MIGRAINE: Management Update

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Disclosure: Research, Consultant, Speaker
for Alder, Allergan, Amgen, Avinor, Biohaven, Lundbeck, Novartis, Supernus, Teva

Off-Labeled use of Medications will be discussed
Objectives:

• UNCOVERING THE PATIENT BURDEN
• WHY PATHOPHYSIOLOGY
• NEW TREATMENT STRATEGIES
Migraine is a **LONG-TERM NEUROLOGICAL DISEASE** with **DEBILITATING SYMPTOMS** that impact patients, society, and the healthcare system\(^1\text{-}^6\)

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Case Study MN

MN is a 39-year-old woman with a history of migraine with and without aura [visual] since adolescence. Initially she had headaches 1-2 times monthly until her late 20s. Presently her headaches are occurring 2 times weekly lasting 1-2 days. In the last 3 months she has an average of 12 headache days per month. Her MIDAS is 55 and she has been in the ER one time in the last month for status migrainosus.

Past medical history: Hypertension, tx. with Candesartan

Physical examination: Normal

Past medications: She had an initial trial of propanolol in her late 20s which was unsuccessful.
Diagnostic Criteria for Migraine (ICHD-3-beta)

History of ≥5 headache attacks that last 4-72 hours, with at least 2 of the following features:
- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravated by, or causing avoidance of, routine physical activity

Headache is accompanied by at least 1 of:
- Nausea and/or vomiting
- Phonophobia and/or photophobia

May be accompanied by aura:
Spreads gradually, affecting visual, sensory, speech/language, or motor function

Chronic migraine:
- Headache on ≥15 days/months for at least 3 months
- Features of migraine on at least 8 days/month

A PERSISTENT DISEASE WITH ACUTE ATTACKS

• THE CONTINUUM OF MIGRAINE FREQUENCY

Different Phases of Migraine

**Premonitory hours-days**
- Hypersensitivity to light, sound, and touch\(^2,5\)
- Headache
- Anxiety
- Nausea

**Interictal**
-Depression
- Nausea
- Photophobia
- Cognitive dysfunction\(^2,3\)
-Fatigue

**Postdrome hours-days**
- Throbbing headache\(^2,7,8\)
- Nausea
- Vomiting
- Photophobia

**Headache 4–72 h**
- Yawning\(^2,3,4\)
- Fatigue
- Nausea
- Mood changes

**Aura <1 h**
- Scintillating scotoma\(^1,6\)
- Visual distortion
- Pins and needles
- Phonophobia
- Cognitive dysfunction
- Congestion
- Allodynia

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A DISABLING DISEASE
• THE PROGRESSIVE IMPACT OF MIGRAINE

Migraine Disability Assessment Scale (MIDAS)

MIDAS SCORE CATEGORIES:
- Little or no disability (score 0–5)
- Mild disability (score 6–10)
- Moderate disability (score 11–20)
- Severe disability (score 21–40)
- Very severe disability (score 41–270)

Disability progressively increased with increasing frequency of headache days


Headache-Related Disability by Monthly Headache Frequency (N=8,281)

• In patients with episodic migraine of 4 to 6 headaches per month, ~70% experienced moderate to severe disability
• In chronic migraine patients with ≥15 headaches per month, as many as 90% had moderate to very severe disability
**THE Debilitating impact OF MIGRAINE**

- MIGRAINE IMPOSES SIGNIFICANT BURDEN ON PATIENTS’ LIVES

<table>
<thead>
<tr>
<th>Impact of migraine on patients’ family and social lives based on the CaMEO study (n=4,022)</th>
<th>In a study of work impact of migraine with the AMPP data (n=6,204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed their share of housework in past month</td>
<td>67%</td>
</tr>
<tr>
<td>Missed family activities in past month</td>
<td>66%</td>
</tr>
<tr>
<td>Missed an important event (wedding, graduation, etc) in past month</td>
<td>25%</td>
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**Missed work days (≥1 day per week) in the past 2 weeks**

- **8%** OF EPISODIC MIGRAINE PATIENTS*
- **11%** OF CHRONIC MIGRAINE PATIENTS†

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AMPP = American Migraine Prevalence and Prevention; CaMEO = Chronic Migraine Epidemiology and Outcomes.

*Moderate episodic migraine patients assessed for missed work days had >3 to <10 headache days/month and for family life had 5-9 headache days/month.†

†Chronic migraine patients assessed in both studies had ≥15 headache days/month.

MIGRAINE PATHOPHYSIOLOGY

involves multiple processes
in the central and peripheral nervous system (CNS and PNS)\textsuperscript{1,2}

Pathophysiology of Migraine: Is Becoming Better Understood

• A key pathway for pain in migraine may be the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second order neurons in the trigeminocervical complex

• The headache phase of a migraine attack is thought to originate in activation of nociceptors innervating pial, arachnoid and dural blood vessels, as well as large cerebral arteries and sinuses

TRIGEMINAL NERVE INNERVATES MENINGEAL BLOOD VESSELS & RELEASES NEUROPEPTIDES, SUCH AS CGRP

Trigeminal nerve signals to the meningeal blood vessels by secreting neuropeptides, including CGRP, which signals through its corresponding receptor.\textsuperscript{1,2}
RECURRENT ACTIVATION OF TRIGEMINAL PATHWAY CAN FACILITATE PERIPHERAL AND CENTRAL SENSITIZATION

Frequent activation of the trigeminal system contributes to the development and maintenance of sensitization at the PNS and CNS.¹²
CGRP: A KEY PLAYER IN MIGRAINE PATHOPHYSIOLOGY\textsuperscript{1,2} CGRP levels are elevated during migraine attack\textsuperscript{3}

CGRP = calcitonin gene-related peptide.
*Plasma CGRP levels measured from external jugular blood.\textsuperscript{3}

Evidence Suggests CGRP May Play a Causal Role in Migraine

Each line represents a patient who received CGRP infusion\(^1\)

9 patients infused with CGRP\(^1\)

- All eventually developed a headache
- 8 of 9 experienced an immediate headache
- 3 of 9 had a migraine attack during the delayed period

CGRP = calcitonin gene-related peptide.

CGRP receptors are located at several sites within the trigeminal pathway

CGRP receptors are found in multiple areas:\(^1,2\):
- Meningeal vessels
- Trigeminal ganglion
- Brainstem (e.g., TNC)
- Brain (e.g., thalamus)

CGRP receptors are expressed on numerous cell types:\(^3\):
- Vascular smooth muscle cells
- Neurons
- Glial cells
- Mast cells

CGRP = calcitonin gene-related peptide; CLR = calcitonin receptor-like receptor; RAMP = receptor activity modifying protein.
CGRP may be expressed in additional brain regions in which CGRP receptor localization has not been established.

General Principles for Migraine Management\textsuperscript{1,2}

- Migraine treatment goals may include:
  - Relieving symptoms and restoring function
  - Reducing headache frequency and severity
  - Reducing headache-related disability
  - Preventing disease progression

<table>
<thead>
<tr>
<th>ACUTE TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieve rapid pain relief during an attack, and improve function and reduce disability</td>
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<table>
<thead>
<tr>
<th>PREVENTIVE TREATMENT</th>
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</thead>
<tbody>
<tr>
<td>Reduce migraine attack frequency, severity, and disability</td>
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</table>

Preventive therapy is effective for some patients. Studies indicate that ~45% of patients receiving preventive therapy will experience a reduction in the mean monthly frequency of migraine attacks by ≥50%.3,4

Challenges of PREVENTIVE MIGRAINE TREATMENTS

Two-thirds of PEOPLE who are candidates for PREVENTIVE migraine treatment don’t use it\(^1\)

~80% of PATIENTS are nonadherent with oral preventive therapy after 12 months of treatment\(^2,\)*

*Retrospective claims analysis of a US claims database (Truven MarketScan Databases) was queried to identify patients who were ≥18 years of age, diagnosed with chronic migraine, and initiated an oral migraine preventive medication (antidepressants, beta blockers, or anticonvulsants) between January 1, 2008, and September 30, 2012 (N=8,688).

Patient-reported Reasons for Discontinuation of Preventive treatment

• LACK OF EFFICACY AND/OR MEDICATION SIDE EFFECTS ARE THE COMMON REASONS FOR DISCONTINUATION OF PREVENTIVE TREATMENT\(^1\)

IBMS-II assessed preventive therapy patterns in 1,165 patients with migraine\(^1\)

IBMS = International Burden of Migraine Study.
Preventive Treatments for Migraine

• Preventive treatments are crucial\textsuperscript{1}
• Evidence-based guidelines are available\textsuperscript{1-7}
• \textit{Previously approved preventive treatments were not designed specifically for migraine}\textsuperscript{1}
• Preventive treatments are underutilized\textsuperscript{1}:

Case Study MN

MN is a 39-year-old woman with a history of migraine with and without aura [visual] since adolescence. Initially she had headaches 1-2 times monthly until her late 20s. Presently her headaches are occurring 2 times weekly lasting 1-2 days. In the last 3 months she has an average of 12 headache days per month. Her Midas is 55 and she has been in the ER one time in the last month for status migrainosus.

Past medical history: Hypertension, tx. with Candesartan

Physical examination: Normal

Past medications: She had an initial trial of propanolol in her late 20s which was unsuccessful.
When Should Patients Be Considered for Preventive Treatment?

- Attacks frequently interfere with patients’ daily routines despite acute treatment
- Frequent attacks (≥4 MHDs)
- Contraindication to, failure, or overuse of acute treatments
- AEs with acute treatments
- Patient preference
Table below is taken directly from the AHS Position Statement:

<table>
<thead>
<tr>
<th>Established efficacy</th>
<th>Probably effective</th>
<th>Possibly effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic drugs</td>
<td>Antidepressants</td>
<td>ACE inhibitors: Lisinopril</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Amitriptyline</td>
<td>Alpha-agonists</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Venlafaxine</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Beta-blockers</td>
<td>Guanfacine</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Atenolol</td>
<td>Antiepileptic drugs: Carbamazepine</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Nadolol</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td>Nebivolol</td>
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<tr>
<td>Timolol</td>
<td></td>
<td>Pindolol</td>
</tr>
<tr>
<td>Triptans: Frovatriptan</td>
<td></td>
<td>Antihistamines: Cyproheptadine</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td></td>
<td>Angiotensin receptor blockers: Candesartan</td>
</tr>
</tbody>
</table>

Case Study MN

• After an adequate trial of topiramate patient failed to respond with a decrease in frequency or severity of her migraines.

• The patient informs you that after searching the Internet she wants to try one of the new FDA approved medications for the prevention of migraine, a CGRP antagonist.
Considerations on Guidelines for Migraine Prevention in the Anti-CGRP Era
Synopsis of American Headache Society Consensus Statement
Emerging Options for Treating Migraine

- CGRP is crucial in the pathophysiology of migraine\(^1\)
- mAbs that target CGRP are a mechanism-based and disease-specific class of preventive treatments developed for migraine\(^2\)
- mAbs targeting CGRP have been shown to be effective\(^2\)
- mAbs targeting CGRP are effective in patients who have failed prior preventives and those on concurrent oral preventives\(^2\)
Considerations for Initiating Treatment With Anti-CGRPs

A. Prescribed by a licensed medical provider

B. Patient is at least 18 years of age

C. Diagnosis of ICHD-3 migraine with or without aura (4–7 monthly headache days) and both of the following:
   a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
      1. Topiramate
      2. Divalproex sodium/valproate sodium
      3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
      4. Tricyclic antidepressant: amitriptyline, nortriptyline
      5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
   b. At least moderate disability (MIDAS>11, HIT-6>50)

Considerations for Initiating Treatment With Anti-CGRPs (cont)

D. Diagnosis of ICHD-3 migraine with or without aura‡ (8–14 monthly headache days) and inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
   a. Topiramate
   b. Divalproex sodium/valproate sodium§
   c. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
   d. Tricyclic antidepressant: amitriptyline, nortriptyline
   e. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
   f. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

Considerations for Initiating Treatment With Anti-CGRPs (cont)

E. Diagnosis of ICHD-3 chronic migraine\textsuperscript{1} and EITHER a or b:

a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
   1. Topiramate
   2. Divalproex sodium/valproate sodium\textsuperscript{8}
   3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
   4. Tricyclic antidepressant: amitriptyline, nortriptyline
   5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
   6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

b. Inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA

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Measuring Response to Emerging Preventive Options

• Measuring response to anti-CGRP mAbs will be both patient- and HCP-dependent
• Many patients do not achieve a reduction of at least 50% in MHDs after the first dose
• Benefits of anti-CGRP mAbs may be assessed after 3 months for monthly treatments and 6 months for quarterly treatments

Case Study MN

Two months after starting a CGRP antagonist, MN reports a decrease in headache frequency of 25%. The patient wants to change to another CGRP antagonist. What is your next best preventative migraine treatment choice:

1. Changed back to an oral preventive therapy
2. Add Vitamin B2, riboflavin
3. Continue the present CGRP antagonist for other 4 months
4. Change to another CGRP antagonist
Case Study MN

MN continued the initial CGRP antagonist for 6 months total and continues to report a decrease in headache frequency of 25%, MIDAS is 50.

Your next best step in migraine preventive therapy is:

1. Changed to another CGRP antagonist
2. Go back to MN’s original oral preventive therapy
3. Add magnesium daily
4. Recommend aerobic exercise
What Criteria Warrant Continuation of Anti-CGRP Therapy?

1. Reduction in mean MHDs of ≥50% relative to the pretreatment baseline (diary documentation or healthcare provider attestation)†‡
2. A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:
   a. MIDAS
      i. Reduction of ≥5 points when baseline score is 11-20
      ii. Reduction of ≥30% when baseline score is >20
   b. MPFID
      i. Reduction of ≥5 points
   c. HIT-6
      i. Reduction of ≥5 points

*Initial authorization: 3 months for treatments administered monthly; for treatments delivered quarterly (every 3 months), 2 cycles of treatment (6 months).
†Headache day defined as day in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least moderate level or days in which acute migraine-specific medication (triptans or ergots) was used to treat a headache of any severity or duration.‡ Efficacy is variable; successful therapeutic outcomes depend not only on a reduction in MHD frequency, but also on the persistence and severity of pain and associated symptoms, level of disability, and functional capacity.
Case Study MN

You change to another CGRP antagonist and after two months MN reports a decrease in her headache frequency by 50%, MIDAS is 15. Your next best step in migraine preventive therapy is:

1. Continue the present CGRP antagonist
2. Stop the present CGRP antagonist
3. Add Vitamin B12
4. Changed back to a different oral preventive therapy
Antibodies against the ligand are thought to remove excessive CGRP that is released at the perivascular trigeminal sensory nerve fibers, while the receptor antibody is thought to block CGRP signaling.

CGRP Monoclonal Antibodies
FDA Approved 2018

**Erenumab**: injection is indicated for the preventive treatment of migraine in adults.

**Fremanezumab**: injection is indicated for the preventive treatment of migraine in adults.

**Galcanezumab**: injection is indicated for the preventive treatment of migraine in adults.
CGRP Monoclonal Antibodies
FDA Approved 2018

Erenumab: injection is indicated for the preventive treatment of migraine in adults.

Fremanezumab: injection is indicated for the preventive treatment of migraine in adults.

Galcanezumab: injection is indicated for the preventive treatment of migraine in adults.
12-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trials in Patients With Chronic (HALO-CM) and Episodic (HALO-EM) Migraine \(^1-^3\)

**Baseline Period**
- Run-in
- **Endpoint Evaluation**
  - Fremanezumab-vfrm injection Quarterly
  - Fremanezumab-vfrm injection Monthly
  - Placebo

**Visit**
- Week -4
- Visit 1
- Randomization [1:1:1]
- **Week 0**
- **Week 4**
- **Week 8**
- **Week 12**
- Assessment of primary endpoint

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Please see Important Safety Information and Full Prescribing Information
Primary and Secondary Endpoints Studied in Phase 3 HALO Trials\textsuperscript{1-4}

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINTS</th>
<th>Halo-CM</th>
<th>Halo-EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 12 weeks: reduction from baseline in the average number of</td>
<td>Headache days</td>
<td>Headache days</td>
</tr>
<tr>
<td></td>
<td>Migraine days</td>
<td>Migraine days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY ENDPOINTS</th>
<th>Halo-CM</th>
<th>Halo-EM</th>
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<tbody>
<tr>
<td>Over 12 weeks: reduction in the average number of</td>
<td>Migraine days</td>
<td>Migraine days</td>
</tr>
<tr>
<td>Migraine days</td>
<td>Headache days</td>
<td>Headache days</td>
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<tr>
<td>Percentage of patients with ≥50% reduction in monthly average number of</td>
<td>Migraine days</td>
<td>Migraine days</td>
</tr>
<tr>
<td>Headache days</td>
<td>Migraine days</td>
<td>Migraine days</td>
</tr>
<tr>
<td>Over 12 weeks: reduction in the monthly average number of</td>
<td>Acute med. days</td>
<td>Acute med. days</td>
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<tr>
<td>Acute med. days</td>
<td>Acute med. days</td>
<td></td>
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<tr>
<td>Over 4 weeks: reduction in the average number of</td>
<td>Headache days</td>
<td>Migraine days</td>
</tr>
<tr>
<td>Migraine days</td>
<td>Migraine days</td>
<td></td>
</tr>
<tr>
<td>Over 12 weeks: reduction in patients not receiving concomitant migraine preventives, in the monthly average of</td>
<td>Headache days</td>
<td>Headache days</td>
</tr>
<tr>
<td>Headache days</td>
<td>Migraine days</td>
<td></td>
</tr>
<tr>
<td>At Week 12: reduction in the average score</td>
<td>HIT-6 score</td>
<td>MIDAS score</td>
</tr>
<tr>
<td>MIDAS score</td>
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</tbody>
</table>

Patients on Fremanezumab-vfrm injection demonstrated significant improvements across all 25 primary and secondary endpoints studied\textsuperscript{3,4}

- **Headache day**: a calendar day in which headache pain lasted at least 4 consecutive hours and had a peak severity of at least a moderate level, or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any severity or duration. **Migraine day**: a calendar day with at least 2 consecutive hours in Halo-EM, and 4 consecutive hours in Halo-CM, of a headache meeting criteria for migraine (with or without aura) or probable migraine, or a calendar day on which headache of any duration was treated with migraine-specific medications.
- **HIT-6, 6-item Headache Impact Test. MIDAS, Migraine Disability Assessment.**

Please see Important Safety Information and Full Prescribing Information
Baseline Demographic and Disease Characteristics Were Similar Across Study Groups\textsuperscript{1-3}

<table>
<thead>
<tr>
<th></th>
<th>HALO-Chronic Migraine</th>
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<th>HALO-Episodic Migraine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Quarterly (n=376)</td>
<td>Monthly</td>
<td>Placebo (n=375)</td>
<td>Quarterly (n=291)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>42.0 (12.4)</td>
<td>40.6 (12.0)</td>
<td>41.4 (12.0)</td>
<td>41.1 (11.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>331 (88)</td>
<td>330 (87)</td>
<td>330 (88)</td>
<td>251 (86)</td>
</tr>
<tr>
<td>Current preventive medication use, n (%)</td>
<td>77 (20)</td>
<td>85 (22)</td>
<td>77 (21)</td>
<td>58 (20)</td>
</tr>
<tr>
<td>Current acute headache medication use, n (%)</td>
<td>359 (95)</td>
<td>360 (95)</td>
<td>358 (95)</td>
<td>281 (97)</td>
</tr>
<tr>
<td>Discontinued prior preventive treatment, n (%)</td>
<td>130 (35)</td>
<td>141 (37)</td>
<td>136 (36)</td>
<td>58 (20)</td>
</tr>
<tr>
<td>Use of migraine-specific acute headache medications per month (days), mean (SD)</td>
<td>11.3 (6.2)</td>
<td>11.1 (6.0)</td>
<td>10.7 (6.3)</td>
<td>6.6 (3.1)</td>
</tr>
<tr>
<td>Headache days per month, mean (SD)</td>
<td>13.2 (5.5)</td>
<td>12.8 (5.8)</td>
<td>13.3 (5.8)</td>
<td>9.3 (2.7)</td>
</tr>
<tr>
<td>Disability score: HIT-6 score (points), mean (SD)</td>
<td>64.3 (4.7)</td>
<td>64.6 (4.4)</td>
<td>64.1 (4.8)</td>
<td>41.7 (33)</td>
</tr>
</tbody>
</table>


Please see Important Safety Information and Full Prescribing Information
Reduction in Monthly Headache Days of ≥Moderate Severity$^{1-3}$

- **HALO-CM Primary Endpoint:** A reduction in the average number of monthly headache days of ≥moderate severity was demonstrated during the 12-week period, with results seen as early as Week 1$^{2,3}$
  - 4.6 fewer headache days per month, on average, with monthly dosing (vs 2.5 with placebo)*

*Mean number of headache days of at least moderate severity at baseline for each treatment group: Quarterly, 13.2; Monthly, 12.8; Placebo, 13.3.
Mean (±SE) number of headache days of at least moderate severity per month was reduced by 4.3±0.3 days in the Fremanezumab-vfrm injection quarterly group vs 2.5±0.3 days in the placebo group (P<0.001 for both Fremanezumab-vfrm groups versus placebo).


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Please see Important Safety Information and Full Prescribing Information
Reduction in Monthly Migraine Days\textsuperscript{1-3}

- **HALO-EM Primary Endpoint:** A reduction in the average number of monthly migraine days was demonstrated during the 12-week period, with results seen as early as Week 1
  - 3.7 fewer migraine days per month, on average, with monthly dosing (vs 2.2 with placebo)*

Mean (±SE) average number of migraine days per month was reduced by 3.4 ± 0.25 days in the Frenamezuab-vfrm quarterly group compared with 2.2 ± 0.24 days in the placebo group (P<0.001 for both Frenamezuab-vfrm groups versus placebo).


*Mean number of migraine days at baseline for each treatment group: Quarterly, 9.3; Monthly, 8.9; Placebo, 9.1.

Mean (±SE) average number of migraine days per month was reduced by 3.3 ± 0.28 days in the Frenamezuab-vfrm injection quarterly group compared with 2.3 ± 0.24 days in the placebo group (P<0.001 for both Frenamezuab-vfrm groups versus placebo).

Please see Important Safety Information and Full Prescribing Information
Patients Who Achieved ≥50% and ≥75% Reduction in Monthly Headache Days of ≥Moderate Severity in HALO-CM¹,²

• ≥50% reduction over 12-week period (Secondary Endpoint)

- Quarterly: 40.8%
- Monthly: 37.6%
- Placebo: 18.1%

• ≥75% reduction on average in a month (Post hoc Analysis†)

- Quarterly: 20.1%
- Monthly: 20.6%
- Placebo: 10.4%

*P<0.001 versus placebo. †No determination of statistical significance can be made and no conclusions should be drawn.

Please see Important Safety Information and Full Prescribing Information

Patients Who Achieved ≥50% and ≥75% Reduction in Monthly Migraine Days in HALO-EM\(^1,2\)

- *\(P<0.001\) versus placebo.
- †No determination of statistical significance can be made and no conclusions should be drawn.

- \(^1\) Fremanezumab-vfrm injection Current Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.
- \(^2\) Data on file. Teva Pharmaceuticals USA, Inc.

Please see Important Safety Information and Full Prescribing Information
Adverse Reactions Reported by ≥2% of Patients on Fremanezumab-vfrm injection and Greater Than Placebo\(^1\)

<table>
<thead>
<tr>
<th>Injection-site reactions*</th>
<th>225 mg Monthly (n=290)</th>
<th>675 mg Quarterly (n=667)</th>
<th>Placebo Monthly (n=668)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43</td>
<td>45</td>
<td>38</td>
</tr>
</tbody>
</table>

*Injection site reactions include multiple related adverse event terms, such as injection site pain, induration, and erythema.

- Most injection-site reactions were rated as mild to moderate\(^3\)
- ≤2% of patients discontinued due to adverse reactions in both phase 3 trials\(^3\)
- Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported in clinical trials.\(^1\) Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration

Fully humanized:\(^1\)

Humanization is a process designed to reduce immunogenicity\(^2\)

Less than 1% of patients in both phase 3 trials developed antibodies to Fremanezumab-vfrm\(^1\)

Important Safety Information

• **Contraindications:** Fremanezumab-vfrm) injection is contraindicated in patients with serious hypersensitivity to Fremanezumab-vfrm or to any of the excipients.

• **Hypersensitivity Reactions:** Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration. If a hypersensitivity reaction occurs, consider discontinuing Fremanezumab-vfrm and institute appropriate therapy.

• **Adverse Reactions:** The most common adverse reactions (≥5% and greater than placebo) were injection site reactions.

    Please see the Full Prescribing Information for Fremanezumab-vfrm
**Erenumab:** injection is indicated for the preventive treatment of migraine in adults.

**Fremanezumab:** injection is indicated for the preventive treatment of migraine in adults.

**Galcanezumab:** injection is indicated for the preventive treatment of migraine in adults.
Eptinezumab Reduced Migraine Activity and Achieved High Migraine Responder Rates Over Weeks 1–12: Results From the Phase 3 PROMISE-2 Trial in Chronic Migraine

Paul Winner, 1 Peter J. Goadsby, 2 Abraham J. Nagy, 3 Jan Brandes, 4 David Biondi, 5 Suman Bhattacharya, 5 Roger Cady, 5 Joe Hirman, 6 Eric Kassel 5

1Premiere Research Institute, Palm Beach Headache Center, West Palm Beach, FL; 2NIHR-Wellcome Trust Clinical Research Facility, King’s College, London, UK; 3Nevada Headache Institute, Las Vegas, NV; 4Nashville Neuroscience Group, Nashville, TN; 5Alder BioPharmaceuticals, Inc., Bothell, WA; 6Pacific Northwest Statistical Consulting, Inc., Woodinville, WA
Key SecondaryEndpoints:
≥75% and ≥50% Migraine Responder Rates: Weeks 1–12

* A stratified Cochran–Mantel–Haenszel test used for statistical analysis; † p=0.0001 vs. placebo; ‡ p <0.0001 vs. placebo.

<table>
<thead>
<tr>
<th>Subjects, %*</th>
<th>Placebo (n=366)</th>
<th>Eptinezumab 100 mg (n=356)</th>
<th>Eptinezumab 300 mg (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥75% Migraine Responders</td>
<td>15.0</td>
<td>26.7†</td>
<td>33.1‡</td>
</tr>
<tr>
<td>≥50% Migraine Responders</td>
<td>39.3</td>
<td>57.6‡</td>
<td>61.4‡</td>
</tr>
</tbody>
</table>
Characteristics of Therapeutic mAbs

- Low risk of drug-drug interactions
- Low off-target toxicity
- Pharmacokinetics supports less frequent dosing interval
- Break down to amino acids

### Small Molecule vs Antibody Drugs

<table>
<thead>
<tr>
<th>Small Molecules</th>
<th>Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size &lt; 1 kD</td>
<td>Size ≈ 150 kD</td>
</tr>
<tr>
<td>Orally administered</td>
<td>Must be injected</td>
</tr>
<tr>
<td>Many enter cells and cross BBB</td>
<td>Do not enter cells or cross BBB</td>
</tr>
<tr>
<td>Half-life minutes to hours</td>
<td>Half-life 1-4 weeks</td>
</tr>
<tr>
<td>Chemically synthesized</td>
<td>Manufactured in tissue culture</td>
</tr>
</tbody>
</table>

BBB, blood-brain barrier.

Small Molecule Under Study

• Ditan
  Lasmiditan – antagonist to 5HT 1F receptor
  [selective 5-HT1F inhibition of dural extravasation and inhibition of TCC neuronal activation]

• Gepants [Oral CGRP receptor antagonists]
  • Ubrogepant  (FDA Approved Dec. 2019)
  • Rimegepant
  • Atogepant
Pharmacologic Rx : Prevention

- Beta Blockers
- Topiramate
- Divalproex
- TCAs
- CCB’s
- ACEs

- ARBs
- Cyproheptadine
- OnabotulinumtoxinA
- Riboflavin
- Coenzyme Q
- Mg++
Long-Term Safety and Tolerability COMPEL Study

PREEMPT Protocol

Neuromodulation FDA Approved

• nVNS: noninvasive vagal nerve stimulation: GammaCore/ElectroCore for acute treatment in adults
• sTMS: Single–pulse transcranial magnetic stimulation: eNeuro for acute and preventive treatment of adults and adolescence
• eTNS: external trigeminal nerve stimulation: Cefaly for acute and preventive treatment of migraine in adults
Nutraceuticals

- B2 (25-400 mg), chelated magnesium (400-600 mg), Mig 99 (feverfew) Class B
- Coenzyme Q10 (300 mg) Class C
- Petasites (Petadolex) 50-75 mg bid Class A*
- Magnesium can cause diarrhea
- CoQ10 can cause rash
- Petadolex has been associated with liver toxicity

Tepper SJ Continuum 2015;21(4):1018-1031
Acute Migraine Medications

• **Nonspecific**
  – NSAIDs
  – Combination analgesics
  – Opioids
  – Neuroleptics/antiemetics

• **Specific**
  – Dihydroergotamine (New delivery systems)
  – Triptans (New delivery systems)
  – NSAIDs (New delivery systems)
Triptans for Acute Treatment of Migraine

- Almotriptan*
- Eletriptan
- Naratriptan
- Rizatriptan #
- Sumatriptan
- Zolmitriptan*
- Frovatriptan
- Treximet*

* FDA approved Adolescent
# FDA approved Children & Adolescent
MIGRAINE:
Management Update

Summary:
• UNCOVERING: PATIENT BURDEN
• Mechanism/Management
• NEW TREATMENT STRATEGIES
Thank You for Your Attention!

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