Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value

Public Meeting – June 14, 2018
Welcome and Introduction

• Why are we here today?
  • Innovation promising substantial benefits to patients and their families

• You lose your sense of who you are, how to speak, how to think, how to move. You become a shell of your former self. The light hurts, that woman’s perfume on the subway makes you sick, the sound of a baby’s cry sends you into paralysis.
  -- Patient comment on ICER draft report

• I'm terrified of the day when I won't be able to work, as I have to spend so much money on medications and doctor appointments just to get out of bed, that there is no way a social security/disability income would support me let alone my family.
  -- Patient comment on ICER draft report
Welcome and Introduction

• Why are we here today?

  • New mechanisms of action often raise questions about appropriate use, cost
    • “An estimated 3.5 million patients have already tried a migraine preventative therapy and approximately 80% stop that therapy within a year, according to Amgen’s calculations.”
      -- Xconomy.com 6-1-18

  • Patients can have difficulty accessing new drugs

  • Need for objective evaluation and public discussion of the evidence on effectiveness and value
Welcome and Introduction

• California Technology Assessment Forum (CTAF)

• The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2018

Funding Sources - %

- Non-profit foundations: 78%
- Manufacturer grants, contracts, and contributions: 10%
- Contributions from health plans and provider groups: 9%
- Government grants and contracts: 3%
Welcome and Introduction

How was the ICER report on CGRP inhibitors for migraine developed?

• Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
• “Academic in confidence” data submitted by manufacturers
• Internal ICER staff evidence analysis
• University of Illinois, Chicago cost-effectiveness modeling
• Public comment and revision
• Expert report reviewers
  • Andrew Hershey, MD, PhD, FAHS (Cincinnati Children’s Hospital, AAN)
  • Annette Langer-Gould, MD, PhD (Kaiser Permanente)
  • Sonja Potrebic, MD, PhD (Kaiser Permanente)
  • Meghan Buzby, MBA (American Migraine Foundation)
• How is the evidence report structured to support CTAF voting and policy discussion?
Goal: Sustainable Access to High-Value Care for All Patients

Long-Term Value for Money
- Comparative Clinical Effectiveness
- Incremental Cost-Effectiveness
- Other Benefits or Disadvantages
- Contextual Considerations

Short-Term Affordability
- Potential Budget Impact
Agenda

10:00am: Welcome and Opening Remarks
10:15 am: Presentation of the Evidence
   Evidence Review: Alexandra G. Ellis, PhD
   Cost Effectiveness: Surrey Walton, PhD
11:15 am: Manufacturer Public Comment and Discussion
11:45 pm: Public Comments and Discussion
12:15 pm: Lunch
1:00 pm: CTAF Deliberation and Votes
2:15 pm: Break
2:25 pm: Policy Roundtable
3:40 pm: Reflections and Wrap Up
4:00 pm: Meeting Adjourned
Evidence Review

Alexandra G. Ellis, PhD
Senior Scientist, HTA and Economic Evaluation
Key Review Team Members

Ifeoma Otuonye, MPH
Katherine Fazioli, BS

Disclosures:
We have no conflicts of interest relevant to this report.
Migraine

• Recurrent headache disorder affecting 20% of women and 6-10% of men in the US
• Associated with moderate-to-severe pain and other symptoms (e.g., nausea, vomiting, or sensitivity to light or to sound)
• Headaches among the top 5 reasons for emergency department (ED) visits
Diagnosis

• Chronic migraine
  • 15 or more headache days per month
  • 8 or more days with migraine features
  • Approximately 10% of patients with migraine

• “Episodic” migraine
  • Migraine not classified as chronic migraine
  • Not a clinical diagnosis
  • Approximately 90% of patients with migraine
Living With Migraine: Insights from Patients

- Feel frustrated, depressed, defeated, isolated, or a burden to society
  - Some patients experience suicidal thoughts
- Strained relationships with family, friends, and coworkers
  - Do not plan due to uncertainty when the next attack will occur
  - Feel stigmatized and that migraine pain is not taken seriously
Treatments for Migraine

• Non-pharmacologic
  • Diet, exercise, cognitive behavioral therapy, neuromodulator devices

• Pharmacologic
  • Acute (NSAIDs, triptans, Excedrin, opioids*)
  • Preventive

* Not recommended for first-line acute treatment
Preventive Treatments for Migraine

• Migraine (episodic or chronic)
  • Antidepressants (e.g., amitriptyline)
  • Anti-seizure medications (e.g., topiramate)
  • Beta-blockers (e.g., propranolol)

• Chronic migraine
  • Onabotulinum toxin A (Botox®, Allergan)
Preventive Therapy

- No strict guidelines on who is eligible
- Adequate therapeutic trial takes 2-6 months
- Patients frequently discontinue or switch therapies due to lack of efficacy or tolerability
  - Difficulty concentrating, remembering, or speaking clearly
  - Weight gain or loss
Treatments For Migraine: Insights from Patients

• “Guess and test” strategies can take many years before finding an effective treatment
• Some treatments work for a time, but stop working or are not tolerable
• Side-effects from some interventions can be as debilitating as migraine
CGRP Inhibitors

• Calcitonin gene-related peptide (CGRP)
• CGRP inhibitors for preventive therapy for patients with chronic or episodic migraine
  • Erenumab (Aimovig™, Amgen/Novartis)
    • FDA approved in May 2018
  • Fremanezumab (Teva)
  • Galcanezumab (Eli Lilly)
Scope of the Review

• **Population**: Adults with chronic or episodic migraine eligible for preventive treatment
  • Patients for whom preventive therapy has failed

• **Interventions**: Erenumab, fremanezumab, galcanezumab

• **Comparators**:
  • Oral preventives (amitriptyline, propranolol, topiramate)
  • Onabotulinum toxin A (chronic migraine only)
  • Placebo (i.e., no active preventive therapy)
Scope of the Review

• Efficacy
  • Monthly migraine days
  • ≥ 50% reduction in monthly migraine days
  • Days using acute medication per month
  • Quality of life

• Tolerability and harms
  • All-cause withdrawal
  • Withdrawal due to adverse events (AEs)
  • Serious AEs (SAEs)
  • Commonly reported AEs
Chronic Migraine: Evidence base

• 3 trials of CGRP inhibitors
• 13 trials of onabotulinum toxin A or topiramate
  • 11 trials included in efficacy analyses
• No trials of amitriptyline or propranolol
## Chronic Migraine: CGRP Inhibitor Trials

<table>
<thead>
<tr>
<th>Study / Phase</th>
<th>Arm</th>
<th>N</th>
<th>Mean Age (Years)</th>
<th>% Add-On Preventive Therapy</th>
<th>Mean Migraine Days per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tepper 2017</strong></td>
<td>Erenumab 70 mg</td>
<td>191</td>
<td>41.4</td>
<td>0</td>
<td>17.9</td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td>Erenumab 140 mg</td>
<td>190</td>
<td>42.9</td>
<td>0</td>
<td>17.8</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>286</td>
<td>42.1</td>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td><strong>Bigal 2015a</strong></td>
<td>Fremanezumab 675/225 mg</td>
<td>88</td>
<td>40.0</td>
<td>40</td>
<td>17.2</td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td>Placebo</td>
<td>89</td>
<td>40.7</td>
<td>43</td>
<td>16.8</td>
</tr>
<tr>
<td><strong>Silberstein</strong></td>
<td>Fremanezumab 675 mg quarterly</td>
<td>376</td>
<td>42.0</td>
<td>20</td>
<td>16.2</td>
</tr>
<tr>
<td><strong>2017</strong></td>
<td>Fremanezumab 675/225 mg</td>
<td>379</td>
<td>40.6</td>
<td>22</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>HALO-CM Phase III</strong></td>
<td>Placebo</td>
<td>375</td>
<td>41.4</td>
<td>21</td>
<td>16.4</td>
</tr>
</tbody>
</table>

All trials included a 4-week baseline period, followed by a 12-week randomized phase.
Chronic Migraine: Monthly Migraine Days

- Placebo
- Topiramate 100 mg/day
- Erenumab 70 mg
- Erenumab 140 mg
- Fremanezumab 675 mg quarterly
- Fremanezumab 675/225 mg monthly
- Onabotulinum toxin A
# Chronic Migraine: Monthly Migraine Days

<table>
<thead>
<tr>
<th></th>
<th>Difference in Change From Baseline vs. Placebo (95% CrI)</th>
<th>Expected Change From Baseline (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Reference</td>
<td>-4.0 (NA)</td>
</tr>
<tr>
<td>Erenumab 70 mg</td>
<td>-2.4 (-4.8, 0.0)</td>
<td>-6.4 (-8.8, -4.0)</td>
</tr>
<tr>
<td>Erenumab 140 mg</td>
<td>-2.4 (-4.8, 0.0)</td>
<td>-6.4 (-8.8, -4.0)</td>
</tr>
<tr>
<td>Fremanezumab 675 mg quarterly</td>
<td>-1.3 (-3.5, 0.9)</td>
<td>-5.3 (-7.5, -3.1)</td>
</tr>
<tr>
<td>Fremanezumab 675/225 mg</td>
<td>-1.7 (-3.5, 0.1)</td>
<td>-5.7 (-7.5, -3.9)</td>
</tr>
<tr>
<td>Onabotulinum toxin A 155U</td>
<td>-2.0 (-3.6, -0.3)</td>
<td>-6.0 (-7.6, -4.3)</td>
</tr>
<tr>
<td>Topiramate 100 mg/day</td>
<td>-1.7 (-4.2, 0.8)</td>
<td>-5.7 (-8.2, -3.2)</td>
</tr>
</tbody>
</table>

Crl: credible interval, NA: not applicable, bold text: statistically significant

Data on subgroup results among patients from whom preventive therapies have failed submitted in confidence.
Chronic Migraine: Other Efficacy Outcomes

- Differences in definitions of 50% responders prohibited quantitative synthesis
- Approximately 2 fewer days using acute medications with CGRP inhibitors vs placebo
- Quality of life measures infrequently and inconsistently assessed
  - Where reported, larger improvements with active therapies than placebo
Episodic Migraine: Evidence Base

- 8 trials of CGRP inhibitors (1 open-label extension)
  - 6 trials of CGRP inhibitors included in efficacy analyses
  - 2 newly-published trials of galcanezumab
- 24 trials of oral preventive therapies
  - 16 trials included in efficacy analyses
# Episodic Migraine: CGRP Inhibitor Trials

<table>
<thead>
<tr>
<th>Study/Phase</th>
<th>Arm</th>
<th>N</th>
<th>Mean Age (Years)</th>
<th>% Add-On Preventive Therapy</th>
<th>Mean Migraine Days per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun 2016 Phase II*</td>
<td>Erenumab 70 mg</td>
<td>107</td>
<td>42.6</td>
<td>0</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>160</td>
<td>41.4</td>
<td>0</td>
<td>8.8</td>
</tr>
<tr>
<td>Goadsby 2017 STRIVE Phase III</td>
<td>Erenumab 70 mg</td>
<td>317</td>
<td>41.1</td>
<td>2.8</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>Erenumab 140 mg</td>
<td>319</td>
<td>40.4</td>
<td>2.5</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>319</td>
<td>41.3</td>
<td>3.1</td>
<td>8.2</td>
</tr>
<tr>
<td>Dodick 2018 ARISE Phase III</td>
<td>Erenumab 70 mg</td>
<td>286</td>
<td>42.0</td>
<td>6.6</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>291</td>
<td>42.0</td>
<td>5.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Bigal 2015b Phase II</td>
<td>Fremanezumab 225 mg</td>
<td>96</td>
<td>40.8</td>
<td>34.0</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>104</td>
<td>42.0</td>
<td>27.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Dodick 2018 HALO-EM Phase III</td>
<td>Fremanezumab 225 mg</td>
<td>290</td>
<td>42.9</td>
<td>21.4</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>Fremanezumab 675 mg quarterly</td>
<td>291</td>
<td>41.1</td>
<td>19.9</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>294</td>
<td>41.3</td>
<td>21.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Skljarevski 2018a Phase II</td>
<td>Galcanezumab (all doses)</td>
<td>273</td>
<td>40.6</td>
<td>0</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>137</td>
<td>39.5</td>
<td>0</td>
<td>8.0</td>
</tr>
<tr>
<td>Stauffer 2018 EVOLVE 1 Phase III*</td>
<td>Galcanezumab 120 mg</td>
<td>213</td>
<td>40.9</td>
<td>0</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Galcanezumab 240 mg</td>
<td>212</td>
<td>39.1</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>433</td>
<td>41.3</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td>Skljarevski 2018b EVOLVE 2 Phase III*</td>
<td>Galcanezumab 120 mg</td>
<td>231</td>
<td>40.9</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Galcanezumab 240 mg</td>
<td>223</td>
<td>41.9</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>461</td>
<td>42.3</td>
<td>0</td>
<td>9.2</td>
</tr>
</tbody>
</table>

*24-week randomized phase; all other trials were 12 weeks
Episodic Migraine: Monthly Migraine Days

- Erenumab 70 mg
- Erenumab 140 mg
- Fremanezumab 675 mg quarterly
- Fremanezumab 225 mg monthly
- Galcanezumab 120 mg
- Propranolol 160 mg/day
- Amitriptyline 25-100 mg/day
- Topiramate 100 mg/day
- Topiramate 200 mg/day
- Topiramate 50 mg/day
- Fremanezumab 225 mg monthly
- Placebo
### Episodic Migraine: Monthly Migraine Days

<table>
<thead>
<tr>
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<td>Reference</td>
<td>-2.7 (NA)</td>
</tr>
<tr>
<td>Erenumab 70 mg</td>
<td>-1.3 (-1.9, -0.7)</td>
<td>-4.0 (-4.6, -3.4)</td>
</tr>
<tr>
<td>Erenumab 140 mg</td>
<td>-1.9 (-2.9, -1.0)</td>
<td>-4.6 (-5.6, -3.7)</td>
</tr>
<tr>
<td>Fremanezumab 675 mg quarterly</td>
<td>-1.2 (-2.3, -0.1)</td>
<td>-3.9 (-5.0, -2.8)</td>
</tr>
<tr>
<td>Fremanezumab 225 mg</td>
<td>-1.6 (-2.6, -0.7)</td>
<td>-4.3 (-5.3, -3.4)</td>
</tr>
<tr>
<td>Galcanezumab 120 mg*</td>
<td>-1.9 (-3.2, -0.6)</td>
<td>-4.6 (-5.9, -3.3)</td>
</tr>
<tr>
<td>Topiramate 50 mg/day</td>
<td>-0.2 (-1.1, 0.7)</td>
<td>-2.9 (-3.8, -2.0)</td>
</tr>
<tr>
<td>Topiramate 100 mg/day</td>
<td>-1.2 (-1.7, -0.6)</td>
<td>-3.9 (-4.4, -3.3)</td>
</tr>
<tr>
<td>Topiramate 200 mg/day</td>
<td>-1.0 (-1.6, -0.4)</td>
<td>-3.7 (-4.3, -3.1)</td>
</tr>
<tr>
<td>Amitriptyline 25-100 mg/day</td>
<td>-1.1 (-2.4, 0.2)</td>
<td>-3.8 (-5.1, -2.5)</td>
</tr>
<tr>
<td>Propranololol 160 mg/day</td>
<td>-1.2 (-2.2, -0.3)</td>
<td>-3.9 (-4.9, -3.0)</td>
</tr>
</tbody>
</table>

CrI: credible interval, NA: not applicable, bold text: statistically significant

*Results from EVOLVE 1 & 2 are similar in magnitude*

Data on subgroup results among patients from whom preventive therapies have failed submitted in confidence
Episodic Migraine: Other Efficacy Outcomes

• Odds for 50% reduction in migraine days per month approximately 2 times higher with CGRP inhibitors than placebo

• Approximately 1 fewer day using acute medications with CGRP inhibitors vs placebo

• Quality of life measures infrequently and inconsistently assessed
  • Where reported, greater improvements with active therapies than placebo
Tolerability and Harms

• CGRP inhibitors well-tolerated with non-serious and uncommon harms
• No differences in the meta-analyzed odds of discontinuations or SAEs with the CGRP inhibitors versus other preventive therapies
• Most commonly reported AEs with CGRP inhibitors involved injection-site reactions
• Fatigue, memory-loss, difficulty concentrating, and paresthesia commonly reported in oral preventive therapies but not CGRP inhibitors
Controversies and Uncertainties

• **Short-term trials**: Uncertainty in any durability of effects from prolonged use

• **First in CGRP inhibitor class**: Concerns about the long-term effects of continuous blocking of CGRP or its receptor

• **Results may not generalize**: Patients likely to be treated with CGRP inhibitors include those who tried more than three prior treatments and those with comorbidities
Summary

• Preventive treatment with CGRP inhibitors provide some clinical benefit
• Few harms observed
• The short-term trials limit certainty about the safety of these agents with a novel mechanism of action
• Longer-term studies ongoing
ICER Evidence Ratings

- Chronic migraine and eligible to receive preventive therapy with oral agents or onabotulinum toxin A
  - Insufficient (“I”) for erenumab and fremanezumab
- Chronic migraine for whom prior preventive therapy has failed
  - Comparable or better (“C+”) for erenumab and fremanezumab
- Episodic migraine and eligible to receive preventive therapy with oral agents
  - Insufficient (“I”) for erenumab and fremanezumab
- Episodic migraine for whom oral preventive therapies have failed
  - Promising but inconclusive (“P/I”) for erenumab and fremanezumab
- Insufficient (“I”) for galcanezumab for all populations and comparisons
- Insufficient (“I”) for erenumab versus fremanezumab for all populations
Other Benefits and Contextual Considerations

• Monthly (or quarterly) administration may reduce burden of migraine, but subcutaneous injection may add complexity

• If tolerable and effective:
  • Less likely to discontinue treatment
  • Increase ability to work and improve overall productivity

• Novel mechanism of action
Public Comments

• The review should evaluate CGRP inhibitors only in their likely treatment paradigm (i.e., among patients for whom preventive therapies have failed)
  • The wider migraine population and this subgroup were of interest to many stakeholders including clinicians and patients

• Phase II and Phase III studies should not be assessed together
  • Included if similar studies/populations
  • Due to smaller sample sizes or larger variances, Phase II trials have less weight in the analyses

• Galcanezumab should not be included in review
  • Stakeholders beginning to make decisions about erenumab and other CGRP inhibitors
  • Due to limited data, included in clinical review not economic assessment
Cost Effectiveness

Surrey Walton, PhD
Todd Lee, PharmD, PhD
University of Illinois at Chicago College of Pharmacy
Key Review Team Members

Danny Quach, PharmD (UIC)
Varun Kumar, MBBS, MPH, MSc (ICER)
Rick Chapman, PhD, MS (ICER)

Disclosures:
We have no conflicts of interest relevant to this report.
Objective

• To estimate the cost-effectiveness of erenumab and fremanezumab compared to no preventive treatment for patients with chronic and episodic migraines for whom other preventive migraine medications had failed.
Methods in Brief
Methods Overview

• **Model Type**: Semi-Markov models with time-dependent efficacy and mortality rates.

• **Setting**: United States (US)

• **Perspective**: Health sector perspective

• **Time Horizon**: 2 years

• **Discount Rate**: 3% per year (costs and outcomes)

• **Cycle Length**: 1 month

• **Outcomes by Intervention**: Costs, quality-adjusted life years (QALYs), migraine days reduced

• **Primary Outcome**: Cost per QALY Gained
Patient Population

- US patients seeking care for migraine

<table>
<thead>
<tr>
<th>Patient Baseline Characteristics</th>
<th>Chronic Migraine</th>
<th>Episodic Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>39 Years</td>
<td>40 Years</td>
</tr>
<tr>
<td>Proportion Female</td>
<td>80.5%</td>
<td>76.4%</td>
</tr>
<tr>
<td>Mean Migraine Days per Month</td>
<td>17.7</td>
<td>8.0</td>
</tr>
</tbody>
</table>
## Parameters: Drug Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Schedule</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab (Chronic and Episodic)</td>
<td>140 mg</td>
<td>1 injection per month</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Fremanezumab (Chronic and Episodic)</td>
<td>225 mg*</td>
<td>1 injection per month</td>
<td>Subcutaneous</td>
</tr>
</tbody>
</table>

* 675 mg dose for first month in fremanezumab chronic migraine patients
Model Overview

Treatment Model

CGRP Inhibitors Treatment 1

No Preventive Treatment 2

Death 3

Placebo Model

No Preventive Treatment 1

Death 2
Model Transitions

- Discontinuation from “CGRP Inhibitor Treatment” to “No Preventive Treatment” was based on the ICER NMA.

- Mortality was based on age- and gender-adjusted mortality estimates for the general population (CDC/NCHS National Vital Statistics System).
Key Assumptions

- CGRP inhibitors have no direct effect on mortality, outcomes, or cost of treating underlying conditions other than migraines.
- Effect of migraine days on utilities based on disutility weights for mild, moderate, and severe migraine days from the literature.
- Changes in the distribution of mild, moderate, and severe migraine days were modeled based on available evidence for fremanezumab that was also applied to erenumab.
- Reduction in migraine days resulted in proportional reductions in other forms of health care utilization for migraine such as number of hospitalizations, ED visits, PCP visits.
- AEs were assumed to result in a cost associated with a primary care physician office visit and an assumed disutility of 0.05.
- Costs of CGRPs were based on erenumab’s initial launch price discounted by 27% and rounded.
### Key Model Inputs: Clinical Inputs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chronic Migraine: Monthly Discontinuation Rate (95% CI)</th>
<th>Episodic Migraine: Monthly Discontinuation Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab 140 mg monthly</td>
<td>0.031 (0.010, 0.084)</td>
<td>0.041 (0.017, 0.090)</td>
</tr>
<tr>
<td>Fremanezumab 675/225 mg monthly</td>
<td>0.062 (0.034, 0.114)</td>
<td>0.084 (0.044, 0.160)</td>
</tr>
</tbody>
</table>

Monthly migraine day reduction data from the trials have been redacted here, but included in the model since they were submitted to us as academic-in-confidence data.
### Key Model Inputs: Drug Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annual WAC</th>
<th>Annual Net Drug Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab 140 mg</td>
<td>$6,900</td>
<td>$5,000</td>
</tr>
<tr>
<td>Fremanezumab 675*/225 mg</td>
<td>NA</td>
<td>$5,000</td>
</tr>
</tbody>
</table>

NA: not available

*675 mg fremanezumab dose is given for first month in chronic patients only. Same estimated costs.

Also an administration fee of $74 per monthly injection is added to the estimated drug costs in the first month.
## Key Model Inputs: Acute Drug Use Days and Costs

<table>
<thead>
<tr>
<th>Migraine Type</th>
<th>Baseline Acute Drug Use Days per Month</th>
<th>Acute Drug Cost per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>7.62</td>
<td>$24</td>
</tr>
<tr>
<td>Episodic</td>
<td>2.97</td>
<td>$21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Medication Use Days Reduction per Month (Chronic Migraines)</th>
<th>Acute Medication Use Days Reduction per Month (Episodic Migraines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab 140 mg</td>
<td>2.67</td>
<td>1.76</td>
</tr>
<tr>
<td>Fremanezumab 675/225 mg</td>
<td>2.33</td>
<td>1.31</td>
</tr>
</tbody>
</table>
# Key Model Inputs: Healthcare Utilization Costs per Month at Baseline

<table>
<thead>
<tr>
<th>Direct Costs Type</th>
<th>Chronic Migraines</th>
<th>Episodic Migraines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Visits*</td>
<td>$16</td>
<td>$6</td>
</tr>
<tr>
<td>Hospitalizations**</td>
<td>$1</td>
<td>$1</td>
</tr>
<tr>
<td>PCP/Nurse Practitioner/ Specialist Visits</td>
<td>$93</td>
<td>$30</td>
</tr>
<tr>
<td>Other Direct Costs</td>
<td>$31</td>
<td>$10</td>
</tr>
</tbody>
</table>

* The cost of one ED visit was $949 and the rates were 1.7% per month for chronic and 0.7% for episodic. (costs: Ininga 2011, rates: Mesalli 2016)

** The cost of one hospitalization was $8,996 and the rate was 0.00009% per month. (costs: Ininga 2011, rates: Lucado 2006). Rest are Mesalli 2016.
### Key Model Inputs: Adverse Events Monthly Rates and Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monthly Rate (Chronic)</th>
<th>Monthly Cost (Chronic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab 140 mg</td>
<td>0.027</td>
<td>$2</td>
</tr>
<tr>
<td>Fremanezumab 675/225mg</td>
<td>0.117</td>
<td>$9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monthly Rate (Episodic)</th>
<th>Monthly Cost (Episodic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab 140 mg</td>
<td>0.056</td>
<td>$4</td>
</tr>
<tr>
<td>Fremanezumab 675/225mg</td>
<td>0.066</td>
<td>$5</td>
</tr>
</tbody>
</table>

NMA for rates. Assigned physician office visit cost ($73.93).
## Key Model Inputs: Utilities

<table>
<thead>
<tr>
<th>Model Inputs</th>
<th>Base-Case Value</th>
<th>Distribution Within Migraine Days**</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Migraine Day</td>
<td>0.440</td>
<td>51.9%</td>
<td>Xu 2011, Lipton 2007</td>
</tr>
<tr>
<td>Moderate Migraine Day</td>
<td>0.773</td>
<td>41.0%</td>
<td>Xu 2011, Lipton 2007</td>
</tr>
<tr>
<td>Mild Migraine Day</td>
<td>0.835</td>
<td>7.1%</td>
<td>Xu 2011, Lipton 2007</td>
</tr>
<tr>
<td>No Migraine Day*</td>
<td>0.959</td>
<td>For all non-migraine days</td>
<td>Xu 2011</td>
</tr>
</tbody>
</table>

*Utility associated on days that patient did not experience a migraine
**Based on patients with 4-14 Migraines days per month
In addition, adverse events resulted in a assigned disutility of 0.05
Results
# Model Results: Incremental Cost per QALY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Incremental Cost-Effectiveness Ratios (Chronic)</th>
<th>Incremental Cost-Effectiveness Ratios (Episodic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab</td>
<td>$90,000</td>
<td>$150,000</td>
</tr>
<tr>
<td>Fremanezumab</td>
<td>$120,000</td>
<td>$150,000</td>
</tr>
</tbody>
</table>

Costs and QALYs are discounted at 3% per annum
Results are rounded to the nearest $10,000, as confidential data were used in their generation
One-Way Sensitivity Analyses
Erenumab vs. No Preventive Treatment (Episodic)

- Erenumab Efficacy: Migraine Day Reduction
- Erenumab Drug Costs
- Migraine Day Utility
- Migraine Free Day Utility
- Erenumab Efficacy: Acute Drug Cost Reduction
- Erenumab Discontinuation Odds Ratios
- Acute Medication Costs Per Day
- Direct Medical Costs
- Adverse Event Disutility
- Erenumab Adverse Events Costs

Incremental Cost-Effectiveness Ratio ($/QALY gained)

Data Input High Value  Data Input Low Value
Probabilistic Sensitivity Analyses

Chronic Migraine

- **Erenumab 140mg Monthly**
- **Fremanezumab 625/225mg Monthly**

<table>
<thead>
<tr>
<th>Willingness to Pay ($/QALY Gained)</th>
<th>Probability of being Cost-Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0</td>
<td>0%</td>
</tr>
<tr>
<td>$50,000</td>
<td>66.8%</td>
</tr>
<tr>
<td>$100,000</td>
<td>95.7%</td>
</tr>
<tr>
<td>$150,000</td>
<td>79.2%</td>
</tr>
<tr>
<td>$200,000</td>
<td>23.3%</td>
</tr>
<tr>
<td>$250,000</td>
<td></td>
</tr>
<tr>
<td>$300,000</td>
<td></td>
</tr>
</tbody>
</table>
Probabilistic Sensitivity Analyses

Episodic Migraine

Willingness to Pay ($/QALY Gained)

Probability of being Cost-Effective

$100,000/QALY Gained

$150,000/QALY Gained

Erenumab 140mg Monthly

Fremanezumab 225mg Monthly

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

$0 $50,000 $100,000 $150,000 $200,000 $250,000 $300,000 $350,000 $400,000 $450,000 $500,000

44.2%

33.5%

1.5%

3.3%
## Scenario Analyses

### Chronic

<table>
<thead>
<tr>
<th>Scenario Analysis</th>
<th>Erenumab 140 mg</th>
<th>Fremanezumab 625/225 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs. Current Preventive Treatments</td>
<td>$345,000/QALY</td>
<td>$12,780,000/QALY</td>
</tr>
<tr>
<td>Modified Societal Perspective</td>
<td>$50,000/QALY</td>
<td>$80,000/QALY</td>
</tr>
</tbody>
</table>

### Episodic

<table>
<thead>
<tr>
<th>Scenario Analysis</th>
<th>Erenumab 140 mg</th>
<th>Fremanezumab 225 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs. Current Preventive Treatments</td>
<td>$410,000/QALY</td>
<td>$1,040,000/QALY</td>
</tr>
<tr>
<td>Modified Societal Perspective</td>
<td>$110,000/QALY</td>
<td>$110,000/QALY</td>
</tr>
</tbody>
</table>
Limitations

• The models are inherently based on clinical trial data over relatively short time periods that may not reflect longer time horizons or real world use.

• The model applies to an average patient with chronic or episodic migraine for whom other preventive treatment has failed, but may not reflect particular sub-populations.
Comments Received

• A societal perspective should be employed, as CGRPs will have productivity effects
• CGRPs will help with depression as well as migraine
• CGRPs will reduce issues with opioid addiction
• Non-responders will discontinue leaving only responders such that long-run cost effectiveness of CGRPs will improve over time
• CGRPs may impact schooling achievement and impact future employment status (including job promotions)
Summary

• Erenumab and fremanezumab are projected to reduce migraine days and improve patient health.

• At currently expected discounted prices erenumab and fremanezumab are projected to have incremental cost effectiveness ratios between $90,000 and $150,000 for patients with chronic migraine for whom other preventive therapy has failed.

• CGRPs are projected to have cost effectiveness ratios around but likely above $150,000 when used in patients for whom prior preventive therapy has failed.

• Including productivity effects for CGRPs results in more favorable incremental cost effectiveness ratios.

• CGRPs compared to currently available therapies are projected to have incremental cost effectiveness ratios greatly exceeding commonly-cited thresholds.
Manufacturer Public Comment and Discussion
# Speakers

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandhya Sapra, PhD</td>
<td>Director, Global Health Economics, Global Product Lead, Erenumab</td>
<td>Amgen</td>
</tr>
<tr>
<td>Joshua Cohen, MD, MPH, FAHS</td>
<td>Therapeutic Area Lead, Migraine and Headache, Global Medical Affairs</td>
<td>Teva</td>
</tr>
<tr>
<td>Eric Pearlman, MD, PhD</td>
<td>Medical Fellow, Medical Lead - Migraine</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>Jonathan W. Kowalski, PharmD, MS</td>
<td>Vice President, US Health Outcomes and Value</td>
<td>Allergan</td>
</tr>
</tbody>
</table>
Public Comment and Discussion
Katie Golden
Professional Patient, Advocate, and Writer

Conflicts of interest:

- Other relationship that could be reasonably be considered a financial conflict of interest.

Katie has participated in events run by Amgen and Teva, but received less than $5,000 in honoraria payments in aggregate.

Katie also serves as:
- Steering committee member, Coalition for Headache and Migraine Patients (CHAMP)
- Migraine Advocacy Liaison, US Pain Foundation
- Staff writer, migraine.com
- Senior contributing writer, Invisible Project Magazine
- Member of adult headache prevention treatment guideline committee, AAN/AHS
Conflicts of interest:

- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies

The National Headache Foundation receives over 25% of its funding from life sciences companies, including:

- Allergan
- Allergan Foundation
- Amgen
- DepoMed
- Diamond Headache Clinic, Chicago
- Eli Lilly
- Novartis
- Presence Saint Joseph Hospital, Chicago
- Promius
- Supernus
- Ter Sera Therapeutics
- Teva
Conflicts of interest:

- None declared
Shirley Kessel
Miles for Migraine
Executive Director

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

Miles for Migraine receives sponsorship for programs from the organizations below. Less than 30% of Shirley’s compensation comes from these funds.

- Companies that sponsor MFM salaries
  - Allergan Foundation
  - Depomed
  - eNeura
- Companies that support MFM programs
  - Alder Biopharmaceuticals
  - Amgen
  - Eli Lilly
  - Novartis
  - Teva
  - Supernus Pharmaceuticals
Conflicts of interest:

- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies

- Several health plans or life sciences companies serve on the IBI board:
  - United HealthCare
  - Health Care Service Corporation
  - Teladoc

- IBI receives membership dues from the pharmaceutical manufacturers, including:
  - Abbot
  - AbbVie (board member)
  - Amgen (board member)
  - GlaxoSmithKline
  - Johnson & Johnson (board member)
  - Merck
  - National Pharmaceutical Council
  - Novo Nordisk (board member)
  - Pfizer (board member)
  - PhRMA
  - Sanofi (board member)
  - Walgreens
Lunch Meeting will resume at 1:00 pm
Voting Questions
0. What Los Angeles building served as inspiration for the Disney theme park ride “The Tower of Terror”?

A. Chateau Marmont Hotel
B. Los Angeles City Hall
C. The Bradbury Building
D. Hollywood Tower
1. Is the evidence adequate to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab?

A. Yes
B. No
Patient population for questions 1-4: Adult patients with 15 or more headache days per month (i.e., chronic migraine).

2. Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies (e.g., amitriptyline, topiramate, or propranolol)?

A. Yes
B. No
Patient population for questions 1-4: Adult patients with 15 or more headache days per month (i.e., chronic migraine).

3. Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and onabotulinum toxin A (Botox®, Allergan)?

A. Yes
B. No
Patient population for questions 1-4: Adult patients with 15 or more headache days per month (i.e., chronic migraine).

4. For patients who have no other options for preventive therapy, is the evidence adequate to demonstrate a net health benefit for treatment with CGRP inhibitors compared with no treatment?

A. Yes
B. No
Patient population for questions 5-7: Adult patients with 14 or fewer migraine days per month.

5. Is the evidence adequate to distinguish the net health benefits among the CGRP inhibitors erenumab, fremanezumab, and galcanezumab?

A. Yes
B. No
Patient population for questions 5-7: Adult patients with 14 or fewer migraine days per month.

6. Is the evidence adequate to distinguish the net health benefit between treatment with CGRP inhibitors and oral preventive therapies (e.g., amitriptyline, topiramate, or propranolol)?

A. Yes
B. No
Patient population for questions 5-7: Adult patients with 14 or fewer migraine days per month.

7. For patients who have no other options for preventive therapy, is the evidence adequate to demonstrate a net health benefit for treatment with CGRP inhibitors compared with no treatment?

A. Yes  
B. No
**Patient population for questions 8-9: Adult patients with migraine for whom other preventive treatments have failed.**

8. Does treating patients with CGRP inhibitors offer one or more of the following “other benefits?” (select all that apply)

A. Reduced complexity
B. Reduce important health disparities
C. Reduce caregiver/family burden
D. Novel mechanism of action or approach
E. Significant impact on improving return to work/overall productivity
F. Other important benefits or disadvantages. ________
Patient population for questions 8-9: Adult patients with migraine for whom other preventive treatments have failed.

9. Are any of the following contextual considerations important in assessing CGRP inhibitors’ long-term value for money? (select all that apply)

A. Care of individuals with condition of high severity
B. Care of individuals with condition with high lifetime burden of illness
C. First to offer any improvement
D. Compared to comparator, there is significant uncertainty about long-term risk of serious side effects
E. Compared to the comparator, significant uncertainty about magnitude or durability of the long term benefits of this intervention
F. Other important contextual considerations. _____
Patient population for question 10: Adult patients with 15 or more headache days per month (i.e., chronic migraine) for whom other preventive therapies have failed.

10. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with erenumab versus no treatment?

A. Low
B. Intermediate
C. High
Patient population for question 11: Adult patients with 14 or fewer migraine days per month for whom other preventive therapies have failed.

11. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with erenumab versus no treatment?

A. Low
B. Intermediate
C. High
Break
Meeting will resume at 2:25 pm
Policy Roundtable
## Policy Roundtable Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>COI Declaration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amy Benavente, BA</td>
<td>Executive Director, Reimbursement, Access, and Value, Neuroscience, Amgen</td>
<td>Full-time employee of Amgen</td>
</tr>
<tr>
<td>Jill Dehlin, RN, MA, MPH, CHES</td>
<td>Migraine Patient, Former President of American Headache and Migraine Association</td>
<td>None</td>
</tr>
<tr>
<td>Aaron Deves, BS</td>
<td>Global Disease Lead, Migraine and Headache, Teva Pharmaceuticals</td>
<td>Full-time employee of Teva</td>
</tr>
<tr>
<td>Kevin Lenaburg, MA</td>
<td>Executive Director, Coalition for Headache and Migraine Patients (CHAMP), Caregiver for Person With Migraine</td>
<td>CHAMP receives funding from Alder, Amgen, Eli Lilly, MigraineAgain, migraine.com, Novartis, Teva, The Migraine World Summit, Supernus</td>
</tr>
<tr>
<td>Everett Neville, RPh</td>
<td>Executive Vice President, Strategy, Supply Chain, and Specialty, Express Scripts</td>
<td>Full-time employee of Express Scripts</td>
</tr>
<tr>
<td>Sonja Potrebic, MD, PhD</td>
<td>Residency Program Director, Headache Specialist, and Co-Assistant Chief of Neurology, Southern California Permanente Medical Group, Kaiser Permanente</td>
<td>None</td>
</tr>
<tr>
<td>Richard KP Sun, MD, MPH</td>
<td>Medical Consultant and Chief, Clinical Programs and Appeals Section, Health Plan Administration Division, California Public Employees' Retirement System (CalPERS)</td>
<td>None</td>
</tr>
<tr>
<td>Yvette Yeung, MD</td>
<td>Neurologist, Clinical Pod Lead, HealthCare Partners Medical Group</td>
<td>None</td>
</tr>
</tbody>
</table>
CTAF Panel Reflections
Next Steps

• Meeting recording posted to ICER website next week

• Final Report published in early July. Includes description of CTAF votes, deliberation; policy roundtable discussion

• Materials available at

https://icer-review.org/topic/migraines/
Adjourn