 (41)</td>
<td>141 (38)</td>
</tr>
<tr>
<td><strong>Days of use of acute migraine–specific medication per month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−1.9 ± 0.3</td>
<td>−4.2 ± 0.3</td>
<td>−3.7 ± 0.3</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-</td>
<td>−2.3 ± 0.3</td>
<td>−1.8 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.001 for all pairwise comparisons between Ajovy and placebo

**Conclusion:** Ajovy demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary Outcome:** not applicable
- **Secondary Outcome(s):** 5 patients must be treated with monthly or quarterly Ajovy for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

**Number Needed to Harm (NNH):**
- For chronic migraine prophylaxis, 344 patients treated with monthly Ajovy (120 patients treated with quarterly Ajovy) to avoid one additional patient discontinuing the study drug due to adverse effects
Emgality (Galcanezumab-gnlm)

FDA Approved Dosing: One time loading dose of 240 mg, followed by monthly 120 mg dose injected subcutaneously.

Dosage Forms:
- 120 mg/mL single-dose prefilled pen
- 120 mg/mL single-dose prefilled syringe

Clinically Significant Side Effects:
- Injection site reactions
- Anaphylaxis - Postmarketing
Randomization 2:1:1

- Emgality SC 240 mg loading dose + 120 mg once monthly (N = 210; 231)
- Emgality SC 240 mg once monthly (N = 208; 223)
- Placebo (N = 425; 461)

Patient eligibility criteria:
- Age 18 to 65 years
- Diagnosis of migraine for at least 1 year prior to enrollment
- Experienced 4 to 14 migraine headache days (MHDs) and ≥ 2 migraine attacks per month during baseline period
- Migraine onset prior to age 50 years

Exclusion criteria:
- History of failure to 3 or more classes of migraine preventive treatments
- Currently receiving preventive migraine medication within 30 days of the baseline period (4 months for botulinum toxin-A or toxin-B)

Efficacy endpoints:
- Primary: Mean change of monthly MHDs from baseline to month 6
- Secondary: Proportion of patients with reduction in monthly MHDs (≥ 50%, 75%, and 100% response rates), MHDs requiring acute medication use

Primary analysis 4/24/2020
## EVOLVE-1: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Emgality 120 mg†</th>
<th>Emgality 240 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline</td>
<td>-2.8</td>
<td>-4.7</td>
<td>-4.6</td>
</tr>
<tr>
<td>LS mean change difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-1.9 (-2.5 to -1.4)</td>
<td>-1.8 (-2.3 to -1.2)</td>
</tr>
<tr>
<td>≥50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients, %</td>
<td>38.6</td>
<td>62.3</td>
<td>60.9</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>-</td>
<td>2.6 (2.0 to 3.4)</td>
<td>2.5 (1.9 to 3.2)</td>
</tr>
<tr>
<td>Days of use of acute migraine–specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline</td>
<td>-2.2</td>
<td>-4.0</td>
<td>-3.8</td>
</tr>
<tr>
<td>LS mean change difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-1.8 (-2.3 to -1.3)</td>
<td>-1.6 (-2.1 to -1.1)</td>
</tr>
</tbody>
</table>

†P<0.001 for all pairwise comparisons between Emgality and placebo

**Conclusion:** Emgality demonstrated a statistically significant reduction in migraine days per month compared to placebo.

**Number Needed to Treat (NNT):**

**Primary Outcome:** not applicable

**Secondary outcome(s):**

- Five patients must be treated with Emgality for one additional patient to experience at least a 50% reduction in migraine days per month. Six patients must be treated with Emgality for one additional patient to experience at least a 75% reduction in migraine days per month. Eleven patients must be treated with Emgality 120 mg and 12 patients must be treated with Emgality 240 mg for one additional patient to experience a 100% reduction in migraine days per month.

**Number Needed to Harm (NNH):**

- For every 52 patients treated for episodic migraine, one patient discontinued Emgality 120 mg due to adverse effects. For every 100 patients treated for episodic migraine, one patient discontinued Emgality 240 mg due to adverse effects.
**EVOLVE-2: Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Emgality 120 mg†</th>
<th>Emgality 240 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline (95% CI)</td>
<td>-2.3 (-2.7 to -1.9)</td>
<td>-4.3 (-4.8 to -3.8)</td>
<td>-4.2 (-4.7 to -3.7)</td>
</tr>
<tr>
<td>LS mean change difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-2.0 (-2.6 to -1.5)</td>
<td>-1.9 (-2.4 to -1.4)</td>
</tr>
<tr>
<td>≥ 50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients, % (95% CI)</td>
<td>36 (33 to 39)</td>
<td>59.3 (55 to 64)</td>
<td>56.5 (52 to 61)</td>
</tr>
<tr>
<td>Days of use of acute migraine–specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline (95% CI)</td>
<td>-1.9 (-2.2 to -1.5)</td>
<td>-3.7 (-4.1 to -3.2)</td>
<td>-3.6 (-4.1 to -3.2)</td>
</tr>
</tbody>
</table>

†P<0.001 for all pairwise comparisons between Emgality and placebo

**Conclusion:** Emgality demonstrated a statistically significant reduction in migraine days per month compared to placebo. 

**Number Needed to Treat (NNT):**
- **Primary Outcome:** not applicable
- **Secondary outcome(s):** Five patients must be treated with Emgality for one additional patient to experience at least a 50% reduction in migraine days per month. Seven patients must be treated with Emgality for one additional patient to experience at least a 75% reduction in migraine days per month. Eighteen patients must be treated with Emgality 120 mg and 13 patients must be treated with Emgality 240 mg for one additional patient to experience a 100% reduction in migraine days per month.

**Number Needed to Harm (NNH):**
- For every 238 patients treated for episodic migraine, one patient discontinued Emgality 120 mg due to adverse effects.
- For every 43 patients treated for episodic migraine, one patient discontinued Emgality 240 mg due to adverse effects.

4/24/2020
REGAIN: (Chronic Migraine Prophylaxis) MC, DB, R, PC, P3 Study

Randomization 2:1:1

- Emgality SC 240 mg loading dose + 120 mg once monthly (N = 273)
- Emgality SC 240 mg once monthly (N = 274)
- Placebo (N = 538)

Patient eligibility criteria:
- Age 18 to 65 years
- Diagnosis of migraine for at least 1 year prior to enrollment
- Chronic migraine defined as ≥ 15 headache days per month, of which at least 8 are MHDs
- Migraine onset prior to age 50 years

Exclusion criteria:
- History of persistent daily headache, cluster headache, or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine and migraine with brainstem aura (basilar-type migraine)

Efficacy endpoints:
- Primary: Mean change of monthly MHDs from baseline to month 3
- Secondary: Proportion of patients with reduction in monthly MHDs (≥ 50%, 75%, and 100% response rates), MHDs requiring acute medication use
REGAIN: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Emgality 120 mg†</th>
<th>Emgality 240 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline</td>
<td>-2.74</td>
<td>-4.83</td>
<td>-4.62</td>
</tr>
<tr>
<td>LS mean change difference vs. placebo</td>
<td>-</td>
<td>-2.09</td>
<td>-1.88</td>
</tr>
<tr>
<td>≥ 50% Reduction from baseline in migraine days per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients, %</td>
<td>15.4</td>
<td>27.6</td>
<td>27.5</td>
</tr>
<tr>
<td>Days of use of acute migraine-specific medication per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline</td>
<td>-2.23</td>
<td>-4.74</td>
<td>-4.25</td>
</tr>
</tbody>
</table>

†P<0.001 for all pairwise comparisons between Emgality and placebo

Conclusion: Emgality demonstrated a statistically significant reduction in migraine days per month compared to placebo.

Number Needed to Treat (NNT):
Primary Outcome: not applicable
Secondary outcome(s): Nine patients must be treated with Emgality for one additional patient to experience at least a 50% reduction in migraine days per month. Forty patients must be treated with Emgality 120 mg and 24 patients must be treated with Emgality 240 mg for one additional patient to experience at least a 75% reduction in migraine days per month.

Number Needed to Harm (NNH):
Emgality 120 mg: not applicable. For every 277 patients treated for episodic migraine, one patient discontinued Emgality 240 mg due to adverse effects.
FDA Approved Dosing: 100 mg IV every 3 months.
• Some patients may benefit from a dosage of 300 mg IV every 3 months.

Dosage Forms:
• Single-dose vial: 100 mg/mL

Clinically Significant Side Effects:
• Nasopharyngitis
• Hypersensitivity
**PROMISE-I: (Episodic Migraine Prophylaxis)**  
MC, DB, R, PC, P3 Study

Randomization 1:1:1:1

- **Vyepti 30 mg (N = 223)**
- **Vyepti 100 mg (N = 221)**
- **Vyepti 300 mg (N = 222)**
- **Placebo (N = 222)**

**Primary analysis**

- **56 wks**
- **0 wks**
- **12 wks**

**Patient eligibility criteria:**
- Age 18 to 75 years
- Diagnosis of migraine for at least 1 year prior to enrollment
- Experienced ≤ 14 headache days per month and ≥ 4 monthly migraine days (MMDs) during pre-screening period
- Migraine onset prior to age 50 years
- Allowed use of acute migraine medication

**Exclusion criteria:**
- Regular use (>7 days) prophylactic headache medication within 3 months prior to randomization
- Botulinum toxin injections in the head, face, or neck within 5 months of randomization

**Efficacy endpoints:**
- **Primary:** Mean change in MMDs over weeks 1-12
- **Secondary:** Proportion of patients with reduction in migraine (≥ 75% MRR over weeks 1-4, ≥ 75% MRR over weeks 1-12, ≥ 50% MRR over weeks 1-12), and proportion of patients with a migraine on the day after dosing

4/24/2020
## PROMISE-I: Results

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Placebo</th>
<th>Vyepti 100 mg</th>
<th>Vyepti 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Monthly Migraine Days (MMDs), weeks 1-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-3.2</td>
<td>-3.9</td>
<td>-4.3</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>-0.7 (-1.3 to -0.1)</td>
<td>-1.1 (-1.7 to -0.5)</td>
</tr>
<tr>
<td>≥ 75% Reduction from baseline in migraine days per month, weeks 1-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients, %</td>
<td>20.3</td>
<td>30.8</td>
<td>31.5</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>10.5 (2.4 to 18.6)</td>
<td>11.2 (3.2 to 19.3)</td>
</tr>
<tr>
<td>≥ 75% Reduction from baseline in migraine days per month, weeks 1-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients, %</td>
<td>16.2</td>
<td>22.2</td>
<td>29.7</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>6.0 (-1.4 to 13.3)</td>
<td>13.5 (5.8 to 21.2)</td>
</tr>
<tr>
<td>50% Reduction from baseline in migraine days per month, weeks 1-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients, %</td>
<td>37.4</td>
<td>49.8</td>
<td>56.3</td>
</tr>
<tr>
<td>Difference vs. placebo (95% CI)</td>
<td>-</td>
<td>12.4 (3.2 to 21.5)†</td>
<td>18.9 (9.8 to 28.0)</td>
</tr>
</tbody>
</table>

* Vyepti 30 mg outcomes & secondary endpoint of proportion of patients with a migraine on the day after dosing outcomes not reported as they failed to be statistically significant; † endpoints failed to be statistically significant due to a failed test earlier in the serial testing algorithm (based on serial procedure used to account for multiplicity in doses and endpoints, in line with industry guidance issued by US FDA

**Conclusion:** Vyepti demonstrated a statistically significant reduction in MMDs compared to placebo.

**Number Needed to Treat (NNT):**
- **Primary outcome:** Not applicable
- **Secondary outcomes:** Ten patients must be treated with Vyepti 100 mg and 9 patients with Vyepti 300 mg for one additional patient to experience at least a 75% reduction in migraine days per month in the first month after treatment. Eight patients must be treated with Vyepti 300 mg for one additional patient to experience at least a 75% reduction in migraine days per month within 3 months after treatment. Nine patients must be treated with Vyepti 100 mg and 6 patients with Vyepti 300 mg for one additional patient to experience at least a 50% reduction in migraine days per month within 3 months after treatment.

**Number Needed to Harm (NNH):**
- For every 37 patients treated for episodic migraine, one patient discontinued Vyepti 30 mg due to adverse effects. For every 8134 patients treated for episodic migraine, one patient discontinued Vyepti 100 mg due to adverse effects. For every 222 patients treated for episodic migraine, one patient discontinued Vyepti 300 mg due to adverse effects.
PROMISE-II
(Chronic Migraine Prophylaxis):
P3, MC, DB, R, PC Study

Randomization 1:1:1

0 wks

Vyepti 100 mg IV q 3 months (n = 356)

Vyepti 300 mg IV q 3 months (n = 350)

Placebo (n = 366)

12 wks

Primary analysis

36 wks

Patient eligibility criteria:
- Age 18 to 65 years
- Diagnosis of migraine for ≥1 year prior to enrollment
- Experienced ≥ 15 to ≤ 26 headache days per month and ≥ 8 MMDs during screening period
- Migraine onset prior to age 50 years
- Allowed use and continuation of an established stable regimen of acute migraine or headache preventive medication

Exclusion criteria:
- Botulinum toxin injections in the head or neck within 5 months of randomization

Primary Efficacy endpoint:
- Mean change from baseline in MMDs over months 1 through 3

Secondary Efficacy endpoints:
- Proportion of patients with a ≥ 75% reduction from baseline in MMDs over months 1 through 3
- Proportion of patients with a ≥ 50% reduction from baseline in MMDs over months 1 through 3

4/24/2020
## PROMISE-II: Results

### Mean Monthly Migraine Days (MMDs), months 1-3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Vyepti 100 mg†</th>
<th>Vyepti 300 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline</td>
<td>-5.6</td>
<td>-7.7</td>
<td>-8.2</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-</td>
<td>-2.0</td>
<td>-2.6</td>
</tr>
</tbody>
</table>

### ≥ 75% Reduction from baseline in migraine days per month, months 1-3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Vyepti 100 mg†</th>
<th>Vyepti 300 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients, %</td>
<td>15.0</td>
<td>26.7</td>
<td>33.1</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-</td>
<td>11.7</td>
<td>18.1</td>
</tr>
</tbody>
</table>

### 50% Reduction from baseline in migraine days per month, months 1-3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Vyepti 100 mg†</th>
<th>Vyepti 300 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients, %</td>
<td>39.3</td>
<td>57.6</td>
<td>61.4</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>-</td>
<td>18.2</td>
<td>22.1</td>
</tr>
</tbody>
</table>

† p < 0.001 for all pairwise comparisons between Vyepti and placebo

### Conclusion

Vyepti demonstrated a statistically significant reduction in MMDs compared to placebo.

### Number Needed to Treat (NNT):

- **Primary outcome**: Not applicable
- **Secondary outcomes**: Nine patients must be treated with Vyepti 100 mg and 6 patients with Vyepti 300 mg for one additional patient to experience at least a 75% reduction in migraine days per month in the first month after treatment. Six patients must be treated with Vyepti 100 mg and 5 patients with Vyepti 300 mg for one additional patient to experience at least a 50% reduction in migraine days per month within 3 months after treatment.

### Number Needed to Harm (NNH):

- Not calculable
Trillium OHP Utilization

1st Quarter 2020 Paid Claims:
- New Acute Treatment Agents: None
- New Prophylactic Treatment Agents:
  - Aimovig: 31 paid claims for 17 utilizers
  - Ajovy: 2 paid claims for 1 utilizer
  - Emgality: 8 paid claims for 4 utilizers

1st Quarter 2020 PA Requests:
- New Acute Treatment Agents: None
- New Prophylactic Treatment Agents:
  - Aimovig: 19 requests; 63% approval rate
  - Ajovy: 2 requests; 100% approval rate
  - Emgality: 3 requests; 100% approval rate
References


Thanks to Envolve Pharmacy Solution (Pharmacy Benefit Manager) for providing the content presented in the clinical study slides

• Contents adapted from the new drug presentations given at CPAC (clinical pharmacy advisory committee) and from the type 1 drug reviews produced for P&T committee review

4/24/2020