Clinical Challenges in Migraine:
The Role of Emerging Therapies in New Treatment Paradigms

Migraine Treatment Prevention
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Faculty Disclosure
Dr. Merle Diamond has received honoraria related to speakers' bureau activities from Allergan, Inc., Avanir Pharmaceuticals, Inc., Depomed, Inc., PERNIX Therapeutics, and Teva Pharmaceutical Industries Ltd.
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Key Facts in Preventive Treatment
- 53% of migraineurs meet disability and frequency criteria for prevention
- <5% of migraineurs are on preventive therapy
- Patients are:
  - Dissatisfied with current treatment, and
  - Largely refractory or intolerant

Main Goals of Migraine Preventive Therapy
- Restore function
- Prevent progression to chronic migraine
- Headache frequency, severity and intensity

Addressing the Unmet Need in Preventive Treatment
- Approximately 80% of patients discontinue oral preventive therapy after 1 year of treatment.1
- More than 40% of patients receiving therapy still experience at least one migraine-related issue, including headache-related disability, treatment dissatisfaction, and/or excessive opioid use.2
- Up to 13% of patients with migraine receiving acute and/or preventive therapy still have at least 1 emergency department visit a year.3

Migraine Transformation
- Episodic Migraine
- Chronic Daily Headache
- Time

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Migraine Preventive Treatment

Consider When:
- Headache frequency greater than 6 per month
- Headache related disability occurs too often regardless of headache frequency
- Acute medications are:
  - Ineffective or not tolerated
  - May augment efficacy
  - Likely to be overused
  - Contraindicated

Special circumstances exist:
- Profound disability
- Prolonged migraine aura
- History of migraine related stroke

Preventive Therapy for Migraine: Caveats

- Advise patient re: latency & side effects
- Start low, go slow, but strive for a therapeutic dose
- Treat for an adequate duration; set realistic goals
- Evaluate response with calendars
- Prescribe concomitant acute therapy, but avoid interfering or overused medication

Preventive Medication Reduces Costs

18-month Comparison study; Acute/Preventive Therapies

- Office visits: 51%
- ED visits: 82%
- MRI scans: 88%
- Medication Costs: 518$ per Month/Patient
- CT scans: 75%
Migraine Prevention Mechanisms

- Raise Threshold to Migraine Activation
  - Inhibit migraine generation (e.g., cortex, PAG)
- Stabilize More Reactive Nervous System
  - Block neurogenic inflammation
  - Effect on sodium and/or calcium ion channels
  - Modulate sympathetic or serotonergic tone
- Enhance antinociception
- Inhibit cortical spreading depression
- Inhibit sensitization
- Inhibit neurogenic inflammation
- Effect on sodium and/or calcium ion channels
- Modulate sympathetic or serotonergic tone

Drugs that are useful in the prophylaxis of migraine suppress cortical spreading depression


All Approved Drugs Similarly Prevent Migraine

215 publications of RCTs provided mostly low-strength evidence because of the risk of bias and imprecision

**Approved Drug**
- Topiramate (9 RCTs)
- Divalproex (3 RCTs)
- Timolol (3 RCTs)
- Propranolol (4 RCTs)

**Off Label Drug**
- Metoprolol (4 RCTs)
- Atenolol (1 RCT)
- Nadolol (1 RCT)
- Captopril (1 RCT)
- Lisinopril (1 RCT)
- Candesartan (1 RCT)

- Topiramate and antidepressants more adverse events
- No significant differences between labelled drugs
- ACE inhibitors and BB most tolerable and effective
- Long term (>3 month data lacking)
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Migraine Comorbidity and Coexisting Conditions Therapeutic Opportunities and Limitations

<table>
<thead>
<tr>
<th>Disorder (+ migraine)</th>
<th>Consider</th>
<th>Avoid or Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>TCAs, SSRI, SNRIs</td>
<td>β-blockers</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Valproate, topiramate</td>
<td>TCAs, SMRs, SNRIs</td>
</tr>
<tr>
<td>Anemia</td>
<td>TCAs, SMRs, β-blockers</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>TCA</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Aspirin, ergot, triptans</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>β-blockers, Ca++ channel antagonists, if uncontrolled, ergot &amp; triptans</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Topiramate, SMRs</td>
<td>TCA, valproate, gabapentin</td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
<td>Ca++ channel antagonists</td>
<td>β-blockers, ergots</td>
</tr>
</tbody>
</table>

Nonpharmacologic Therapies Tested in Clinical Trials

Behavioral Treatments
- Relaxation training*
- Hypnotherapy
- Thermal biofeedback training
- Electromyographic biofeedback therapy*
- Cognitive / behavioral therapy (CBT)*

Physical Treatments
- Acupuncture
- Ocular adjustment
- Occlusal adjustment
- Thermal biofeedback training*
- Hypnotherapy
- Relaxation training*
- Behavioral Treatments
- TMS
- Transcutaneous electrical nerve stimulation (TENS)

AHS Guidelines: Migraine Preventive Therapies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Level I: Medications are established as effective or moderately effective (≥ Class I or ≥ 2 Class II studies)</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Depression, TCAs, SMRs, SNRIs, ergots, triptans, Ca++ blockers, gabapentin, lamotrigine, flesinoxan, lamotrigine, valproate, gabapentin, amlodipine</td>
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<tr>
<td>Clonazepam*</td>
<td>Depression, TCAs, SMRs, SNRIs, ergots, triptans, Ca++ blockers, gabapentin, lamotrigine, flesinoxan, lamotrigine, valproate, gabapentin, amlodipine</td>
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<tr>
<td>Divalproex sodium*</td>
<td>Depression, TCAs, SMRs, SNRIs, ergots, triptans, Ca++ blockers, gabapentin, lamotrigine, flesinoxan, lamotrigine, valproate, gabapentin, amlodipine</td>
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<tr>
<td>Fluoxetine</td>
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<td>Gabapentin</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td>Mirtazapine</td>
<td>Depression, TCAs, SMRs, SNRIs, ergots, triptans, Ca++ blockers, gabapentin, lamotrigine, flesinoxan, lamotrigine, valproate, gabapentin, amlodipine</td>
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<tr>
<td>Methylphenidate</td>
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<tr>
<td>Oxybutynin</td>
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<td>Propranolol*</td>
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<tr>
<td>Sertraline</td>
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<tr>
<td>Venlafaxine</td>
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<tr>
<td>Zonisamide</td>
<td>Depression, TCAs, SMRs, SNRIs, ergots, triptans, Ca++ blockers, gabapentin, lamotrigine, flesinoxan, lamotrigine, valproate, gabapentin, amlodipine</td>
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*Demonstrated efficacy in clinical trials

Levels of evidence:
- Level A: Medications with established efficacy (≥ Class I or ≥ 2 Class II studies)
- Level B: Medications are probably effective (1 Class I or 2 Class II studies)
- Level C: Medications are possibly effective (1 Class II study)
- Level U: Inadequate or conflicting data to support or refute medication use
- Other: Medications that are established as possibly or probably ineffective

Other:
- Antiepileptic drugs
- Antidepressants/SSRI/SSNRI/TCA
- ACE inhibitors
- Carbonic anhydrase inhibitors
- Established as not effective
- Divalproex sodium*
- Amitriptyline
- Angiotensin receptor blockers
- Acetazolamide
- Established as effective or moderately effective (≥ Class I or ≥ 2 Class II studies)
- Lamotrigine
- Topiramate*
- β-blockers
- α-agonists
- Acenocoumarol
- Probably not effective
- Metoprolol
- Clonidina
- Clomipramina
- Propranolol*
- Triptans (MRM)*
- Antiepileptic drugs
- Antidepressants
- SSRI/SSNRI
- Acebutolol
- Timolol*
- Naratriptan
- Carbamazepina
- Fluoxetine
- Nabumetone a
- Frovatriptan
- Nebivolol
- Oxcarbazepine
- Pindolol a
- Protriptyline a
- Sodium valproate
- Venlafaxine
- Candesartan
- Antihistamines
- TCAs
- Cyproheptadine
- Protriptyline a
- Sodium valproate
- Venlafaxine
- Candesartan
- Antihistamines
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- Cyproheptadine
- Protriptyline a
- Sodium valproate
- Venlafaxine
- Candesartan
- Antihistamines
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Classification of Migraine Preventive Therapies (available in the US) of Herbal Preparations, Minerals, Vitamins, NSAIDs, and Others

<table>
<thead>
<tr>
<th>Level &amp; Indications</th>
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<th>Level &amp; Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal preparations, vitamins, minerals, and others</td>
<td>NSAIDs</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>± Medications with established efficacy (Class I trials)</td>
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<td>± Medications with established efficacy (Class I trials)</td>
</tr>
<tr>
<td>Probable or established efficacy (Class II trials)</td>
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<td>Probable or established efficacy (Class II trials)</td>
</tr>
<tr>
<td>Probable or established efficacy (Class III trials)</td>
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<td>Probable or established efficacy (Class III trials)</td>
</tr>
<tr>
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- **Level A:** medications with established efficacy (at least Class I trials)
- **Level B:** medications are probably effective (one Class I or at least two Class II studies)
- **Level C:** medications are possibly effective (one Class II study)
- **Level U:** inadequate or conflicting data to support or refute medication use

Other: medications that are established as possibly or probably ineffective

Herbal preparations, vitamins, minerals, and other CNS-active agents

Petasites
Naproxen sodium
NSAIDs
Acetylsalicylic acid
Aspirin
Flurbiprofen
Fenoprofen
Indomethacin
Ketoprofen
Leukotriene receptor antagonists
Montelukast
Mefenamic acid
Migraleine
Riboflavin
Serotoninergic agents
Sumatriptan
Onabotulinum Toxin A

How Onabotulinum Toxin A Might Work

- **Synapse:**
  - Inhibits release of Ach at NMJ, inhibiting striated muscle contractions
  - Pain relief often occurs before muscle paralysis
  - Blocks peripheral sensitization
  - Blocks release of glutamate and SP from nociceptive neurons
  - C-fos expression prevented upon peripheral exposure

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Side Effects Affect Patient Choices

- Most rejected: weight gain, memory loss, depression
- Better acceptance is >10 symptomatic medications/month (especially for loss of energy and somnolence)
- Older patients reject for tremor
- Weight loss better accepted with higher BMI

Nonpharmacologic Strategies

- Lifestyle modifications
- Consider behavioral techniques
- Sleep
- Exercise
- Diet
- Stress management
- Stop smoking

What Do We Need for Optimal Migraine Prevention?

We need preventive medication that:
- Can be given infrequently
- Has a high rate of adherence and persistence
- Has few AEs
- Is easy to administer
- Has proven efficacy to decrease headache days
- Works when other preventive therapies do not
- Is cost effective

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Summary

- There are barriers to consultation which in turn prevent accurate diagnosis and therapy
- Current migraine preventives
  - Are not that effective
  - Have to be given at least daily
  - Have many AEs
  - Result in low adherence and persistence rates
- The 50% responder rates are 50% or less
- We are in need of effective preventive therapies, given less frequently with fewer adverse events

From Bench to Practice: Expert Perspectives on Emerging Strategies and Novel Agents for Migraine Prevention

The Science of Migraine

Stewart J. Tepper, MD
Professor of Neurology
Geisel School of Medicine at Dartmouth

Faculty Disclosure

Dr. Stewart Tepper has received honoraria as a consultant from Acorda, Alder BioPharmaceuticals Inc., Allergan, Inc., Amgen Inc., ATI, Avanir Pharmaceuticals, Inc., BioVision Inc., electroCore, LLC, Eli Lilly and Company, eNeura Inc., Kimberly-Clark, PERNIX Therapeutics, Pfizer Inc., TEVA Pharmaceutical LTD, and Zosano Pharma Corporation; and honoraria related to formal advisory activities from Alder, Allergan, Amgen, ATI, Avanir, Dr. Reddy’s Laboratories Ltd., Kimberly-Clark, Scion NeuroStim, TEVA, and Pfizer Inc. Dr. Tepper has also received royalties or licensing fees from Springer and the University of Mississippi Press. He has disclosed a financial relationship with the American Headache Society, Dartmouth-Hitchcock Medical Center, and has stock options with ATI.
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Migraine Pathophysiology

Migraine Pathogenesis
Activation of the Trigeminovascular System in Migraine

Calcitonin Gene-Related Peptide (CGRP)

- Neuropeptide belonging to calcitonin family
  - Calcitonin
  - Amylin
  - Adrenomedullin
  - Intermedin

- In humans two forms
  - α-CGRP: 37-amino acid peptide
  - β-CGRP: main isoform of enteric NS; differs in 3 amino acids
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**CGRP Receptors Occur at All Sites Involved in Migraine Pathogenesis**

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**CGRP: Vasodilation and Neurogenic Inflammation**

*CGRP First Identified as a Potential Mediator of Trigeminal Inflammation*

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**Activation of Brainstem During Migraine Attacks; CGRP Binds Here**

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CGRP and Migraine Connection
- CGRP immunoreactive nerves innervate human cerebral arteries
- CGRP is a potent vasodilator of human cerebral arteries
- CGRP is released into the jugular venous system during migraine
- CGRP infusion evokes migraine
- Serum CGRP levels are elevated in migraine
- CGRP receptor antagonist small molecule gepants effectively terminate migraine attacks
- Anti-CGRP and anti-CGRP receptor monoclonal antibodies prevent Episodic Migraine (EM) and Chronic Migraine (CM)

CGRP Infusion Triggers Migraine

The Small Molecule CGRP Receptor Antagonists: Gepants

Acute Treatment of Episodic Migraine
- Oleceproant IV worked and comparable to triptan proof of concept, fully published
- BI 442701xk effective oral vs placebo in Phase 2, fully published
- Telcagepant showed promise and efficacy comparable to triptans, but development stopped due to liver toxicity, Phase 3 studies fully published
- Rimegepant (BMS-927711) effective vs placebo in Phase 2 fully published; being readied for Phase 3
- Ubrogepant effective vs placebo in Phase 2 fully published; Phase 3 underway

Preventive Treatment of Episodic Migraine
- Telcagepant studied in two incomplete studies, with one terminated early due to hepatotoxicity and the other for evaluation of liver in MRM mini-prevention
- Atogepant vs placebo underway in Phase 2 for migraine prevention

Gepants have NEVER failed on EFFICACY
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CGRP Receptor Antagonist Small Molecules: Gepants Effectively Abort Migraine Attacks

Olcegepant IV CGRP Receptor Antagonist Small Molecules: Gepants Effectively Abort Migraine Attacks


Slide courtesy of Messoud Ashina MD, PhD, DMSc


Slide courtesy of Messoud Ashina MD, PhD, DMSc

The Development of Monoclonal Antibodies to CGRP or the CGRP receptor

• The monoclonal antibodies (MABs) are big molecules that do not cross the blood brain barrier
• MABs are eliminated by the reticuloendothelial system, so no risk for hepatotoxicity, as long as the gepant liver problem was metabolic degradation and not mechanism based
• Because they work, it means that peripheral, not central CGRP action is likely sufficient to trigger migraine or cluster headache

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Small Molecules (gepants) vs Large Molecules (Monoclonal Antibodies, MABs)

<table>
<thead>
<tr>
<th>Small Molecules</th>
<th>Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target specificity lower</td>
<td>Target specificity high</td>
</tr>
<tr>
<td>Clearance (liver, kidneys)</td>
<td>Clearance RES</td>
</tr>
<tr>
<td>Size &lt; 1 kD</td>
<td>Size ~150 kD</td>
</tr>
<tr>
<td>Oral</td>
<td>Parenteral</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 3-6 weeks</td>
</tr>
<tr>
<td>Immunogenicity (No)</td>
<td>Immunogenicity (yes)</td>
</tr>
</tbody>
</table>

Small Molecule ~0.2–1 kDa

IgG1 Monoclonal Antibody ~150 kDa

mAbs Have Minimal Access to CNS Due to Size and BBB

- mAbs are largely confined to the vasculature, with variable distribution across different tissue types, depending mainly on the extent to which the mAb can cross the capillary endothelium

![Graph showing mAb tissue redistribution](image)

mAb Tissue Redistribution
Percentage of Plasma Concentration

- Brain
- Heart
- Liver
- Spleen
- Kidney
- Lung

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.1%</td>
</tr>
<tr>
<td>Heart</td>
<td>2.1%</td>
</tr>
<tr>
<td>Liver</td>
<td>1.7%</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.1%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.3%</td>
</tr>
<tr>
<td>Lung</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

*Figure demonstrates distribution of a murine IgG1 mAb in wild-type mice following intra-peritoneal administration; results may not be representative of all mAbs

Erenumab
Galcanezumab
Fremanezumab
Eptinezumab

All Positive in Phase 2, and All That Have Reported Are Positive in Phase 3

All 4 have demonstrated clinical meaningful responder rates

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- All 4 positive for prevention of Episodic Migraine (EM) and Chronic Migraine (CM) in Phase 2
- All 4 positive for prevention of EM in Phase 3
- 3 of 4 have already reported or published positive findings for CM prevention in Phase 3
- All 4 have quick onset, separating from placebo in <1 week; Phase 2 fremanezumab study showed significance over placebo within 1 week even in the more refractory, more typical CM patients
- Almost all secondary endpoints are also positive, with reduction of acute medication days, high responder rates, and improved impact, disability, and or QOL measures
- Immunogenicity appears to be very low <3%. Less than 1% neutralizing antibodies; no impact on safety or efficacy at this point

≥ 50% Responder Rates From Reduction of Migraine Days, Episodic Migraine (EM), Phase 2

≥ 75% Responder Rates for Prevention of EM, Phase 2
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Erenumab

Submitted to the FDA for the indication of prevention of migraine in May 2017

<table>
<thead>
<tr>
<th>Erenumab</th>
<th>Galcanezumab</th>
<th>Fremanezumab</th>
<th>Eptinezumab</th>
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<tbody>
<tr>
<td>Studied for</td>
<td>EM, CM</td>
<td>EM, CM, eCM, cCH</td>
<td>EM, CM, eCM, cCH</td>
</tr>
<tr>
<td>Dosing</td>
<td>Monthly SC</td>
<td>Monthly SC</td>
<td>Monthly or Q3 month SC; IV load for CH</td>
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<tr>
<td>Target</td>
<td>CGRP receptor</td>
<td>CGRP peptide or ligand</td>
<td>CGRP peptide or ligand</td>
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<tr>
<td>Regulatory status 7/2017</td>
<td>Submitted to FDA for migraine prevention; CM registration study fully published</td>
<td>Presented (+) Phase 3 CM &amp; EM</td>
<td>Presented (+) Phase 3 CM; Announced (+) Phase 3 EM</td>
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Galcanezumab
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**Galcanezumab**

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<th>Erenumab</th>
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<td>Announced (+) Phase 3 EM</td>
<td>Continuing Phase 3 CM</td>
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**Phase 3 EM Prevention, Erenumab & Galcanezumab: 1° Endpoint: Migraine Day Reduction at 3 Mos vs. Placebo**

Phase 3 CM Prevention, Erenumab & Galcanezumab: 1° Endpoint: Migraine Day Reduction at 3 Mos vs. Placebo

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Phase 3 CM Erenumab Adverse Events

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<tr>
<th>Category</th>
<th>Placebo (n = 382)</th>
<th>70 mg (n = 383)</th>
<th>140 mg (n = 383)</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects reporting AEs, n (%)</td>
<td>10 (4.8)</td>
<td>8 (4.8)</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Number of subjects with AEs leading to IP discontinuation, n (%)</td>
<td>2 (0.7)</td>
<td>9 (3.2)</td>
<td>6 (1.8)</td>
</tr>
</tbody>
</table>

Most Frequent AEs
- Injection site pain
- Upper respiratory tract infection
- Nausea
- Nasopharyngitis
- Constipation
- Muscle spasms
- Migraine

Abbreviations: AE, adverse event; IP, investigational product; SAE, serious adverse event.

n = number of subjects with ≥1 occurrence of an AE.

No SAE or AE leading to IP discontinuation was experienced by >1 subject.

Includes AEs reported by ≥2% of all erenumab subjects.

Galcanezumab Phase 3 EVOLVE-2 EM Prevention Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo N=461</th>
<th>GMB 120 mg N=226</th>
<th>GMB 240 mg N=228</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AEs</td>
<td>217 (63.5)</td>
<td>247 (65.0)</td>
<td>246 (71.4)*</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5 (1.4)</td>
<td>5 (2.1)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>4 (1.7)</td>
<td>5 (2.2)</td>
<td>9 (3.9)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; GMB, galcanezumab. n=patients in safety population; n=patients within each specific category.

*p<0.05 (vs. placebo)

Most common treatment-emergent AEs (≥5% of galcanezumab-treated patients): injection site pain, nasopharyngitis, injection site reaction, upper respiratory tract infection, alopecia, pruritus, injection site edema, injection site pruritus, fatigue, and diarrhoea.

Note: red text indicates a statistically significant higher rate of incidence compared with placebo.

Skljarevski et al. AHS meeting. June 2017.

Fremanezumab
**Clinical Challenges in Migraine:**
The Role of Emerging Therapies in New Treatment Paradigms

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**Fremazumab**

<table>
<thead>
<tr>
<th></th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
<th>Fremanezumab</th>
<th>Eptinezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studied for</td>
<td>EM, CM</td>
<td>EM, CM, cCH, eCH</td>
<td>EM, CM, cCH, eCH</td>
<td>EM, CM</td>
</tr>
<tr>
<td>Dosing</td>
<td>Monthly SC</td>
<td>Monthly SC</td>
<td>Monthly or Q3 month SC; IV load for CH</td>
<td>Q3 month 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>7/2017</td>
<td>Submitted to FDA for migraine prevention; CM registration study fully published</td>
<td>Presented (+) Phase 3 EM &amp; CM</td>
<td>Announced (+) Phase 3 EM; Continuing Phase 3 CM</td>
</tr>
</tbody>
</table>

---

**HALO Phase 3 – Prevention of Episodic Migraine**

*Triumph Over All Primary and Secondary Endpoints Across Both Monthly and Quarterly Dose Regimens*

- **Primary Endpoints:** Decreased Migraine Days, 3rd month;
- Relief experienced within 1 week and continued to experience reduction in migraine for up to 3 months compared to placebo;
- **Monthly SC Dosing**
  - Placebo: 1.3-2 days
  - Fremanezumab: 1.8-2.3 days, p<0.0001
  - 4% of days with disability decreased by 64.7%
- **2° endpoint:** Decreased acute medication days:
  - Decreased by 39.0%, p<0.0001
- **Quarterly SC dosing reported highly significant results for decrease in migraine days:**
  - Fremanezumab: 3.4 days or 37.0%,
  - P < 0.0001

**Phase 3 Data: CM Prevention – HALO Study**

*Primary endpoint: change from baseline in headache days of least moderate severity*

*Change from baseline: headache days of at least moderate severity during first 4 weeks*

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HALO CM Fremanezumab Phase 3 Prevention of CM: Adverse Events

<table>
<thead>
<tr>
<th>Patients with at least 1 AE</th>
<th>Placebo</th>
<th>Quarterly dose</th>
<th>Monthly dose</th>
<th>All Fremanezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment-emergent AEs</td>
<td>115 (41)</td>
<td>183 (48)</td>
<td>188 (48)</td>
<td>172 (48)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>164 (28)</td>
<td>114 (38)</td>
<td>99 (26)</td>
<td>213 (28)</td>
</tr>
<tr>
<td>Injection site infection</td>
<td>68 (18)</td>
<td>76 (28)</td>
<td>90 (24)</td>
<td>164 (22)</td>
</tr>
<tr>
<td>Injection site abscess</td>
<td>60 (18)</td>
<td>60 (21)</td>
<td>75 (20)</td>
<td>155 (21)</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>20 (6)</td>
<td>7 (2)</td>
<td>6 (2)</td>
<td>15 (2)</td>
</tr>
</tbody>
</table>
| No differences seen in HALO vs placebo treatment groups.

Eptinezumab

<table>
<thead>
<tr>
<th>Eptinezumab</th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
<th>Emegrenzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studied for</td>
<td>EM, CM</td>
<td>EM, CM, eCH, cCH</td>
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Eptinezumab Phase 2 Prevention of CM

Eptinezumab Phase 3 Prevention of EM, Met Primary and Key Secondary Endpoints

Monthly migraine days were significantly reduced from baseline over weeks 1 – 12

Eptinezumab Phase 3 EM Prevention Adverse Events

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CGRPs in 2017
- CGRP receptors present at crucial locations in migraine pathophysiology
- CGRP infusion evokes migraine
- Serum CGRP levels are elevated in migraine
- CGRP receptor antagonist small molecule gepants effectively abort migraine attacks
- Anti-CGRP and anti-CGRP receptor monoclonal antibodies prevent episodic migraine and chronic migraine
- The MABs appear safe, tolerable, and effective so far in Phase 2 and Phase 3 trials

The Impact of a Changing Paradigm in Treatment
- Migraine affects almost 730 million people worldwide
- Those with the chronic form suffer 15 or more headache days per month
- The total economic burden of migraine in the US including direct medical costs and indirect costs such as lost work days is estimated at a minimum of $17 billion annually
- The new anti-CGRP mAbs are the first drugs specifically designed to prevent a crippling headache before it begins
- Anti-CGRP mAbs act more quickly than existing migraine preventive treatments; a separation between treatment and placebo groups occurs with all four in less than one week

Thank you!
Clinical Challenges in Migraine:
The Role of Emerging Therapies in New Treatment Paradigms