MIGRAINE PROPHYLAXIS

Erenumab-aooe (AIMOVIG™)
Calcitonin Gene Related Peptide Receptor Antagonist

Chelsey Roscoe, PharmD
PGY1 Resident - CTVHCS

Disclosures

■ No conflicts of interest to disclose

Definitions Slide

■ AAN – American Academy of Neurology
■ AHS – American Headache Society
■ CGRP – Calcitonin Gene receptor peptide
■ AA – amino acid
■ H/O – history of
■ MPFID – Migraine physical function impact diary
■ Wk – week
■ ADR – adverse drug reactions

■ NSAID – non-steroidal anti-inflammatory drug
■ PMH – past medical history
■ w/ – with
■ CM – chronic migraines
■ EM – Episodic migraine
■ QOL – Quality of Life
■ MMD – monthly migraine days

Objectives

■ Understand migraine characterization and pathophysiology
■ Review current migraine prevention treatments and guideline recommendations
■ Evaluate clinical data regarding erenumab-aooe
■ Discuss potential place in therapy for erenumab-aooe

What do you think the “aooe” stands for at the end of erenumab-aooe?

A. Chinese hamster ovary cell line
B. Meaningless suffix required by FDA for biologics
C. A counterion (salt) to enable dissolution
D. Inspired by Tim Allen’s grunt from Home Improvement tv series

Clinical Question: Where does erenumab-aooe fit in to migraine prevention?

—
Migraine Characterization

- With or without aura
- Lasts 4-72 hours
- Two of following characteristics:
  - Unilateral
  - Pulsating
  - Moderate or severe pain
  - Aggravation by activity
- At least one of following:
  - Nausea and/or vomiting
  - Photophobia and phonophobia

Migraine Diagnostic Criteria: Epilepsy Foundation Professional Resources Library

Migraine Epidemiology

Prevalence

- 2nd most common headache disorder
- Affects 28 million people in US

Patient Population

- 25-55 years old
- Women three times as likely to suffer from migraines

Lipton RB et al. Headache. 2001

Infrequent Migraines

1-3 per month

Acute medications only – triptans, analgesics

Episodic Migraines

4-14 per month

Preventative medications – beta blockers, anti-epileptics + acute medications

Chronic Migraines

≥15 per month

Preventative medications – beta blockers, anti-epileptics + acute medications

Migraine Prophylaxis Goals

- Reduce intensity, frequency, and duration of migraine headaches
- Improved responsiveness and decreased need for acute migraine medications
- Improved quality of life

Preventative medications should be started at a low dose and increased slowly. Adequate trial of migraine prophylaxis therapy is at least 2 months of use at the target dose.

Headache: The Journal of Head and Face Pain

Non-Pharmacologic Migraine Prophylaxis

- Avoid excess alcohol, stress, caffeine, and acute headache medications
- Consider yoga, meditation, biofeedback, hypnosis, acupuncture

Chapter 422: Migraine and Other Primary Headache Disorders, Harrison’s Principles of Internal Medicine, 20e

Healthy Diet and Regular Exercise

Avoid Identifiable Triggers

Avoid excess alcohol, stress, caffeine, and acute headache medications

Healthy Diet

and Regular Exercise

Avoid Identifiable Triggers

Healthy Diet

and Regular Exercise

Avoid Identifiable Triggers
**AAN/AHS Guideline (2012) Recommended Therapy for Episodic Migraine Prevention**

- No targeted migraine therapies available as of last guideline update
- Most evidence for beta blockers and anti-epileptics

**AAN/AHS Level A Migraine Prophylaxis**

<table>
<thead>
<tr>
<th>Migraine Agents</th>
<th>Study Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex Sodium/Sodium Valproate</td>
<td>10 studies supporting efficacy</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Four Class I studies and 7 class II studies. Two class I studies show topiramate as effective as divalproex or propranolol. Also as effective as amitriptyline.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Multiple class I studies, 60 trials compared to placebo</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2 class I studies</td>
</tr>
<tr>
<td>Timolol</td>
<td>3 studies versus placebo, effect size comparable to propranolol</td>
</tr>
</tbody>
</table>

**AAN/AHS Level B Migraine Prophylaxis**

<table>
<thead>
<tr>
<th>Migraine Agents</th>
<th>Doses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25-150 mg/day</td>
<td>Moderate to marked sedation, anxiety, arrhythmia, anticholinergic symptoms</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>140 mg ER/day</td>
<td>Insomnia, dizziness, drowsiness, nausea, xerostomia</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100mg/day</td>
<td>Bradycardia, confusion, hypotension, AV Block</td>
</tr>
</tbody>
</table>

**AAN/AHS Onabutulinum Toxin A**

- AAN Guideline Evidence on Onabutulinum Toxin A
  - Inconsistent results from 4 Class II Studies
  - 2 Class I studies
    - One Class I study
      - Ineffective for changes from baseline for total headache episodes
    - Effective for secondary endpoint of change in frequency of total headache days/28 days (-1.4 days, 95% CI -2.4 to -0.40)
  - 2nd Class I Study
    - Effective for reducing total headache days (-2.3 days) P value < 0.001
  - One Class III study demonstrated similar efficacy versus topiramate in CM

**AAN/AHS Onabutulinum Toxin A**

- Episodic Migraines
  - Ineffective (3 class I studies)

- Chronic Migraines
  - Should be offered as treatment option
  - Increase number of headache-free days
  - Improve health-related QOL
Patient Case 1, Part 1

A 42 year old female patient diagnosed with migraines but no other PMH comes to your clinic asking to try Aimovig injections. Patient states she has up to 12 migraines monthly which have caused her to miss work.

What is the characterization of migraine frequency for this patient?
A. Infrequent Migraines
B. Episodic Migraines
C. Chronic Migraines

Patient Case 1, Part 2

A 42 year old female patient diagnosed with migraines but no other PMH comes to your clinic asking to try Aimovig injections. Patient states she has up to 12 migraines monthly which have caused her to miss work. Patient states she has been using Excedrin 3 times per week.

What is the maximum amount of Excedrin per week you would recommend to avoid medication overuse headaches?
A. 1 dose per week
B. 2 doses per week
C. 3 doses per week
D. Patient should buy Excedrin from Costco and take as much as she needs (not to exceed 4000mg acetaminophen daily)

Clinical Question: Where does erenumab fit in to episodic and chronic migraine prevention?

α-CGRP – 37 AA peptide

- Potent vasodilator of intracranial arteries
- Enhancement of substance P
- Promotes mast cell degranulation
- Modulates neuronal excitability
- Aura
- Pain, photophobia, and nausea

AIMOVIG™ (erenumab-aooe)

- Monoclonal antibody antagonist against the calcitonin-gene related peptide receptor
- Self-administered subcutaneous injection once monthly
- Single-dose prefilled SureClick autoinjector
- Recommended dose of Aimovig is 70mg monthly
- Some patients may benefit from 140mg monthly.
AIMOVIG™
(erenumab-aooe)

Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Bioavailability</th>
<th>Tmax</th>
<th>Vd</th>
<th>Excretion</th>
<th>Elimination</th>
<th>Steady state</th>
</tr>
</thead>
<tbody>
<tr>
<td>82%</td>
<td>6 days</td>
<td>3.86 L</td>
<td>Non-specific, non-saturable proteolytic pathway</td>
<td>28 days</td>
<td>3 months</td>
</tr>
</tbody>
</table>

Aimovig Clinical Data

- Phase II Trial, Tepper et al
- Phase III Trial (STRIVE Trial)
- Phase III Trial (ARISE Trial)

Tepper, et al

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (N=286)</th>
<th>Erenumab 70mg (N=191)</th>
<th>Erenumab 140mg (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>42.1 ± 11.3 (18-66)</td>
<td>41.4 ± 11.3 (18-64)</td>
<td>42.9 ± 11.1 (18-64)</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>226 (79%)</td>
<td>166 (87%)</td>
<td>190 (84%)</td>
</tr>
<tr>
<td>Migraine – days per month</td>
<td>16.2 ±4.7</td>
<td>17.9±4.4</td>
<td>17.8±4.7</td>
</tr>
<tr>
<td>Medication Overuse (%)</td>
<td>117 (41%)</td>
<td>79 (41%)</td>
<td>78 (41%)</td>
</tr>
<tr>
<td>Failure of ≥ 1 drug</td>
<td>200 (70%)</td>
<td>127 (67%)</td>
<td>126 (66%)</td>
</tr>
<tr>
<td>Failure of ≥ 2 drugs</td>
<td>142 (50%)</td>
<td>93 (49%)</td>
<td>92 (48%)</td>
</tr>
</tbody>
</table>

Tepper, et al

**Criteria and Methods**

- **Inclusion Criteria**
  - Men and women aged 18-65 w/ h/o chronic migraine
  - ≥ 15 headaches per month
  - 80% compliance with headache diary

- **Exclusion Criteria**
  - >50 yrs of age at onset
  - History of hemiplegic or cluster headaches or chronic migraine w/ continuous pain
  - Patients with no therapeutic response from ≥3 migraine prophylaxis

- **Methods**
  - 4-week baseline phase
  - Included patients in analysis with at least one dose erenumab or placebo
  - Alternative Migraine preventative drugs prohibited during study

Tepper, et al

**Primary Endpoint**

- Monthly Migraine days*
  - Placebo: 4.2 (0.4)
  - Erenumab 70mg: 4.8 (0.4)
  - Erenumab 140mg: 6.6 (0.4)

- Difference* from Placebo
  - -2.5*
  - P value <0.001

* Utilizing least-squares mean data
**Tepper, et al**

### Safety Data

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (N=282)</th>
<th>Erenumab, 70mg (N=190)</th>
<th>Erenumab, 140mg (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events (%)</td>
<td>110 (39%)</td>
<td>83 (44%)</td>
<td>177 (47%)</td>
</tr>
<tr>
<td>Injection site pain (%)</td>
<td>3 (1%)</td>
<td>7 (4%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Nasopharyngitis (%)</td>
<td>16 (6%)</td>
<td>6 (3%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Adverse Event Leading to Treatment Discontinuation (%)</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Serious adverse event (%)</td>
<td>7 (2%)</td>
<td>6 (3%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

*Lancet. 2017; 16: 425-434*

---

### Strengths

- Well designed randomized, double blind multicenter trial
- Reviewed 140mg and 70mg dose
- Showed efficacy for primary outcome in CM
- Included patients receiving at least one dose erenumab in safety analysis
- Utilized appropriate statistics

---

### Limitations

- Trial 3 months in length
- Excluded patients with no response after >3 prophylactic medications
- Slightly more migraine days, medication overuse, and previous treatment failure in placebo group
- Lack of sub analysis of patient population with medication overuse
- Secondary endpoint cumulative monthly headache hours reduction did not reach significance

---

### STRIVE

**Strive Trial (Phase III Trial)**

- **Design:** Multicenter, randomized, double-blind placebo controlled phase III trial
- **Intervention:** erenumab 70mg, 140mg or placebo monthly
- **Primary objective:** change in mean number migraine days per month, from baseline to months 4-6
- **Secondary Objective:** >50% reduction of migraine days per month

*New England Journal of Medicine. 2017; 377(22):2123-2132*

---

### Criteria and Methods

#### Inclusion Criteria

- 4-14 migraine days per month
- 80% adherence to headache diary

#### Exclusion Criteria

- >50 yrs of age at onset
- Hemiplegic or cluster headaches
- Botulinum toxin or used devices/procedures in previous 4 months

#### Methods

- 4-week baseline phase
- Included patients in analysis with at least one dose erenumab or placebo
- Monthly follow-up

*New England Journal of Medicine. 2017; 377(22):2123-2132*

---

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (N=319)</th>
<th>Erenumab 70mg (N=317)</th>
<th>Erenumab, 140mg (N=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>41.3 ± 11.2 (18-65)</td>
<td>41.1 ± 11.3 (18-65)</td>
<td>40.4 ± 11.1 (19-65)</td>
</tr>
<tr>
<td>Female Sex</td>
<td>274 (85.9%)</td>
<td>268 (84.5%)</td>
<td>272 (85.3%)</td>
</tr>
<tr>
<td>Migraine – days per month</td>
<td>8.2 ± 2.5</td>
<td>8.3 ± 2.5</td>
<td>8.3 ± 2.5</td>
</tr>
</tbody>
</table>

*New England Journal of Medicine. 2017; 377(22):2123-2132*
### STRIVE: Primary Endpoint

![Primary Endpoint Graph]

- Change from baseline to months 6-6
- Placebo: 1.3 days
- Erenumab 70 mg: 1.2 days
- Erenumab 140 mg: 1.7 days

### STRIVE: Secondary Endpoint

![Secondary Endpoint Graph]

- Percentage of patients with ≥50% reduction at months 6-6
- Placebo: 26.4%
- Erenumab 70 mg: 55.0%
- Erenumab 140 mg: 56.0%

### STRIVE: Safety Data

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (N=319)</th>
<th>Erenumab, 70mg (N=314)</th>
<th>Erenumab, 140mg (N=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site pain</td>
<td>1 (0.3)</td>
<td>10 (3.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>8 (2.5)</td>
<td>7 (2.2)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>7 (2.2)</td>
<td>8 (2.5)</td>
<td>8 (1.9)</td>
</tr>
</tbody>
</table>

### STRIVE: Strengths

- Large patient population, multicenter
- Primary patient population representative of patients with migraines
- Sensitivity analysis concluded consistent results
- P values indicate statistical significance
- Relatively low adverse effect profile reported

### STRIVE: Limitations

- Excluded patients failing 2 or more previous treatments
- Unclear which migraine preventative medications patients took while in trial or which medication failed previously
- Short trial length (6 months) no long-term data on safety/efficacy
- Patients had low migraine days and MPFID scores at baseline
- Baseline MPFID Score in chart is misleading

### ARISE Trial (Phase III Trial)

- **Design**: Multicenter, randomized, double-blind, placebo-controlled, parallel group
- **Intervention**: Erenumab 70mg or placebo monthly
- **Primary objective**: Change in mean number of migraine days per month from baseline to last month of trial (month 3)
- **Secondary objectives**: >50% reduction of migraine days per month
**Inclusion Criteria**
- Adults 18–65 years old with history of 4–14 migraine days per month
- 80% adherence to headache diary

**Exclusion Criteria**
- Allowed for patients with one preventative drug to enter trial
- Medical conditions that might prevent study completion

**Methods**
- 3 week screening phase
- 4 week baseline phase
- 12 week double blind treatment phase
- 28 week open label treatment phase
- Safety follow up 12 weeks after last dose
- Patients stratified by region, current migraine prevention, prior migraine treatment, or no prior migraine treatment.

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=291)</th>
<th>Erenumab 70mg (N=317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42 ± 12</td>
<td>42 ± 12</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>247 (84.9%)</td>
<td>245 (85.7%)</td>
</tr>
<tr>
<td>Migraine – days per month</td>
<td>8.4 ± 2.6</td>
<td>8.1 ± 2.7</td>
</tr>
<tr>
<td>History of any prior preventative treatment use (%)</td>
<td>132 (45.4)</td>
<td>134 (46.9%)</td>
</tr>
<tr>
<td>Prior preventative treatment failures</td>
<td>115 (87.1%)</td>
<td>117 (87.3%)</td>
</tr>
</tbody>
</table>

**Primary Endpoint**
- Monthly Migraine days
  - Placebo: 1.8 (0.2)
  - Erenumab 70mg: 2.9 (0.2)
- Difference from Placebo: -1.0*
- P value <0.001

**Secondary Endpoint**
- Number of patients with ≥50% reduction from baseline (%)
  - Placebo: 85 (29.5%)
  - Erenumab 70mg: 112 (39.7%)
- Difference from Placebo: 9.8%
- P value <0.01
- OR 1.59 (1.12, 2.27)

**Safety Data**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (N=319)</th>
<th>Erenumab 70mg (N=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events (%)</td>
<td>158 (54.7)</td>
<td>136 (48.1)</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>12 (4.2)</td>
<td>17 (6.0)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>1 (0.3)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Grade 3 event</td>
<td>8 (2.8)</td>
<td>6 (2.1)</td>
</tr>
</tbody>
</table>

**Strengths**
- Large patient population, multicenter
- Primary patient population representative of patients with migraines
- Extended to longer time period for open label time frame
- Stratified patients based on specific characteristics
ARISE Limitations

- Unclear which migraine preventative medications patients took while in trial
- Unclear which specific medications patients failed previously
- Short trial length (3 months)
- Clinically significant outcome is questionable
- Many secondary endpoints did not reach statistical significance

Cost-Effectiveness Analysis
Erenumab and Onabotulinum toxin A

- Study Design: Compared erenumab 140mg SC to onabotulinum toxin A and no preventative treatment
  - 2 year study - Adults with EM and CM who failed prior preventative therapy
  - A Study to Assess the Long-Term Safety and Efficacy of Erenumab in Chronic Migraine Prevention
- Conclusion
  - Erenumab may be cost-effective approach to treat CM versus onabotulinum toxin A and no preventative treatment
  - Societal and payer perspectives
  - Not as cost-effective in EM unless lost productivity considered

Overall Conclusion of Erenumab Clinical Trials

- More effective than placebo for episodic and chronic migraine prophylaxis
  - Clinically significant benefit, particularly in chronic migraines.
- No trials with comparative efficacy to first or second-line agents
- Unclear of usefulness in special populations
- Higher dose questionable increased benefit
- Low side effect profile
- No long term efficacy and safety data currently

Future Trial
A Study to Assess the Long-Term Safety and Efficacy of Erenumab in Chronic Migraine Prevention

- Intervention
  - Erenumab 70mg once a month and/or 140mg SC for up to 52 weeks
- Preliminary Results
  - Primary Outcome: Change in monthly migraine days
    - Baseline: 18.11 migraine days/month
    - 8.29 reduction in monthly migraine days at week 52

On the Horizon

AIMOVIG™
Erenumab-azece FDA approval May 2018

AJOVYT™
Fremanezumab-vbmvd FDA approval Sept 2018

EMGALITY™
Galcanezumab-gnlm FDA approval Oct 2018

Clinical Question: Where does Erenumab fit in to migraine prevention?
Take Home Points on Erenumab

- Would try Level A agents first line
- Erenumab may be a suitable second-line agent
  - Cost-effectiveness analysis indicates only beneficial in chronic migraine
- If patient fails 2 or more preferred agent classes, would consider erenumab

Patient Case 1, Part 3

- A 42 year old female patient diagnosed with migraines but no other PMH comes to your clinic asking to try Aimovig injections. Patient states she has up to 12 migraines monthly which have caused her to miss work. Patient states she also has trouble sleeping. Patient has tried topiramate before, but it caused brain fog. During the visit, the patient mentions her typical diet:
  - Breakfast - Donut & espresso
  - Lunch - 5 tortillas and chicken
  - Dinner - large diet coke, French fries, and chicken nuggets

What is the best treatment option for this patient?
A. Aimovig
B. Propranolol
C. Decreased caffeine, especially in evening + Aimovig
D. Decreased caffeine, especially in evening + propranolol

Patient Case 2

- A 58 year old female patient comes to her neurologist with PMH of migraines, bipolar disorder, opioid and alcohol use disorder, and severe episodes of orthostasis and hypotension. Patient is having migraines on most days with no identifiable diet triggers. Patient has previously failed valproic acid, topiramate, alpha nerve stimulation, and botox injections. The patient is willing to try anything that may help her, and the doctor wants to try Aimovig.

What do you recommend?
A. Butalbital
B. Propranolol
C. Aimovig (erenumab)
D. Frovatriptan

Based on data from this Presentation when would YOU use erenumab in clinical practice?
A. First-line
B. Second-line, after failure of two or more agents
C. Third-line, after trying second-line agents
D. Never, too expensive and not enough long-term data

Acknowledgements
- Evaluator: Geeta Maggu, PharmD, CDE – Clinical Pharmacy Specialist – Pain, CTVHCS
- Preceptors
- Co-residents
Appendix A: Migraine Physical Function Impact Diary (MPFID)

MPFID is a patient-reported outcome instrument (PRO) utilized in clinical practice to measure impact of everyday activities (EA) and physical impairment (PI) in patients with migraine over 24-hour recall. MPFID has been validated in multiple studies. The MPFID Is a 17 item activity domain score which encompasses impact on every day activities, physical impairment, and overall impact of migraines.

Concepts/Items - 24 hour recall
1. Difficulty doing household chores
2. Difficulty doing activities outside the home
3. Difficulty keeping to daily routine or schedule
4. Difficulty doing activities requiring concentration
5. Difficulty doing activities requiring clear thinking
6. Difficulty getting ready for the day
7. Duration of time avoiding interactions with people
8. Duration of time needing to rest or lie down
9. Overall difficulty doing usual activities
10. Duration of time with difficulty moving head
11. Duration of time with difficulty moving body
12. Difficulty getting out of bed
13. Difficulty standing up for short periods
14. Difficulty bending over
15. Difficulty walking inside the house
16. Difficulty walking at normal speed
17. Difficulty doing activities requiring physical effort

Health and Quality of Life Outcomes 2017; 15:224
Neurology 2012; 78 (17): 1337-45
Appendix B: Trigeminovascular Nociceptive Pathway in Migraines

The key pathway for pain in migraine is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex (TCC). These neurons in turn project to the quintothalamic tract and synapse on neurons in the thalamus.

Modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus. A number of neurotransmitters play a role in migraine headaches, including serotonin, melatonin, and dopamine. Activation of cells in the trigeminal nucleus results in the release of vasoactive peptides, particularly calcitonin gene-related peptides at vascular terminals of the trigeminal nerve and within the trigeminal nucleus.
### Appendix C: Erenumab-aooe Trial Data


#### Design
Multicenter, randomized, double blind placebo controlled phase II trial

#### Intervention
Erenumab 70mg, 140mg or placebo monthly

#### Primary Objectives
Change in mean number of migraine days per month from baseline to last 4 weeks of 12 week study

#### Secondary Objectives *refer to study for full list of objectives*
- >50% Reduction of migraine days per month

#### Inclusion Criteria *refer to study for full inclusion criteria*
Men and women aged 18-65 w/ h/o chronic migraine
- ≥ 15 headaches per month
- 80% compliance w/ headache diary

#### Exclusion Criteria *refer to study for full exclusion criteria*
- >50 years of age at onset
- h/o hemiplegic or cluster migraines or chronic migraines w/ continuous pain, patients with no therapeutic response from >3 migraine prophylaxis medications botulinum toxin or used devices/procedures in previous 4 months

#### Methods
4-week baseline phase, 12 week study. patients included in analysis had at least one dose erenumab or placebo, alternative migraine preventative medications prohibited during study.

#### Baseline Characteristics Summary
- Average age ~ 42
- Female sex ~ 80%
- Migraine-days per month ~ 18
- Medication overuse ~ 41%
- Failure of ≥ 2 drugs ~ 50%

#### Results – Primary Outcome *(least-squares mean data)*

<table>
<thead>
<tr>
<th>Change in Monthly Migraine days</th>
<th>Overall difference from placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, -4.2 (0.4)</td>
<td>-2.5 days, p value &lt;0.0001</td>
</tr>
<tr>
<td>Erenumab 70 mg, -6.6 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Erenumab 140mg, -6.6 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

#### Safety Data

<table>
<thead>
<tr>
<th>Injection-site pain (%)</th>
<th>Serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, 1%</td>
<td>Placebo, 2%</td>
</tr>
<tr>
<td>Erenumab 70mg, 4%</td>
<td>Erenumab 70mg, 3%</td>
</tr>
<tr>
<td>Erenumab 140mg, 4%</td>
<td>Erenumab 140mg, 1%</td>
</tr>
</tbody>
</table>
## STRIVE TRIAL – PHASE III Trial  
*New England Journal of Medicine. 2017; 377(22):2123-2132*

### Design
Multicenter, randomized, double blind placebo controlled phase III trial

### Intervention
Erenumab 70mg, 140mg or placebo monthly

### Primary Objectives
Change in mean number of migraine days per month from baseline to months 4-6

### Secondary Objectives *refer to study for full list of objectives*
>50% Reduction of migraine days per month

### Inclusion Criteria *refer to study for full inclusion criteria*
4-14 migraine days per month  
80% compliance w/ headache diary

### Exclusion Criteria *refer to study for full exclusion criteria*
>50 years at age of onset  
h/o hemiplegic or cluster headaches  
botulinum toxin or used devices/procedures in previous 4 months

### Methods
4-week baseline phase, 6 month study. Patients included in analysis had at least one dose erenumab or placebo w/ monthly follow up. Patients allowed to continue stable migraine prevention treatment previously during trial.

### Baseline Characteristics Summary
Average age ~ 41  
Female sex ~ 85%  
Migraine-days per month ~ 8  
Monthly MPFID Score* everyday-activities ~13  
Monthly MPFID Score* physical impairment score ~ 12.3

### Results – Primary Outcome *(least-squares mean data)*
*Change in Monthly Migraine days from baseline to months 4-6*
- Placebo, -1.8  
- Erenumab 70 mg, -3.2  
- Erenumab 140mg, -3.7

### Results – Secondary Outcome
*Percentage of patients w/ a ≥ 50% reduction at months 4-6*
- Placebo, 26.6%  
- Erenumab 70mg, 43.4% (odds ratio vs. placebo, 2.1)  
- Erenumab 140mg, 50% (odds ratio vs. placebo, 2.8)

### Safety Data

<table>
<thead>
<tr>
<th>Injection-site pain (%)</th>
<th>Serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, 0.3%</td>
<td>Placebo, 2.2%</td>
</tr>
<tr>
<td>Erenumab 70mg, 3.2%</td>
<td>Erenumab 70mg, 2.5%</td>
</tr>
<tr>
<td>Erenumab 140mg, 0.3%</td>
<td>Erenumab 140mg, 1.9%</td>
</tr>
</tbody>
</table>

*Monthly MPFID everyday activity domain scores range from 7-35 but study extrapolated scores to a 100-point scale.*
**Design**
Multicenter, randomized, double blind placebo controlled parallel group trial

**Intervention**
Erenumab 70mg or placebo monthly

**Primary Objectives**
Change in mean number of migraine days per month from baseline to last month of trial (month 3)

**Secondary Objectives** *refer to study for full list of objectives*
>50% Reduction of migraine days per month

**Inclusion Criteria** *refer to study for full inclusion criteria*
- Adults 18-65 years old
- 4-14 migraine days per month
- 80% compliance w/ headache diary

**Exclusion Criteria** *refer to study for full exclusion criteria*
- >50 years at age of onset
- h/o hemiplegic or cluster headaches
- botulinum toxin or used devices/procedures in previous 4 months
- medical conditions that might prevent study completion

**Methods**
3 week screening phase, 4-week baseline phase, 12 week double blind phase, and 28 week open-label treatment phase. Safety follow-up at 12 weeks after last dose. Patients stratified by region, current migraine prevention, prior migraine treatment, or no prior migraine treatment.

**Baseline Characteristics Summary**
- Average age - 42
- Female sex ~ 85%
- Migraine-days per month ~ 8.2
- History of any prior preventative treatment use ~ 46%
- Prior preventative treatment failures ~ 87%

**Results – Primary Outcome (least-squares mean data)**

<table>
<thead>
<tr>
<th>Change in Monthly Migraine days</th>
<th>Difference from placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo -1.8 (0.2)</td>
<td>-1.0 day</td>
</tr>
<tr>
<td>Erenumab 70mg -2.9 (0.2)</td>
<td>P value &lt; 0.001</td>
</tr>
</tbody>
</table>

**Results – Secondary Outcome**

<table>
<thead>
<tr>
<th>Percentage of patients w/ a ≥ 50% reduction in migraines</th>
<th>Difference from placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, 29.5%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Erenumab 70mg, 43.4%</td>
<td>P value &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>OR 1.59 (1.12, 2.27)</td>
</tr>
</tbody>
</table>

**Safety Data**

<table>
<thead>
<tr>
<th>Injection-site pain (%)</th>
<th>Grade 3 event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, 4.2%</td>
<td>Placebo, 2.8%</td>
</tr>
<tr>
<td>Erenumab 70mg, 6%</td>
<td>Erenumab 70mg, 2.1%</td>
</tr>
</tbody>
</table>
Appendix D: Proposed Treatment Algorithm

- Implement non-pharmacologic changes
- How often is patient experiencing migraine?
- Review Acute Medication use

1-3 migraines monthly:
  - Consider acute medications only (triptans, analgesics, NSAIDs)

4-30 migraines monthly:
  - Consider divalproex, propranolol, and/or topiramate (2 month trial)

Consider 3 month trial of second line agents (AAN guidelines) or Aimovig. May consider botox in chronic migraines