Acute Treatments for Migraine Effectiveness and Value

Public Meeting — January 23, 2020

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI Username = Sheraton_Conference
Password = elevate

© 2020 Institute for Clinical and Economic Review

Why are we here today?

Migraine has a major and negative impact on my life. In 2005, my husband and I decided that I would stop working due the challenges of living with migraine disease. I was missing work and found it difficult to maintain a regular schedule. Since then I have given birth to two amazing children. If you ask either of them, they will tell you that they wish they had a normal life with a healthy mother. They wish I could take them to the park on nice days and play with them. Often, I am not well enough to do so. They are happy and provided for, but I could be giving them more. I could be contributing to the household and society more.

Over the years I have tried various triptans…and I have always had the same reaction to the medications. Nothing helps and they actually seem to make things worse. For now, I do nothing to treat my attacks and it is no way to live. Some days I feel frantic for relief from the pain and other symptoms, but there is nowhere to turn. I am trapped with this. **I desperately need access to new types of acute treatments**

Patient with Migraine

Why are we here today?

- What happens the day these treatments are approved by the FDA?
- What is the goal of public deliberation on the evidence on benefits to patients and costs to the health care system?

© 2020 Institute for Clinical and Economic Review

© 2020 Institute for Clinical and Economic Review

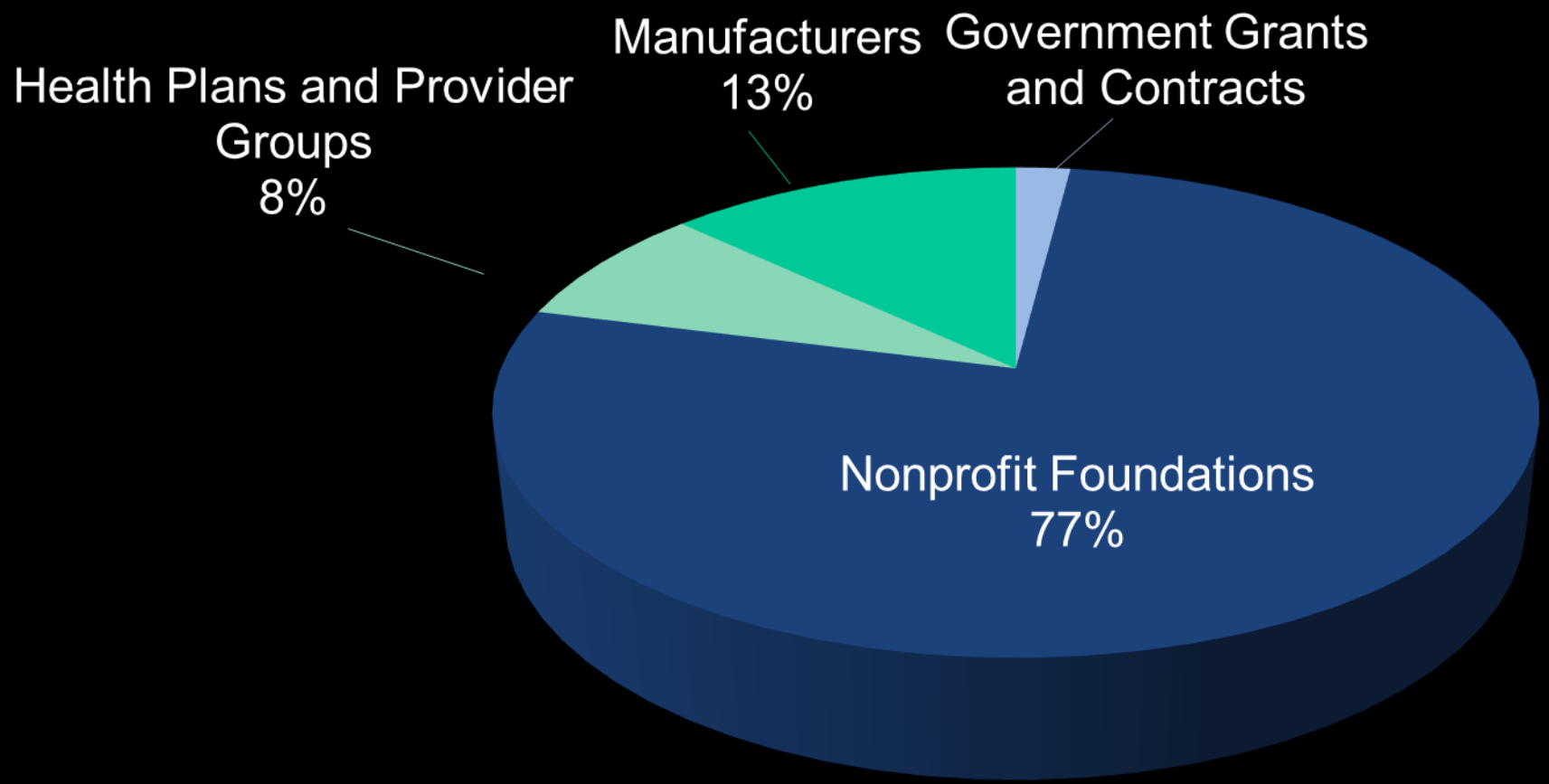
© 2020 Institute for Clinical and Economic Review

Organizational Overview

- Midwest Comparative Effectiveness Public Advisory Council
- The Institute for Clinical and Economic Review (ICER)

© 2020 Institute for Clinical and Economic Review

2020 Funding Sources



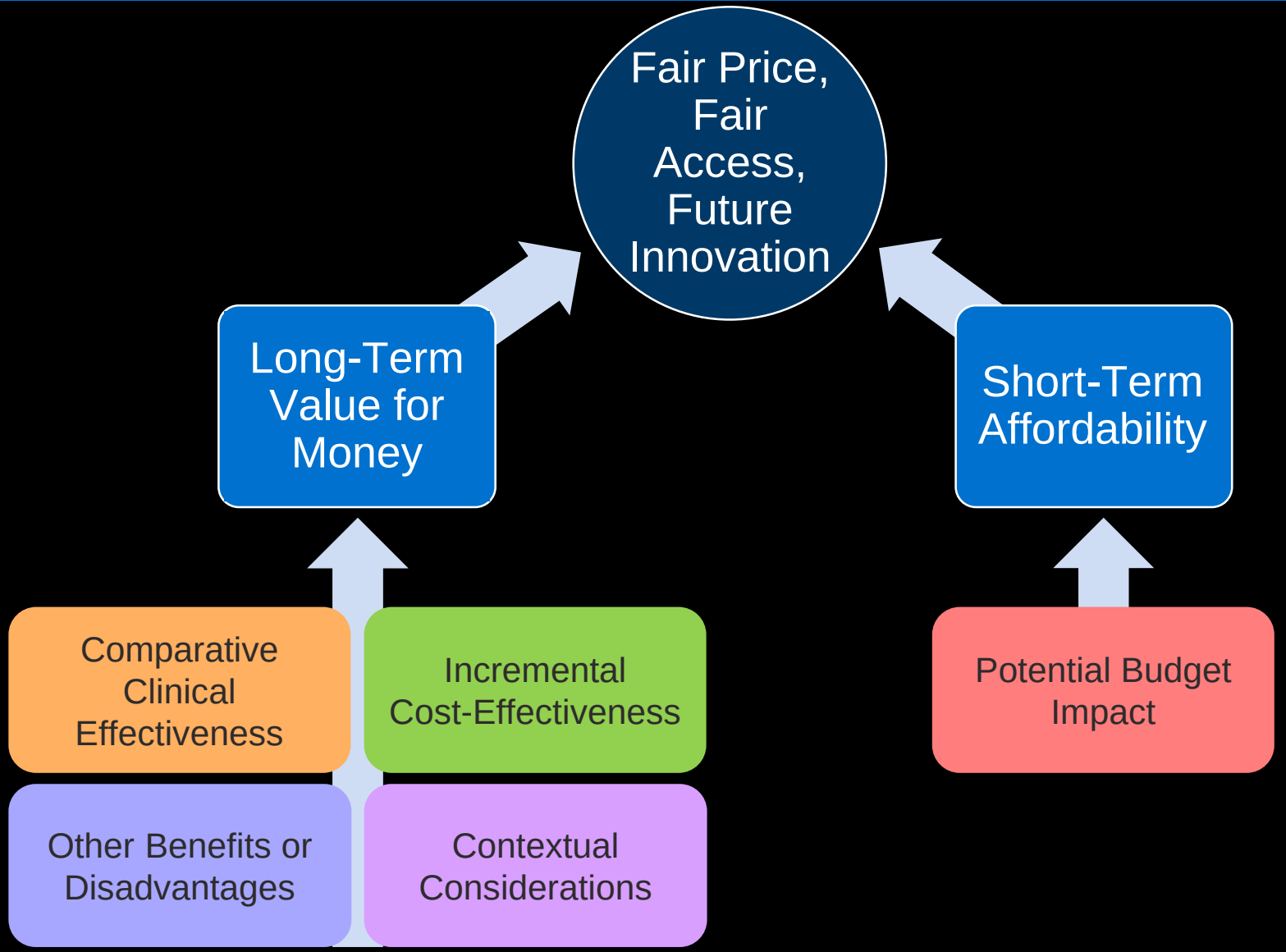
ICER Policy Summit and Non-Report activities only

© 2020 Institute for Clinical and Economic Review

How was the ICER report developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- Cost-effectiveness modeling: Daniel Touchette, PharmD, MA, FCCP and Todd Lee, PharmD, PhD, University of Illinois at Chicago
- Public comment and revision
- Expert reviewers
    - Jeff Klingman, MD, Chief of Neurology at Kaiser Permanente
    - Kevin Lenaburg, Executive Director at the Coalition for Headache and Migraine Patients (CHAMP)
- How is the evidence report structured to support CEPAC voting and policy discussion?

© 2020 Institute for Clinical and Economic Review



© 2020 Institute for Clinical and Economic Review

Agenda

10:00	Meeting Convened and Opening Remarks
10:15	Presentation of the Clinical Evidence
10:45	Presentation of the Economic Model
11:15	Manufacturer Public Comments and Discussion Public Comments and Discussion
11:35	Public Comments and Discussion
12:00	Lunch
1:00	Midwest CEPAC Panel Deliberation and Vote
2:15	Break
2:30	Policy Roundtable Discussion
3:45	Reflections from Midwest CEPAC Panel
4:00	Meeting Adjourned

© 2020 Institute for Clinical and Economic Review

Patient Experts

Katie Golden, BA, Director of Patient Relations, Coalition for Migraine and Headache Patients (CHAMP)

- *COI Disclosures: Received compensation from the following organizations which receive at least 25% funding from pharmaceutical companies:*
  - *CHAMP as Director of Patient Relations – sponsorship includes Allergan, Eli Lilly and Biohaven*
  - *Miles for Migraine as a writer and speaker - sponsorship includes Allergan, Eli Lilly and Biohaven*
  - *U.S. Pain Foundation as Migraine Advocacy Liaison and Editorial Consultant for the INvisible Project Magazine - sponsorship includes Allergan, Eli Lilly and Biohaven*

© 2020 Institute for Clinical and Economic Review

Patient Experts

Sarah Wells Kocsis, MBA, VP of Public Policy, Society for Women's Health Research

- *COI Disclosures: Held senior positions at three diferent health care companies: Amgen, Boston Scientific, and Hologic. Has stock holdings in excess of $10,000 in each of these companies*

© 2020 Institute for Clinical and Economic Review

Clinical Experts

Christopher Gottschalk, MD, FAHS, Director, Headache Medicine; Chief, General Neurology, Yale School of Medicine

- *COI Disclosures: Received consulting fees, is an Advisory Board member, and/or is on the Speaker Bureau at: Amgen/Novartis, Alder, Biohaven, Eli Lilly, and Theranica. Yale School of Medicine was listed as a clinical trial site for Biohaven (BHV 303), but the study was closed due to low enrollment prior to recruitment initiation.*

Jeff Klingman, MD, Chief of Neurology at Kaiser Permanente

- *Dr. Klingman has reported no conflicts of interest.*

© 2020 Institute for Clinical and Economic Review

Evidence Review

Steven J. Atlas, MD, MPH

Physician / Associate Professor of Medicine

Massachusetts General Hospital / Harvard Medical School

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

© 2020 Institute for Clinical and Economic Review

Key Collaborators

- **Steven J. Atlas, MD, MPH**
  Director, Practice Based Research, MGH
- **Foluso Agboola, MBBS, MPH**
  Director, Evidence Synthesis, ICER
- **Noemi Fluetsch, MPH**
  Research Assistant, ICER
- **Eric Borrelli, PharmD, MBA**
  Evidence Synthesis Intern, ICER

Disclosures:

We have no conflicts of interest relevant to this report

© 2020 Institute for Clinical and Economic Review

Background

- Migraine is a common, typically episodic cause of disabling headache often associated with nausea and sensitivity to light and sound
- Migraine attacks are common, serious, and expensive
  - ~40 million (12-15%) adults in the United States
  - Associated with decreased productivity, work loss and disability claims
  - Accounts for $11-50 billion in total costs

© 2020 Institute for Clinical and Economic Review

Impact on Patients

- Migraine is an episodic and chronic disease that can profoundly affect all aspects of their lives and the lives of those close to them
- Existing therapies do not work in all patients, and even if helpful, headaches can recur as treatment wears off, and response can vary from one migraine attack to another and can decrease over time
- Side effects of existing therapies can lead to discontinuation or patients may have contraindications to their use
- For those with moderate or severe migraines, there is no single or combined therapy that offers reliable, long-term control of acute attacks

© 2020 Institute for Clinical and Economic Review

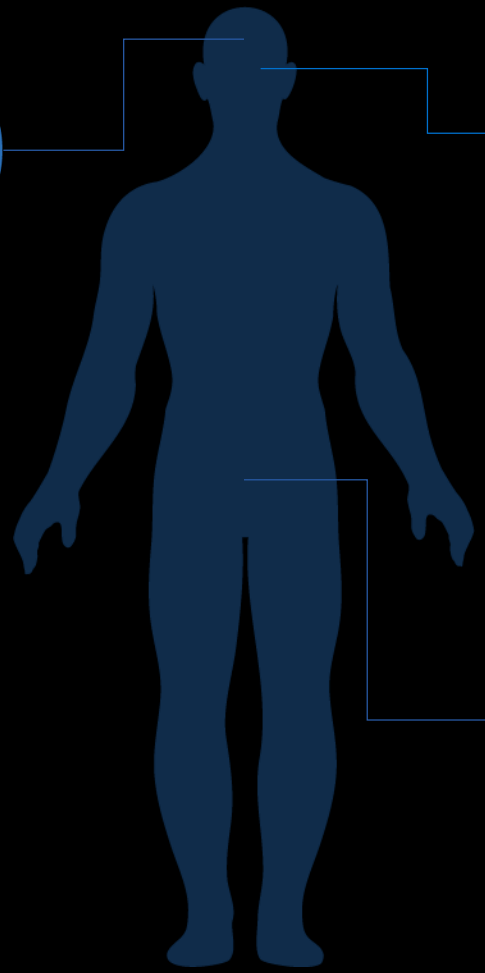
Symptom Chart

Headache

Dizziness

Fatigue

Numbness



Sensitivity to light, sound, and smells

See spots, wavy lines, flashing lights (aura)

Nausea

Vomiting

© 2020 Institute for Clinical and Economic Review

Standard of Care and Management

- Non-specific, over the counter medications such as aspirin, nonsteroidal anti-inflammatory drugs (e.g. ibuprofen), and acetaminophen used alone or in combination
  - First-line treatment for those with mild symptoms
- Specific migraine medications: “Triptans,” or 5-hydroxytryptamine (5-HT) or serotonin receptor agonists most commonly use
  - For those with moderate/severe symptoms or lack of response to non-specific medications
  - Other meds such as ergotamine preparations and anti-emetics less commonly used
- Potential new targets for therapy
  - Selective 5-HT 1f agonist (“Ditans”)
  - Calcitonin gene-related peptide (CGRP) receptor antagonist (“Gepants”)

© 2020 Institute for Clinical and Economic Review

Insights from Discussions with Patients

- Patients highlight need for new therapies
  - Available medications, used alone or in combination, do not reliably manage or prevent migraine attacks
  - Available therapies do not provide symptom relief from migraine attacks with minimal side effects for many individuals
  - For many, triptans do not work, have intolerable side effects, or have contraindications to their use
- Emphasize dramatic impact of migraine on all aspects of life: relationships with friends and family, work, disability and economic hardship

© 2020 Institute for Clinical and Economic Review

Scope of Review

- To evaluate clinical effectiveness of lasmiditan, rimegepant and ubrogepant for acute treatment of migraine with or without aura in adults
- Comparators
  - •Population 1: No additional migraine specific medication (placebo arm of trials) if non-prescription medicines and triptans are ineffective, not tolerated, or contraindicated
  - •Population 2: Triptans (sumatriptan and eletriptan), if eligible to use and non-prescription medicines are ineffective or not tolerated

© 2020 Institute for Clinical and Economic Review

New Treatments for Acute Treatment of Migraine

- Lasmiditan (Reyvow™, Lilly)
  - 50-200mg (50,100mg pills) as needed (only one dose in 24 hours)
  - Approved on October 11, 2019 by the FDA
- Rimegepant (Biohaven)
  - 75mg oral pill as needed daily (details not available at present)
  - Under review by the FDA
- Ubrogepant (Ubrelvy™, Allergan)
  - 50-100mg (50,100mg pills) as needed (second dose at least 2 hours after initial, up to 200mg in 24 hours)
  - Approved on December 23, 2019 by the FDA

© 2020 Institute for Clinical and Economic Review

Key Clinical Outcomes

- Primary
  - Pain freedom at 2 hours post dose
  - Most bothersome symptom at 2 hours post dose
- Secondary
  - Pain relief at 2 hours post dose and sustained pain freedom and relief at 24 hours post dose
  - Relief from other migraine symptoms (e.g., photophobia, phonophobia, nausea, vomiting) and improved function/disability
  - Harms: Side effects, discontinuation

© 2020 Institute for Clinical and Economic Review

Clinical Evidence

Evidence Base:

- We conducted systematic review based on the PICOT criteria
- We identified 33 single-migraine attack trials to include in network meta-analysis (NMA)

Interventions	N of trials	N of patients
Lasmiditan (vs. placebo)	3 trials	4,291
Rimegepant (vs. placebo)*	4 trials	3,869
Ubrogepant (vs. placebo)	3 trials	3,105
Sumatriptan and Eletriptan • 18 sumatriptan vs. placebo • 3 eletriptan vs. placebo • 2 sumatriptan vs. eletriptan	23 trials	12,053

* includes an active comparator arm (sumatriptan)

© 2020 Institute for Clinical and Economic Review

Baseline Characteristics of Treated Patients

- Gender: over 80% were female
- Average age: 40 years
- Average duration of migraine: 20 years
- Frequency of migraine attacks:
  - 3 to 5 per month in intervention trials
  - 1 to 8 per month in triptan trials
- Use of preventive migraine medication:
  - 20 to 25% in intervention trials

© 2020 Institute for Clinical and Economic Review

Trial Design: Use of Medications after 2 hours

- After primary outcome assessed at 2 hours, trials differed in use of rescue treatments for persistent or recurrent symptoms
- Rescue medications could be used between 2 and 24-48 hours
- Optional second dose of study medication
  - Lasmiditan – re-randomized to placebo or lasmiditan (no other meds allowed)
  - Rimegepant – none
  - Ubrogepant – second placebo if initial placebo or re-randomized to placebo or ubrogepant (no other meds allowed)
- Trials differed in use of other medications including triptans, ergots, opioids, and barbiturates

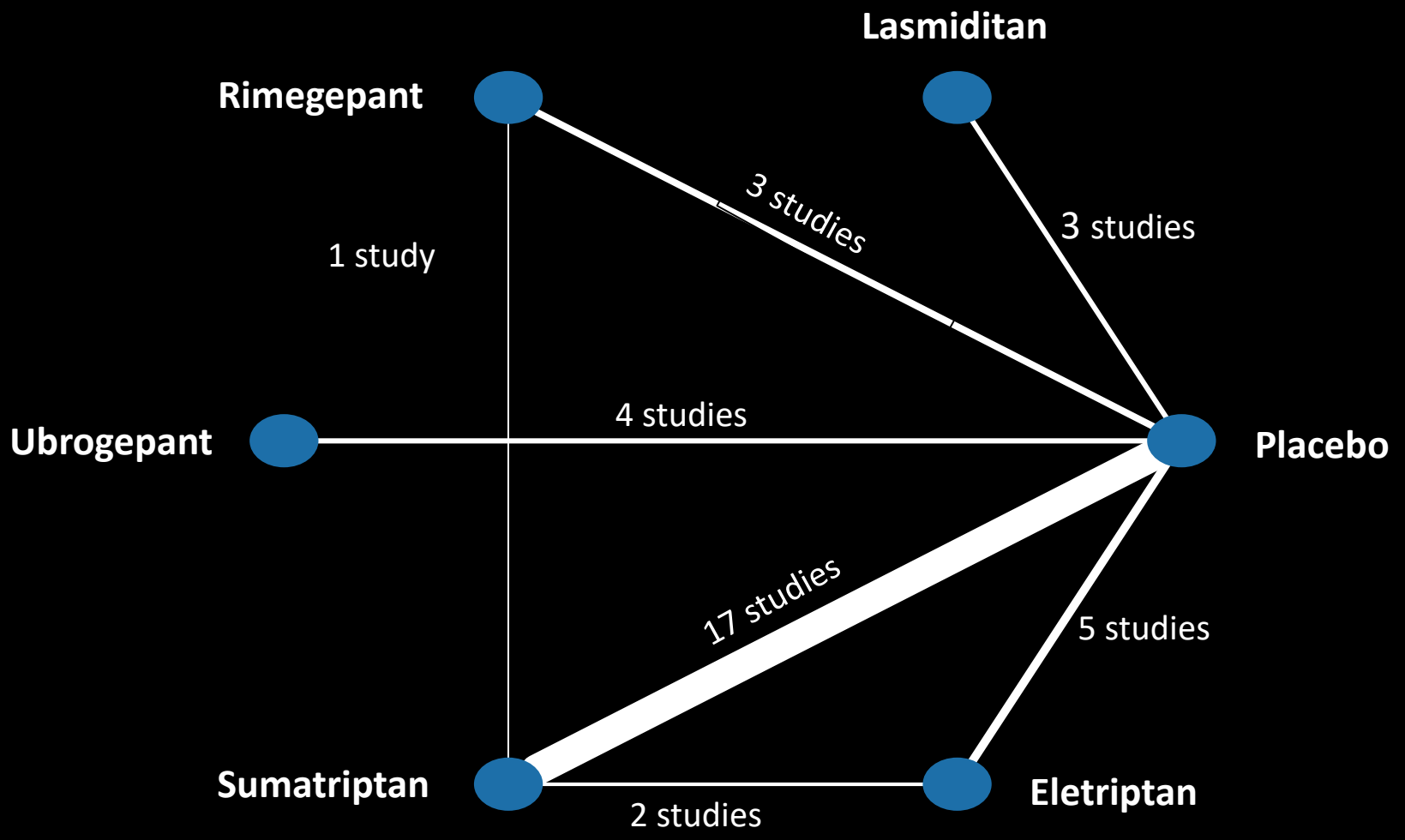
© 2020 Institute for Clinical and Economic Review

Results of Phase III trials: Pain Freedom and Relief

- Greater proportion of patients achieved pain freedom at 2 hours with the interventions compared with placebo
  - Lasmiditan: 28% to 32% versus 15% to 21%
  - Rimegepant: 19% to 21% versus 10% to 14%
  - Ubrogepant: 19% to 21% versus 11% to 14%
- Similar trend with higher proportions observed for pain relief at 2 hours with the interventions compared with placebo

© 2020 Institute for Clinical and Economic Review

Network Diagram: Pain Freedom and Relief



© 2020 Institute for Clinical and Economic Review

NMA Results: Pain Freedom at 2 hours

Lasmiditan					
1.43 (0.97, 2.06)	**Rimegepant**				
1.43 (0.93, 2.14)	1.00 (0.69, 1.46)	**Ubrogepant**			
0.73 (0.53, 1.06)	**0.51 (0.39, 0.7)**	**0.52 (0.37, 0.74)**	**Sumatriptan**		
0.54 (0.36, 0.85)	**0.38 (0.27, 0.57)**	**0.38 (0.26, 0.59)**	**0.73 (0.57, 0.97)**	**Eletriptan**	
3.01 (2.2, 4.14)	**2.11 (1.67, 2.72)**	**2.12 (1.58, 2.88)**	**4.09 (3.43, 4.82)**	**5.60 (4.14, 7.23)**	**Placebo**

Legend: Each box represents the estimated odds ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

© 2020 Institute for Clinical and Economic Review

NMA Results: Pain Relief at 2 hours

- Similar trends as seen for pain freedom observed:
  - Lasmiditan, rimegepant and ubrogepant showed higher odds of achieving pain relief compared to placebo
  - No statistically significant differences between the three interventions
    - Lasmiditan showed a statistically non-significant, higher odds of achieving pain relief compared to rimegepant and ubrogepant
  - All three interventions showed lower odds of achieving pain relief compared to sumatriptan and eletriptan
    - Lasmiditan versus sumatriptan was not statistically significant

ICER © 2020 Institute for Clinical and Economic Review

Other Important Patient Outcomes

- *Sustained pain freedom:* All interventions had higher odds of achieving sustained pain freedom at 24 hours vs. placebo (OR 2.32 – 2.92)
- *Most bothersome symptom (MBS):* All interventions had higher odds of achieving freedom from MBS at two hours vs. placebo (OR 1.58 – 1.69)
- *Disability*: All interventions had higher odds of achieving 'no disability' at two hours vs. placebo (OR 1.51 – 1.70)
- Compared to each other, none of the interventions showed a statistically significant difference for these outcomes

© 2020 Institute for Clinical and Economic Review

Limitations of NMA

- Only one head-to-head trial of one of the interventions versus a triptan (rimegepant vs sumatriptan)
- No study directly comparing the interventions to each other
- Lacking head-to-head data, indirect quantitative methods used
  - More uncertainty than if therapies directly compared
- Adjusted for differences in outcome rates for placebo across studies

© 2020 Institute for Clinical and Economic Review

Harms: Rimegepant and Ubrogepant

- Mild to moderate adverse events (AEs)
  - Nausea was the most commonly reported AE in the trials
- No differences in AE and treatment emergent AEs (TEAEs) between rimegepant and ubrogepant versus placebo and triptans in the single-attack trials
- Low rates of discontinuation were observed in the open-label extension (OLE) studies (2.2% - 2.7%)

© 2020 Institute for Clinical and Economic Review

Harms: Lasmiditan

- Mild to moderate AEs, most commonly involving central nervous system
  - Dizziness (16-18%), somnolence (5-6%), paresthesia (2-7%)
- Lasmiditan had higher rates of AE and TEAEs compared to placebo, rimegepant, eletriptan and sumatriptan in the single-attack trials
- In the lasmiditan OLE study:
  - 12.8% of patients discontinued due to AEs
  - Dizziness most common AE leading to discontinuation

© 2020 Institute for Clinical and Economic Review

Controversies and Uncertainties

- Though patients highlighted the importance of outcomes after two hours, use of rescue medications differed among trials making it difficult to assess the benefits of these new drugs after two hours
- Since most data for these drugs come from trials treating a single migraine attack, outcomes when used over time for repeated attacks are uncertain
- Long-term impact of these new therapies on quality of life and work and productivity outcomes unknown at present

© 2020 Institute for Clinical and Economic Review

Controversies and Uncertainties

- Decreased frequency of migraines over time with ongoing use of new medications
  - High frequency of attacks at baseline may decrease over time simply due to regression to the mean
  - If those with greatest migraine burden don't benefit and drop out, remaining patients with fewer migraines at baseline are left - overestimating any decrease in frequency
  - Why would lasmiditan, which works through a mechanism similar to triptans, show this benefit if triptans don't?
  - A trial comparing telcagepant (a gepant) with rizatriptan (a triptan) in more than 1000 patients showed similar reductions in headache frequency over time
  - Decrease in migraine-specific days per month was considerably smaller in trials of CGRP monoclonal antibodies for prevention of migraine attacks

© 2020 Institute for Clinical and Economic Review

Potential Other Benefits and Contextual Considerations

- For patients not responding to other therapies or having had intolerable side effects or contraindications to their use, these new therapies may offer a new treatment option
- These new drugs have not been shown to cause vasoconstriction, but whether they are safe in those with cardiovascular disease remains to be proven
- How these new drugs compare to each other, especially with prolonged use, remains to be seen

ICER © 2020 Institute for Clinical and Economic Review

Public Comments Received

- Importance of adjusting for differences in placebo rates over time
- Focus on outcomes through 2 hours post dose may miss important differences among medications between 2 - 8 hours
- Outcomes differed among subgroups with prior use of triptans or not (triptan “naïve”) compared to placebo in the trials

© 2020 Institute for Clinical and Economic Review

Summary

- Lasmiditan:
  - Improved outcomes compared to placebo, similar or slightly better than gepants, and similar or slightly worse than triptans
  - Generally well tolerated, but more side effects than rimegepant, ubrogepant and triptans, and more likely to discontinue treatment than gepants
- Rimegepant and Ubrogepant:
  - Improved outcomes compared to placebo, similar or slightly worse than lasmiditan, and worse than triptans
  - Few side effects: Similar to each other and triptans, fewer than lasmiditan

© 2020 Institute for Clinical and Economic Review

ICER Evidence Ratings

- Population 1: lasmiditan, rimegepant and ubrogepant vs. placebo considered “incremental or better” (B+)
- Population 2: lasmiditan, rimegepant and ubrogepant vs. triptans considered “comparable or inferior” (C-)
- For all adults with migraine attacks:
  - Rimegepant vs. urbrogepant considered “comparable” (C)
  - Lasmiditan vs. rimegepant and ubrogepant considered “comparable or inferior” (C-)

© 2020 Institute for Clinical and Economic Review

Questions?

Cost-Effectiveness

Daniel Touchette, PharmD, MA, FCCP

Professor of Pharmacy, Department of Pharmacy Systems Outcomes and Policy; Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research

University of Illinois at Chicago College of Pharmacy

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

© 2020 Institute for Clinical and Economic Review

Key Review Team Members

- Daniel R. Touchette, PharmD, MA
    - Professor of Pharmacy, Department of Pharmacy Systems Outcomes and Policy, University of Illinois at Chicago College of Pharmacy
    - Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research
- Todd A. Lee, PharmD, PhD
    - *Professor of Pharmacy, Department of Pharmacy Systems Outcomes and Policy, University of Illinois at Chicago College of Pharmacy*
    - *Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research*
- *Disclosures:*

Financial support was provided to the University of Illinois at Chicago from the Institute for Clinical and Economic Review.

University of Illinois at Chicago researchers have no conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

© 2020 Institute for Clinical and Economic Review

Objective

Estimate the cost-effectiveness of acute treatments for migraine compared to each other and to three comparators in two separate and distinct sub-populations

© 2020 Institute for Clinical and Economic Review

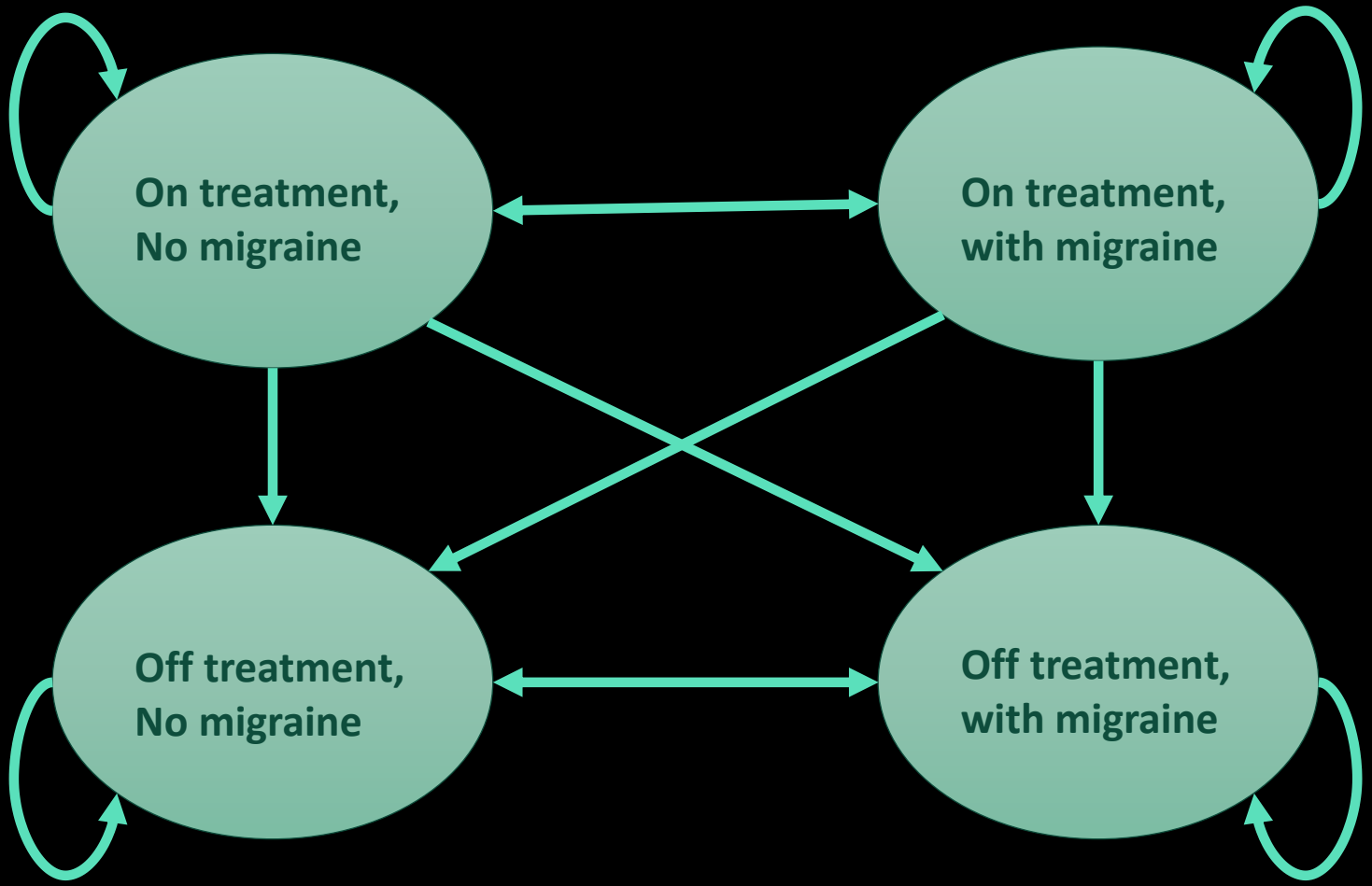
Methods in Brief

Methods Overview

- **Model**: Semi-Markov with time varying proportions of patients with response to treatment
- **Setting**: United States
- **Perspective**: Health Care Sector Perspective
- **Time Horizon**: 2 years
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 48 hours
- **Primary Outcome**: Cost per quality-adjusted life year (QALY) gained
- Other Outcomes: Life-years gained, equal value of life years gained, and cost per hour of migraine pain avoided

© 2020 Institute for Clinical and Economic Review

Model Schematic



© 2020 Institute for Clinical and Economic Review

Model Characteristics

- Target Populations
  - Patients who had migraine attacks that did not respond to non-prescription medicines and for whom triptans had not been effective, were not tolerated, or were contraindicated
  - Patients who had migraine attacks that did not respond adequately to non-prescription medicines, such as non-steroidal anti-inflammatory agents
- Mean Age: 40.8 years
- Gender: 86.0% female
- Migraine Frequency: 4.8 days per month

© 2020 Institute for Clinical and Economic Review

Key Model Assumptions

- Mortality is not associated with acute treatment for migraine
- Patients with moderate or severe pain had a probability of having an emergency department admission or hospitalization
- Acute treatment of migraine with lasmiditan, rimegepant, ubrogepant, and triptans does not affect migraine frequency
- Patients receiving no benefit from treatment discontinued the medication in the first year of treatment only. There was no discontinuation for lack of effectiveness in the second year of the model
- If a migraine treatment resulted in migraine pain of “no pain” or “mild pain” at 2 hours, a person would be able to work

© 2020 Institute for Clinical and Economic Review

Key Model Inputs: No Pain (Pain Free) at Timepoint

- Pain at 2h: Direct input from metaanalysis
- Pain at 8h:
  - If pain free at 2h: “1-sustained pain free at 24h”
  - If not pain free at 2h: Placebo response from Dodick et al
- Pain at 24h
  - If pain free at 8h: Pain free
  - If not pain free at 8h: Placebo response from Dodick et al
- Pain at 48h
  - If pain free at 8h: Pain free
  - If not pain free at 8h: Placebo response from Dodick et al

© 2020 Institute for Clinical and Economic Review

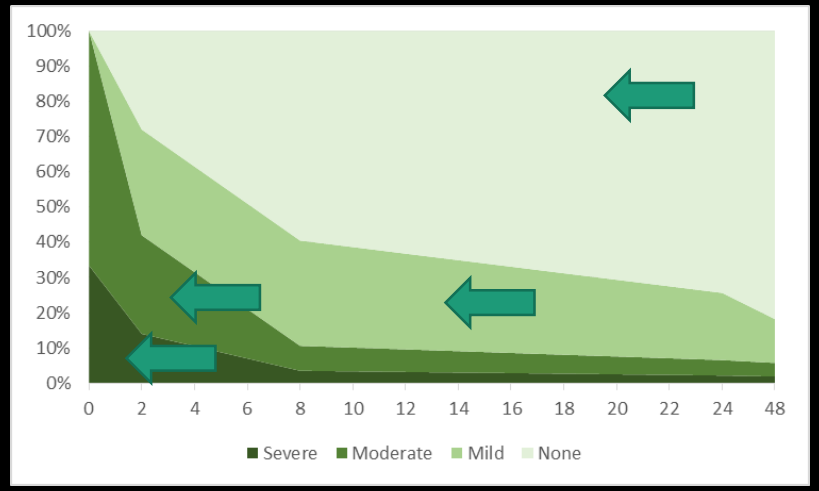
Key Model Inputs: Pain at Timepoint

- Mild Pain
  - Calculated with same methods as No Pain
  - % Pain Relief (from NMA) - % Pain Free (from NMA)
- Moderate Pain and Severe Pain
  - % with no response (i.e. no Pain Freedom or Pain Relief in NMA)
  - Assumed similar proportions of patients with Moderate or Severe Pain as at baseline for each time point

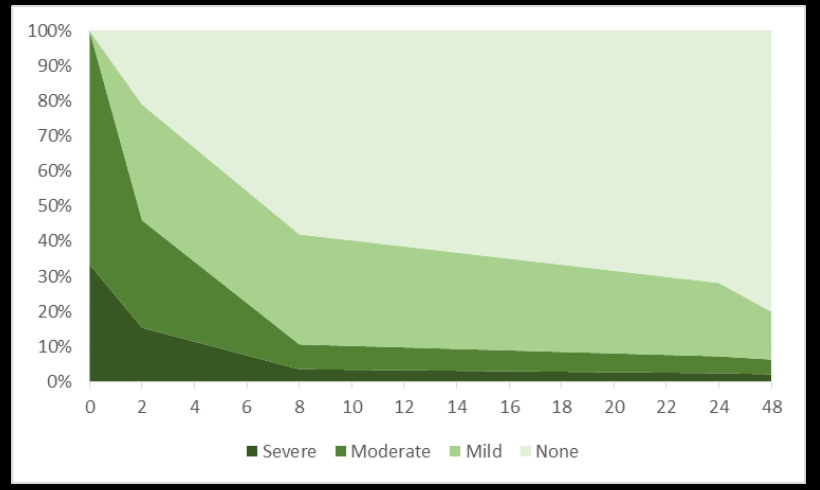
© 2020 Institute for Clinical and Economic Review

Key Model Inputs: Pain at Timepoint

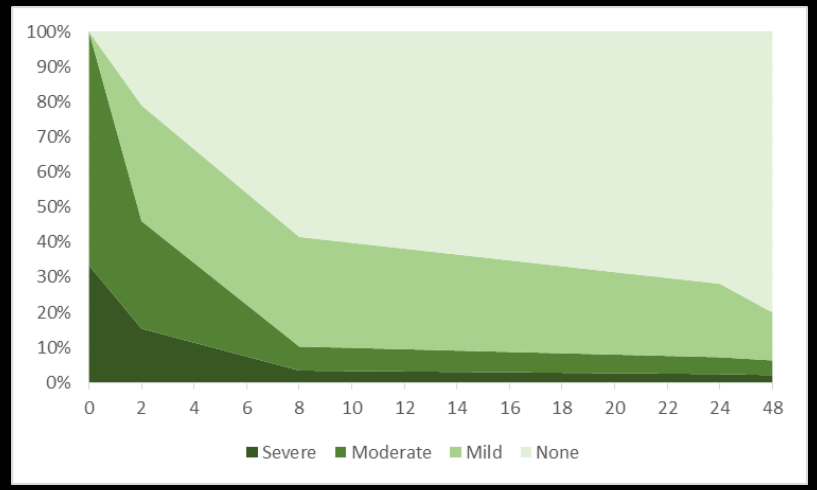
Lasmiditan



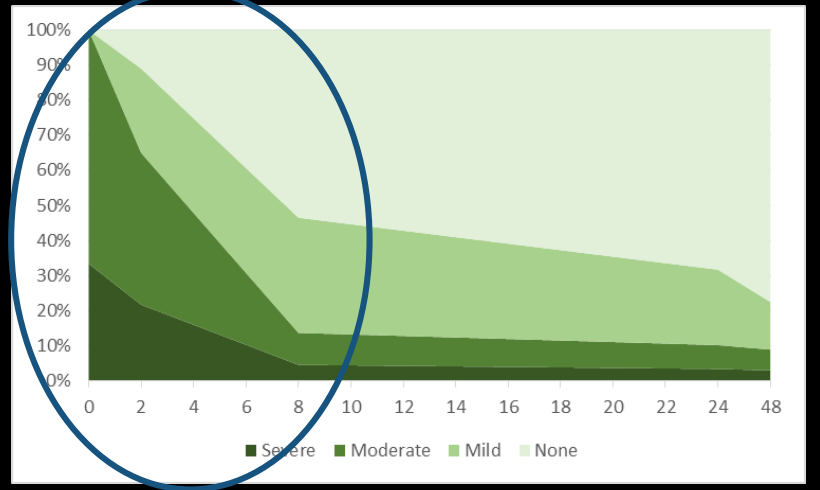
Ubrogepant



Rimegepant



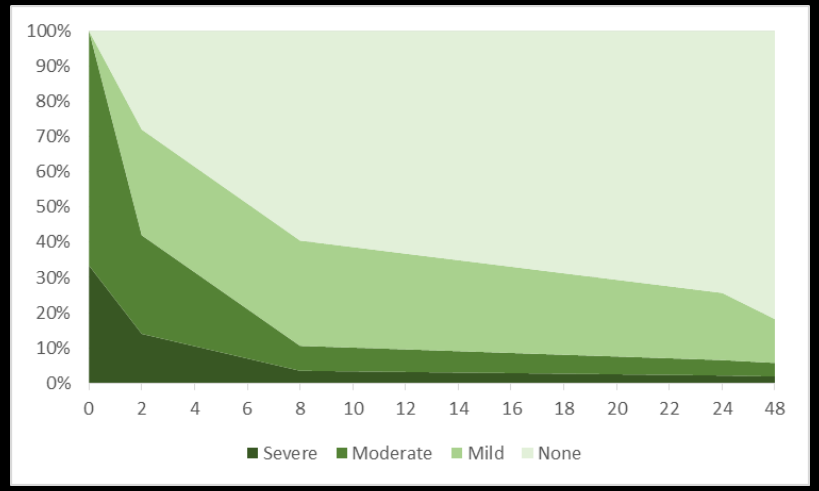
Usual Care



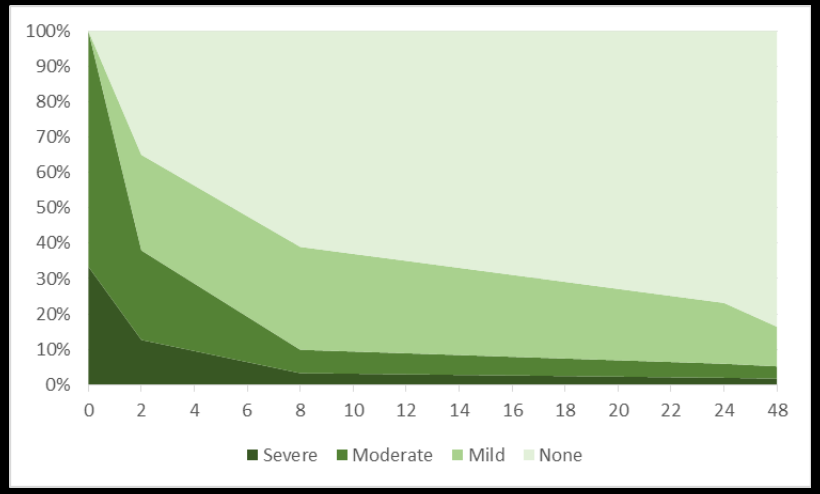
© 2020 Institute for Clinical and Economic Review

Key Model Inputs: Pain at Timepoint

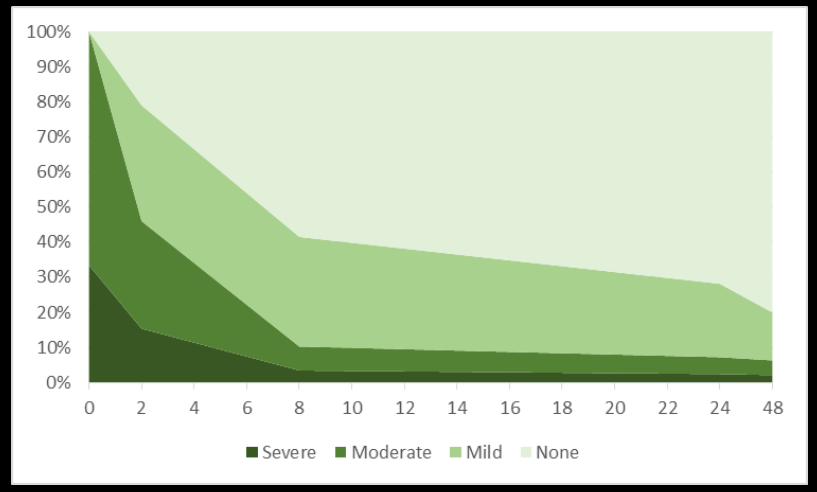
Lasmiditan



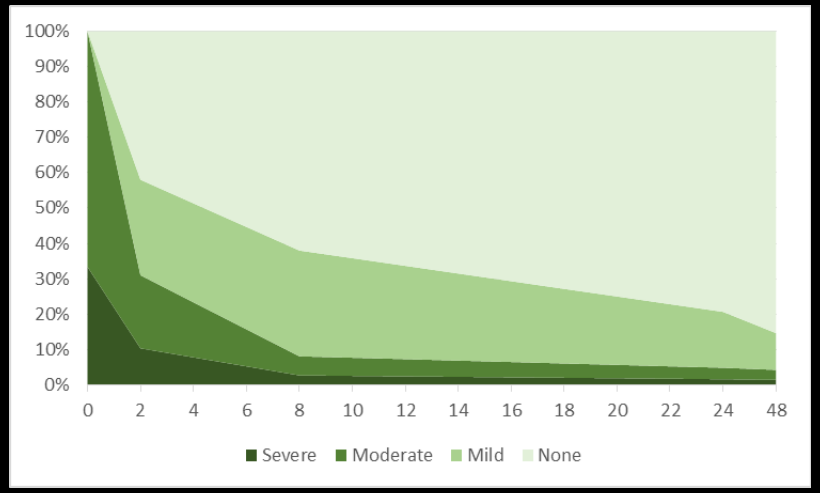
Sumatriptan



Rimegepant



Eletriptan



© 2020 Institute for Clinical and Economic Review

Key Model Inputs: Adverse Drug Events

Adverse Event	Drug	Frequency (%)
Drowsiness	Lasmiditan	5.5
Dizziness	Lasmiditan	14.7
Fatigue	Lasmiditan	3.8
	Sumatriptan	3.0
	Eletriptan	10.0
Paresthesia	Lasmiditan	5.7
	Sumatriptan	5.0
	Eletriptan	4.0

© 2020 Institute for Clinical and Economic Review

Key Model Inputs: Drug Cost per Dose

Drug	Wholesale Acquisition Cost ($)	Cost Input ($)
Lasmiditan	Not Available	Used 78.38, 20% premium pricing above Imitrex (branded sumatriptan)
Rimegepant	Not Available	Used 78.38, 20% premium pricing above Imitrex
Ubrogepant	85.00	Used 62.05, WAC – 27%
Sumatriptan	1.04	
Eletriptan	11.95	
Usual Care (mix)	4.81	Mix of treatments, excluding triptans

© 2020 Institute for Clinical and Economic Review

Key Model Inputs: Utilities

Migraine Symptom	Utility	Solicitation Method
Severe Pain	0.440	EQ-5D
Moderate Pain	0.773	EQ-5D
Mild Pain	0.835	EQ-5D
No Pain	0.959	EQ-5D
Nausea/Vomiting, Photophobia, Phonophobia	Estimates not found in literature	
Adverse Drug Event	-0.013 to -0.069	Time Trade Off
Emergency Department Visit	-0.5 (for 1 day)	Assumed
Hospitalization	-0.5 (for 2 days)	Assumed

© 2020 Institute for Clinical and Economic Review

Results

Base-Case Results

Drug	Cost*	QALYs	Hours of Pain
Lasmiditan*	$13,640	1.8252	1,743
Rimegepant*	$14,500	1.8222	1,870
Ubrogepant	$13,020	1.8221	1,876
Sumatriptan	$6,630	1.8264	1,611
Eletriptan	$6,790	1.8293	1,484
Usual Care	$10,050	1.8142	2,100

QALYs: quality-adjusted life years
*Cost for lasmiditan and rimegepant is based on placeholder prices

© 2020 Institute for Clinical and Economic Review

Base-Case Incremental Results Compared with Usual Care

Drug	Incremental Cost per QALY	Incremental Cost per Hour of Pain Avoided
Lasmiditan	$327,700	$10.10
Rimegepant	$559,500	$19.41
Ubrogepant	$379,000	$13.30

QALY: quality-adjusted life years
*Cost for lasmiditan and rimegepant is based on placeholder prices

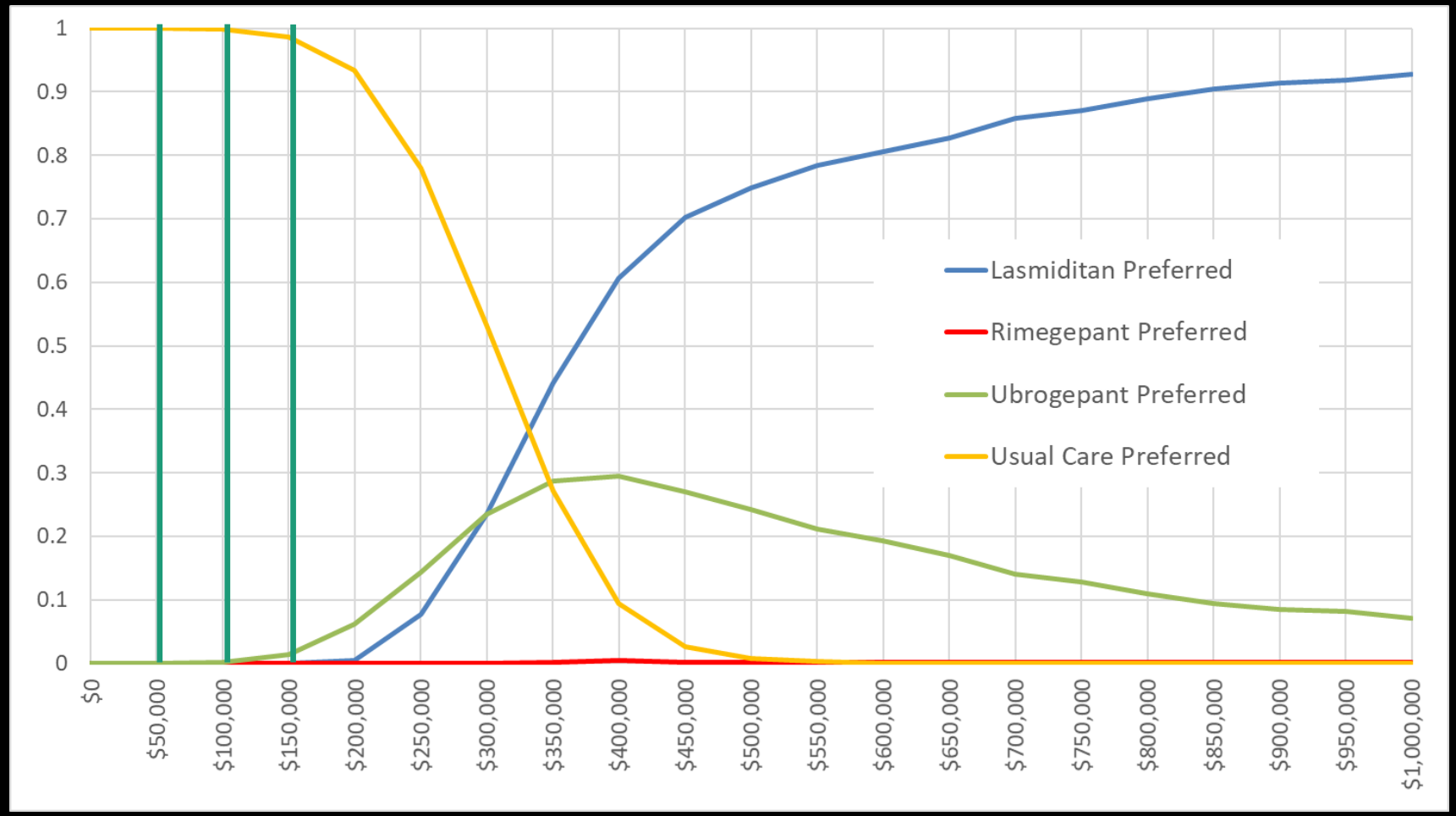
© 2020 Institute for Clinical and Economic Review

One Way Sensitivity Analyses

- Critical Variables
  - None
- Important Variables (in order of importance)
  - Migraine frequency per month (i.e. medication use reduces migraine days per month)
  - Probability of hospitalization
  - Probability of 24h pain relief
  - Probability of ED visits

© 2020 Institute for Clinical and Economic Review

Probabilistic Sensitivity Analysis



© 2020 Institute for Clinical and Economic Review

Scenario Analyses

Scenario	Lasmiditan Cost per QALY*	Rimegepant Cost per QALY*	Ubrogepant Cost per QALY
Base Case	$327,700	$559,500	$379,000
Modified Societal Perspective	$207,800	$422,900	$240,300
Increasing Gepant Effectiveness After 2h	Not evaluated	$138,000	$40,000
5-year Time Horizon	$326,300	$552,100	$373,931

*Incremental cost-effectiveness thresholds for lasmiditan and rimegepant were based on placeholder prices

© 2020 Institute for Clinical and Economic Review

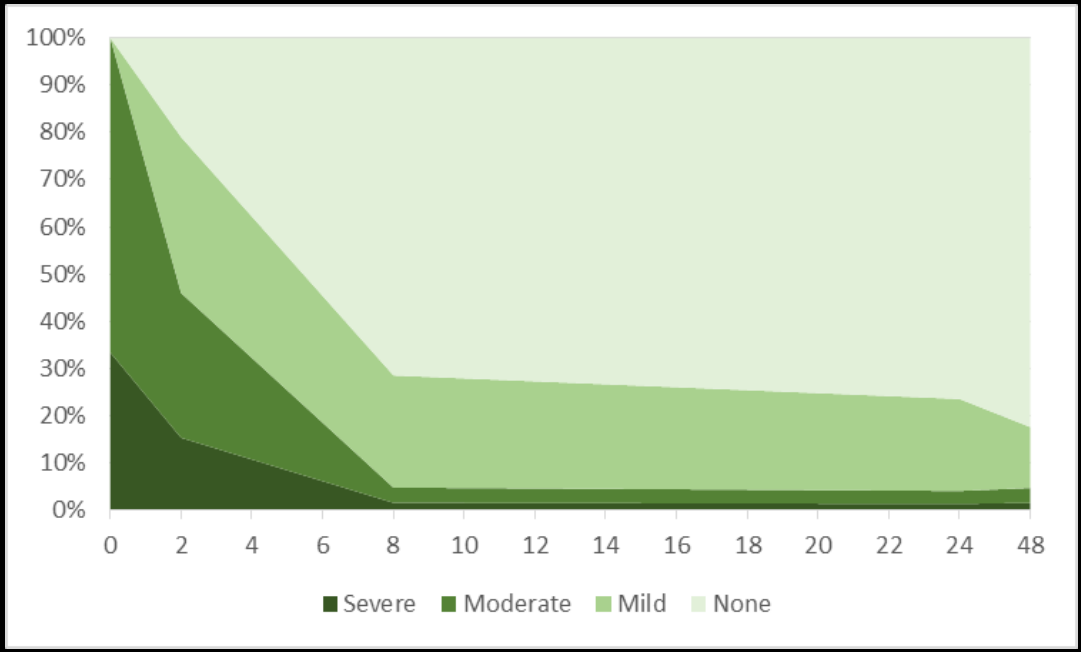
Scenario Analysis

- Emerging evidence from post-hoc analyses, submitted to ICER, strongly suggests that there is a delayed onset of action for ubrogepant (and rimegepant).
- Data from analyses of ubrogepant showed a consistent increased effectiveness at 4 and 8 hours compared with placebo
- However, due to study design, the effect size at 4 and 8 hours was difficult to estimate
- We conducted an additional scenario analysis using our best estimate of the 8 hour effect size
- Since this was a new analysis, conducted after the release of the revised report, we included the newly released WAC price and 27% rebate in the analysis, rather than the placeholder prices

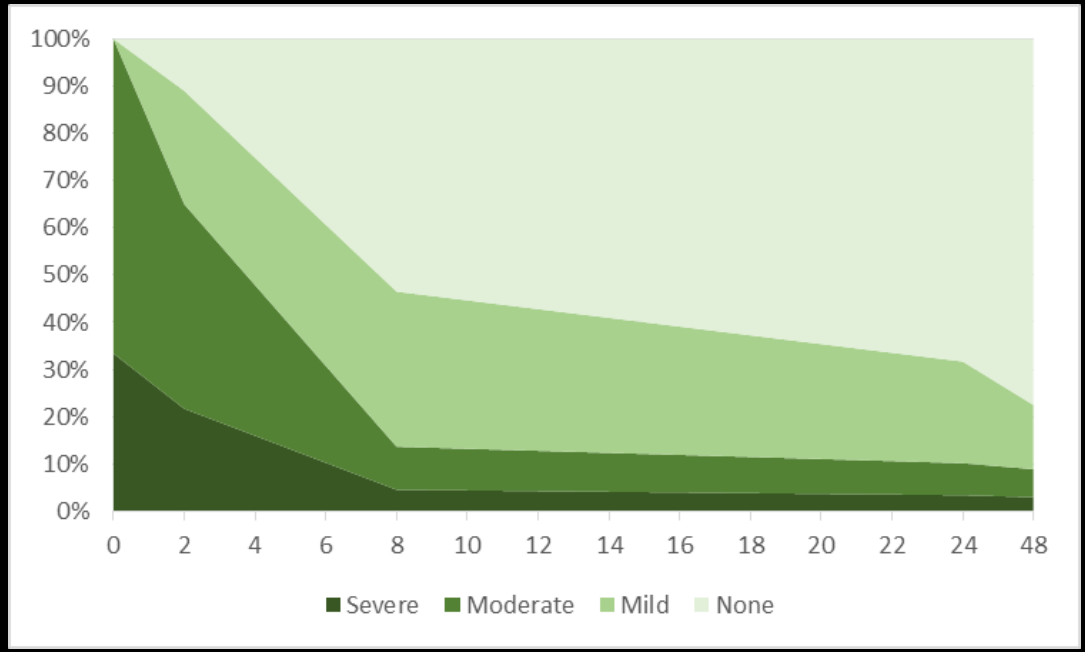
© 2020 Institute for Clinical and Economic Review

Pain at Timepoint

Ubrogepant



Usual Care



© 2020 Institute for Clinical and Economic Review

Scenario Analysis Results

Drug	Cost*	QALYs	Hours of Pain
Ubrogepant	$10,660	1.8295	1,576
Usual Care	$10,050	1.8142	2,100

Drug	Incremental Cost per QALY	Incremental Cost per Hour of Pain Avoided
Ubrogepant	$40,000	3.98

QALYs: quality-adjusted life years
*Cost is based on ubrogepant WAC – 27%

© 2020 Institute for Clinical and Economic Review

Limitations

- Prices are not known for all new treatments except ubrogepant; placeholder prices were used for all new treatments, with exception of ubrogepant price in one scenario analysis.
- Randomization in clinical trials was maintained until the 2h time point. Most results beyond 2h were potentially biased. As a result, the model primarily captured results at 2h and in 2h responders only, and may not adequately address longer-term effectiveness of agents, repeat dosing, and long-term use.
  - Rimegepant and ubrogepant may have a delayed onset of action in some patients
  - Long-term impact on migraine frequency is not known
- Likelihood of discontinuing treatment for lack of effectiveness, and the impact on the effectiveness of treatment in patients continuing to take the medication is not known.

© 2020 Institute for Clinical and Economic Review

Comments Received (and Responses)

- Use clinical trial efficacy observations beyond 2 hours in the cost-effectiveness analysis
- Implement treatment discontinuation effects into the CEA as described in the draft evidence report
- Include adverse event costs in the CEA
- Include cost of relevant usual care comparators

© 2020 Institute for Clinical and Economic Review

Conclusions

- In patients for whom triptans are not effective, not tolerated, or are contraindicated (Population 1), and if these drugs are priced with the place-holder prices used in this analysis, they will exceed commonly accepted thresholds for cost effectiveness
- Using the estimated placeholder prices in the base-case, the triptans are more effective and less expensive than newer agents
- Due to the designs of clinical trials, there is considerable uncertainty around cost-effectiveness estimates generated in the model

ICER © 2020 Institute for Clinical and Economic Review

Questions?

Manufacturer Public Comment and Discussion

Manufacturer Public Commenters

Speaker	Title	Affiliation
Erin Doty, MD	Senior Medical Advisor, Migraine and Headache Disorders	Eli Lilly
Gilbert L'italien, PhD	Senior VP of GHEOR and Epidemiology	Biohaven Pharmaceuticals
Mitchell Mathis, MD	Vice President, Chief Medical Officer, CNS	Allergan

© 2020 Institute for Clinical and Economic Review

Public Comment and Discussion

Eileen Brewer, President Clusterbusters

Conflicts of Interest:

- *Contractor for CHAMP, which receives funding from Eli Lilly and Allergan, among other pharmaceutical companies.*
- *President of Clusterbusters, a research and educational non-profit which receives more than 25% of its funding from pharmaceutical companies including Eli Lilly.*

© 2020 Institute for Clinical and Economic Review

Angie Glaser, Content Editor
Migraine Again

Conflicts of Interest:

- Compensation or sponsored travel received as a patient advocate and for National Headache Foundation, Miles for Migraine, the Alliance for Headache Disorders Advocacy, World Health Education Foundation, and the Coalition of Headache and Migraine Patients (CHAMP).
- Travel to the ICER meeting is supported by CHAMP. Also, I'm employed as a part-time content editor with Migraine Again, LLC, a company that sells digital ad space to pharmaceutical companies and receives more than 25% of its funding from health care companies.

© 2020 Institute for Clinical and Economic Review

Sharol Klise

Conflicts of Interest:

- *Sharol has no reported conflicts of interest.*

© 2020 Institute for Clinical and Economic Review

Nim Lalvani, Director
American Migraine Foundation (AMF)

Conflicts of Interest:

- *Full time employee of the AMF, which receives about 25% of funding from pharmaceutical companies including Eli Lilly and Allergan*

© 2020 Institute for Clinical and Economic Review

Jaime Sanders, Professional Patient Advocate
CHAMP & Headache and Migraine Policy Forum

Conflicts of Interest:

- *Jaime has no reported conflicts of interest.*

© 2020 Institute for Clinical and Economic Review

Lunch

Meeting will resume at 1:00pm

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Voting Questions

WIFI Username = Sheraton_Conference
Password = elevate

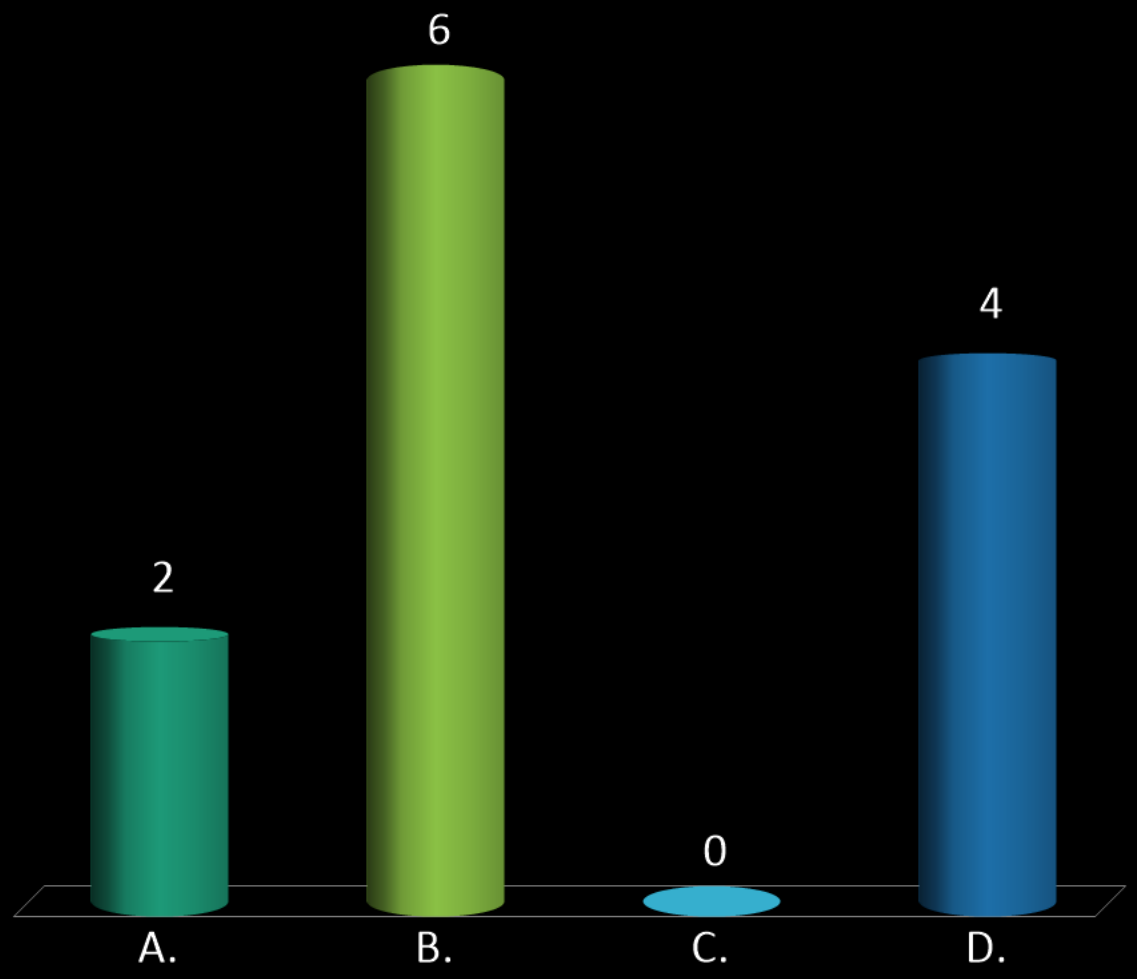
Test Question: What is the official Illinois State Snack?

A. Hotdog

B. Deep dish pizza

C. Frango mint chocolates

D. Popcorn

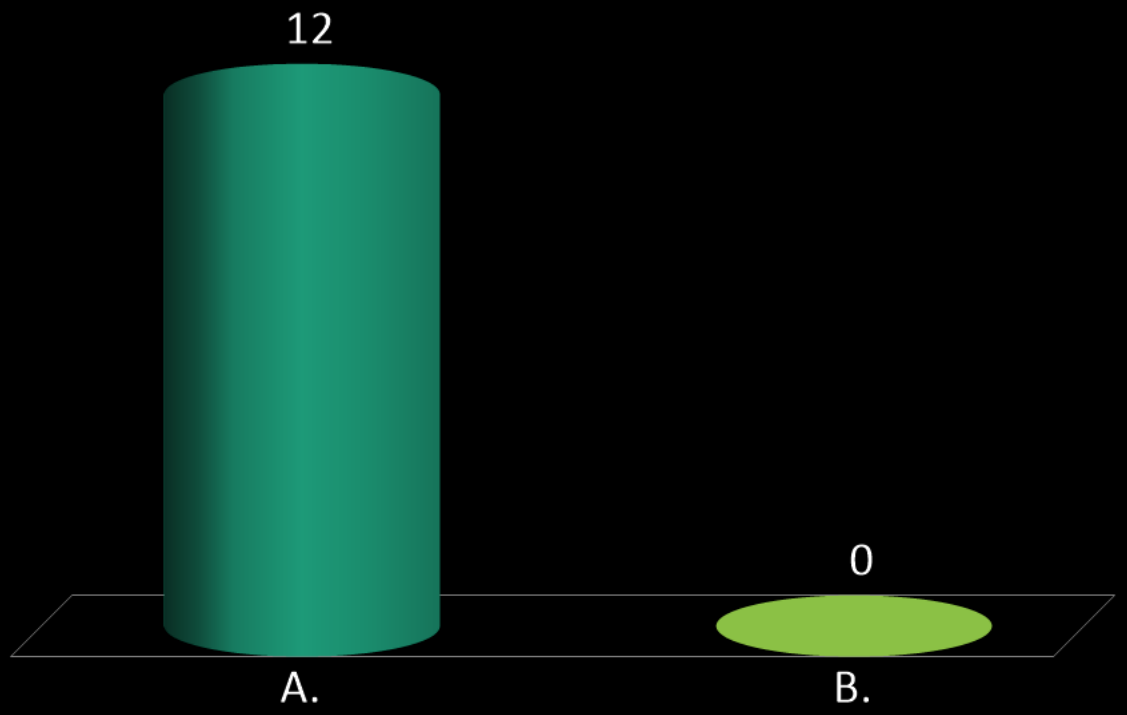


© 2020 Institute for Clinical and Economic Review

1. Is the evidence adequate to demonstrate a net health benefit for treatment with lasmiditan compared with no treatment?

A. Yes

B. No

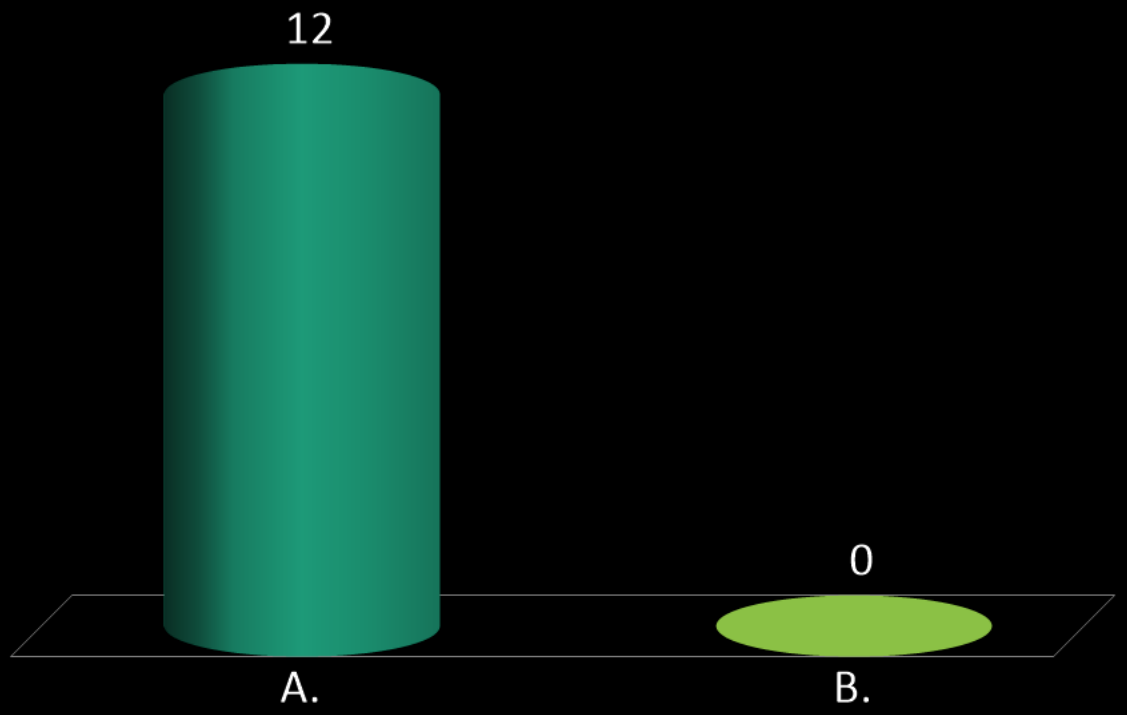


© 2020 Institute for Clinical and Economic Review

2. Is the evidence adequate to demonstrate a net health benefit for treatment with rimegepant compared with no treatment?

A. Yes

B. No

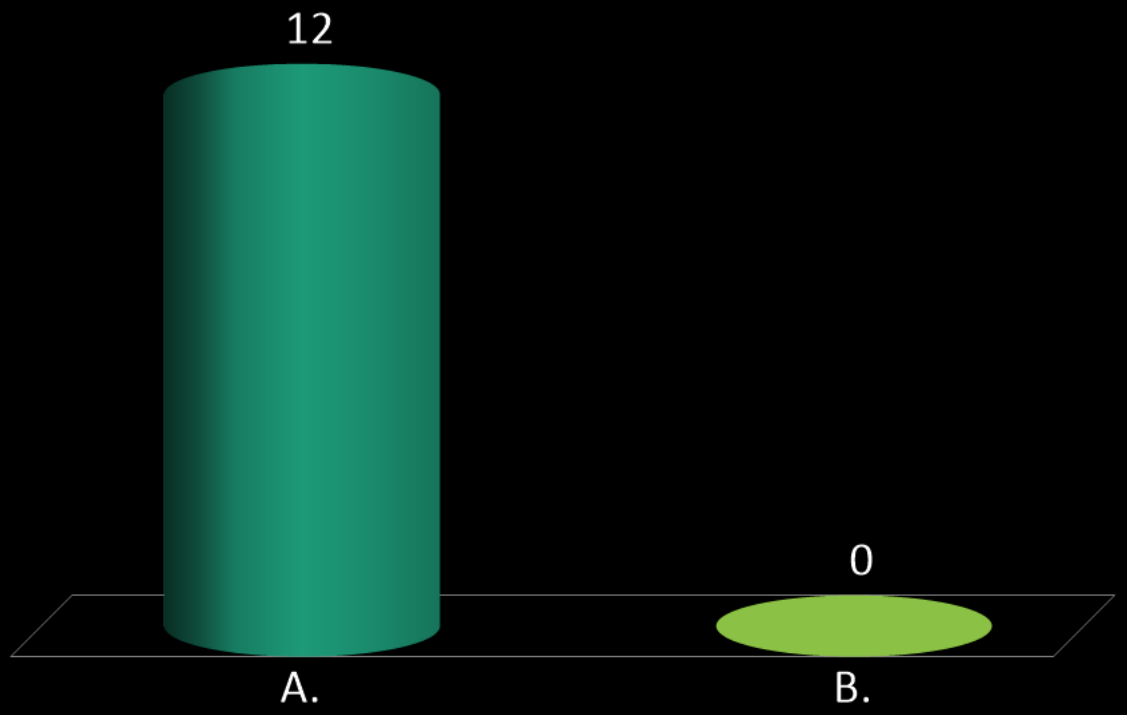


© 2020 Institute for Clinical and Economic Review

3. Is the evidence adequate to demonstrate a net health benefit for treatment with ubrogepant compared with no treatment?

A. Yes

B. No

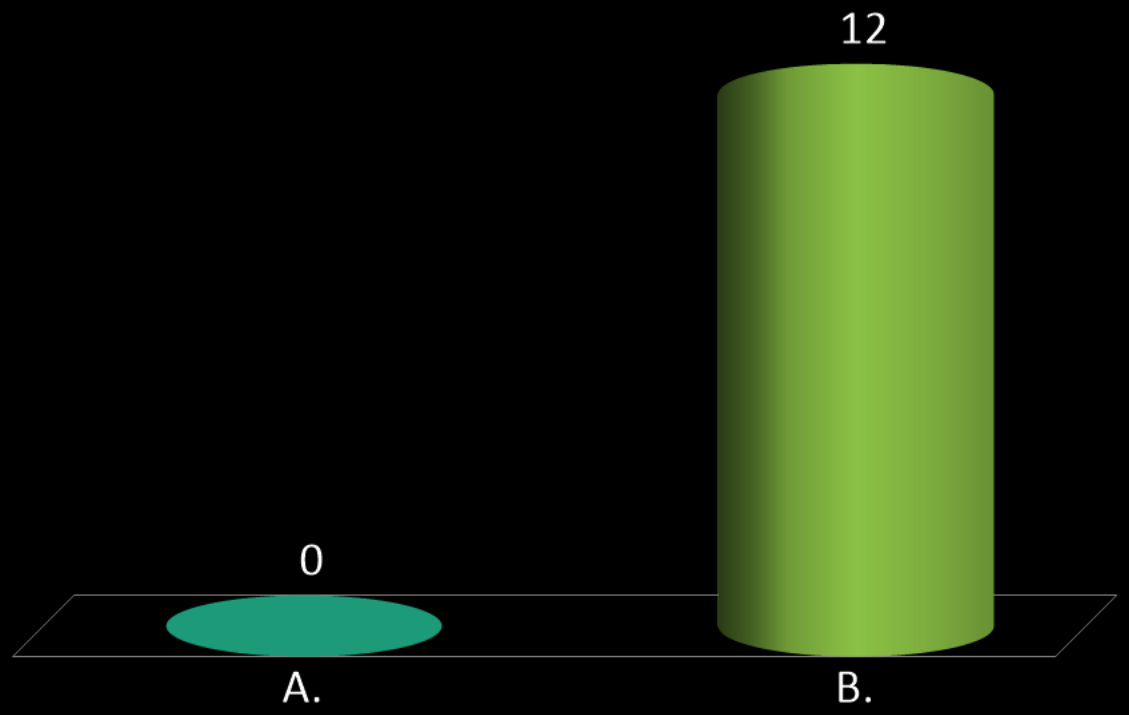


© 2020 Institute for Clinical and Economic Review

4. Is the evidence adequate to distinguish the net health benefits between the gepants, rimegepant and ubrogepant?

A. Yes

B. No

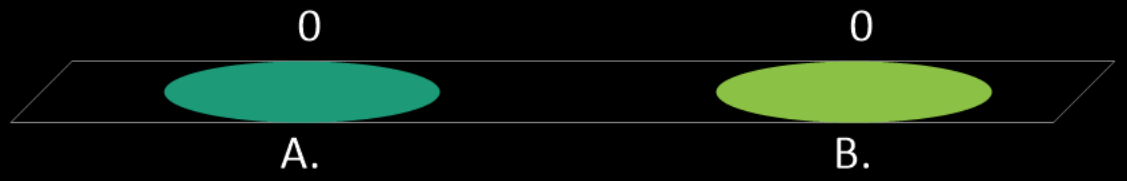


© 2020 Institute for Clinical and Economic Review

4a. If the answer to question 4 is “yes,” which therapy has the greater net health benefit?

A. Rimegepant

B. Ubrogepant

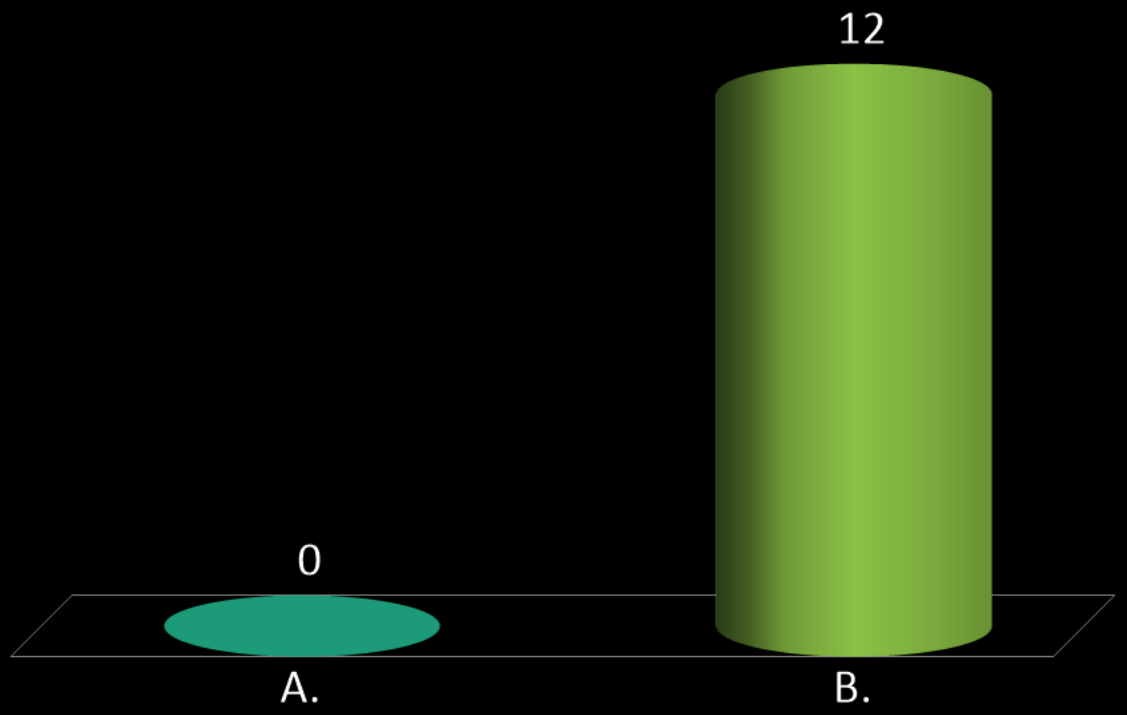


© 2020 Institute for Clinical and Economic Review

5. Is the evidence adequate to demonstrate that the gepants have a superior net health benefit compared to triptans? *(If yes to question 4, ask separately for each gepant.)*

A. Yes

B. No

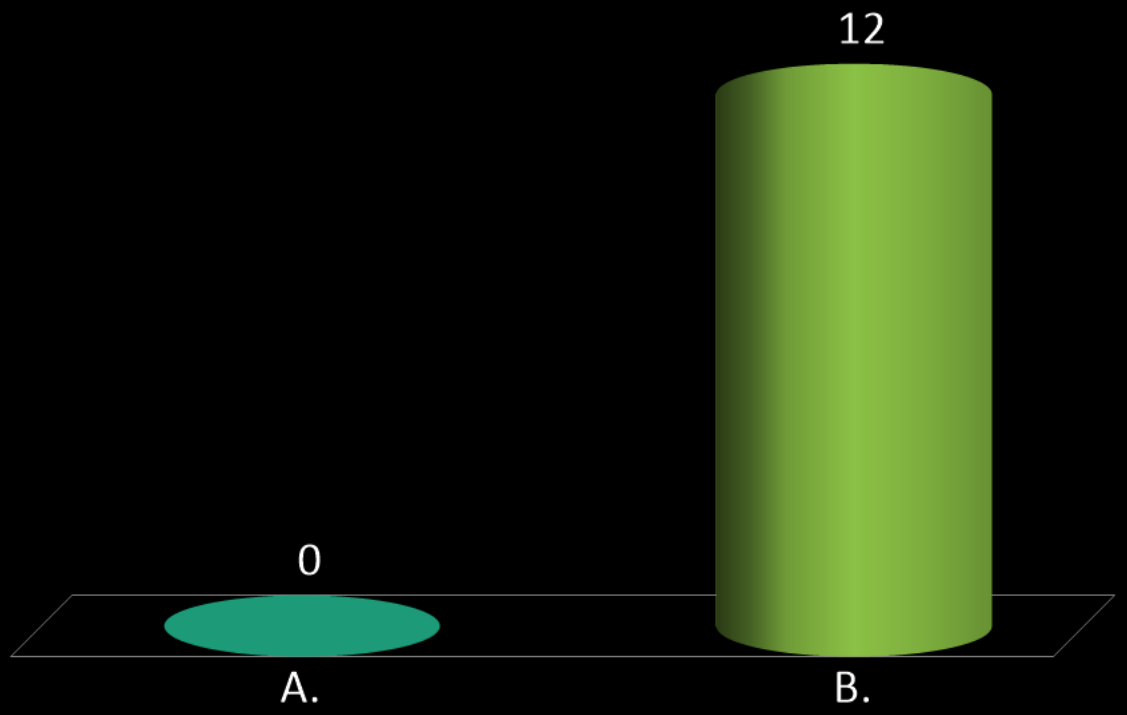


© 2020 Institute for Clinical and Economic Review

6. Is the evidence adequate to demonstrate that lasmiditan has a superior net health benefit compared to triptans?

A. Yes

B. No

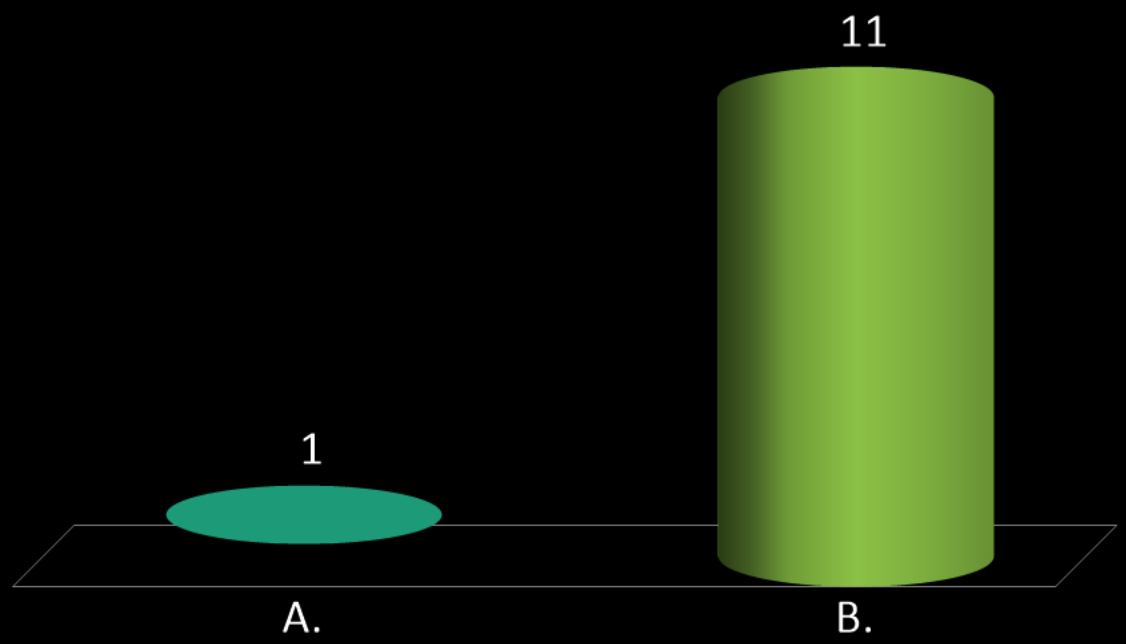


© 2020 Institute for Clinical and Economic Review

7. Is the evidence adequate to distinguish the net health benefits between the gepants and lasmiditan? *(If yes to question 4, ask separately for each gepant.)*

A. Yes

B. No

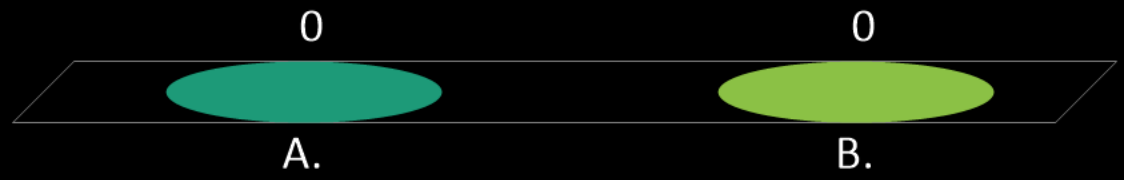


© 2020 Institute for Clinical and Economic Review

7a. If the answer to question 7 is “yes,” which therapy has the greater net health benefit?

A. Gepants

B. Lasmiditan



© 2020 Institute for Clinical and Economic Review

Population for Questions 8-12: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

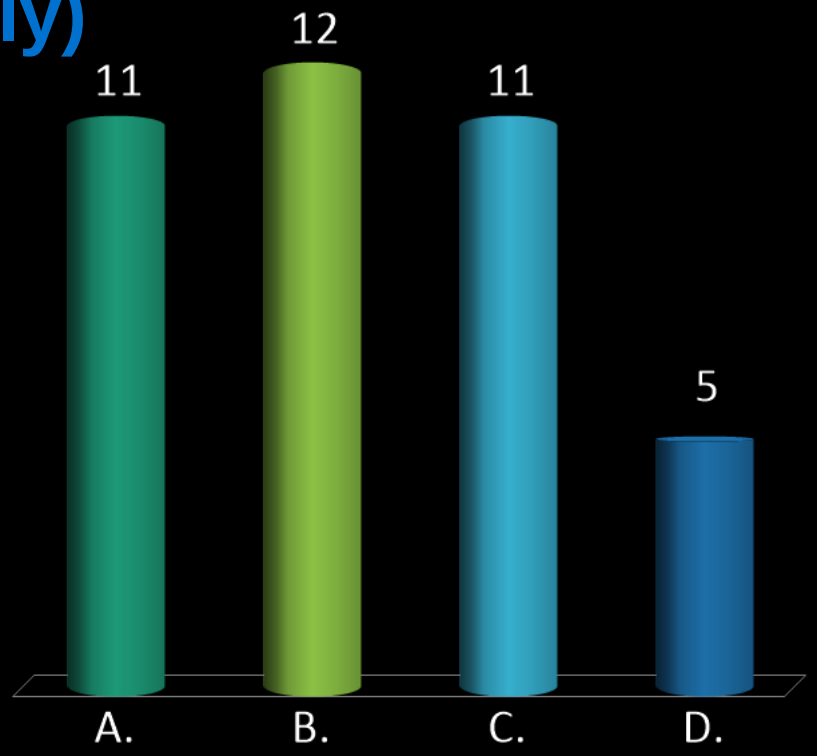
8. Does treating patients with gepants offer one or more of the following "other benefits" compared to over-the-counter therapies? (select all that apply)

A. This intervention will significantly reduce caregiver or broader family burden.

B. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.

C. This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.

D. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: _____



© 2020 Institute for Clinical and Economic Review

Population for Questions 8-12: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

9. Does treating patients with lasmiditan offer one or more of the following "other benefits?" (select all that apply)

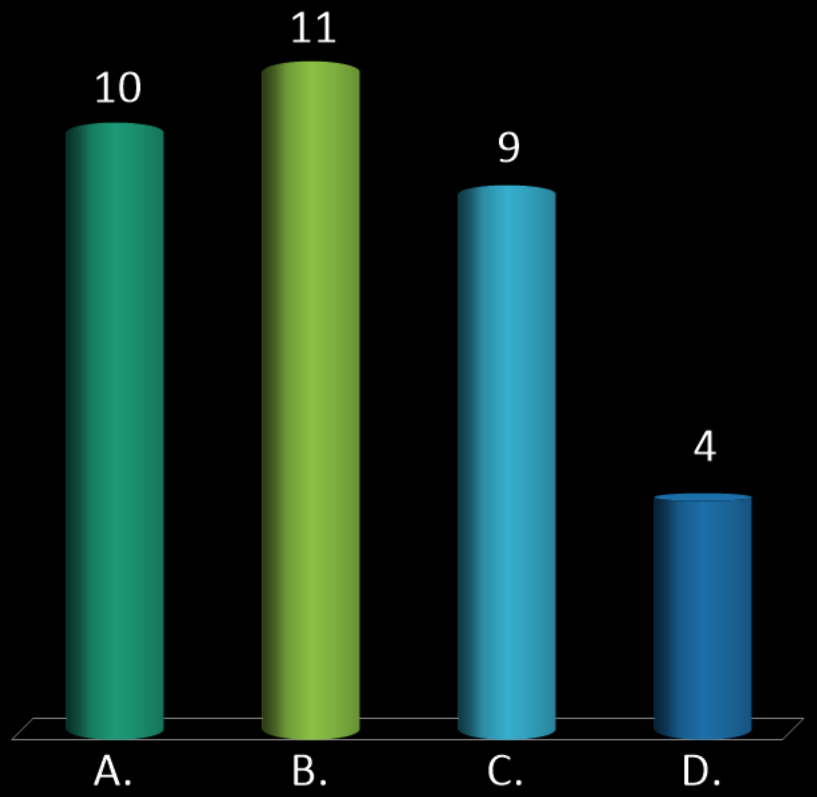
A. This intervention will significantly reduce caregiver or broader family burden.

B. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.

C. This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.

D. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention:

_____



© 2020 Institute for Clinical and Economic Review

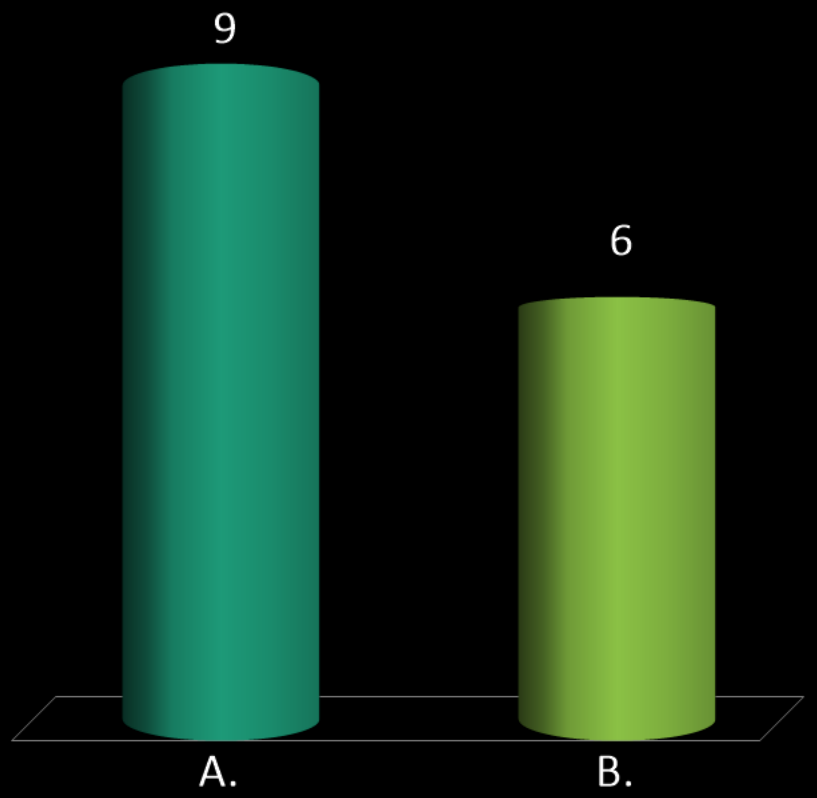
Population for Questions 8-12: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

10. Does treating patients with gepants offer one or more of the following "other benefits?" compared to lasmiditan? (select all that apply)

A. This intervention offers reduced complexity that will significantly improve patient outcomes

B. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention:

_____



© 2020 Institute for Clinical and Economic Review

Population for Questions 8-12: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

11. Are any of the following contextual considerations important in assessing gepants' long-term value for money? (select all that apply)

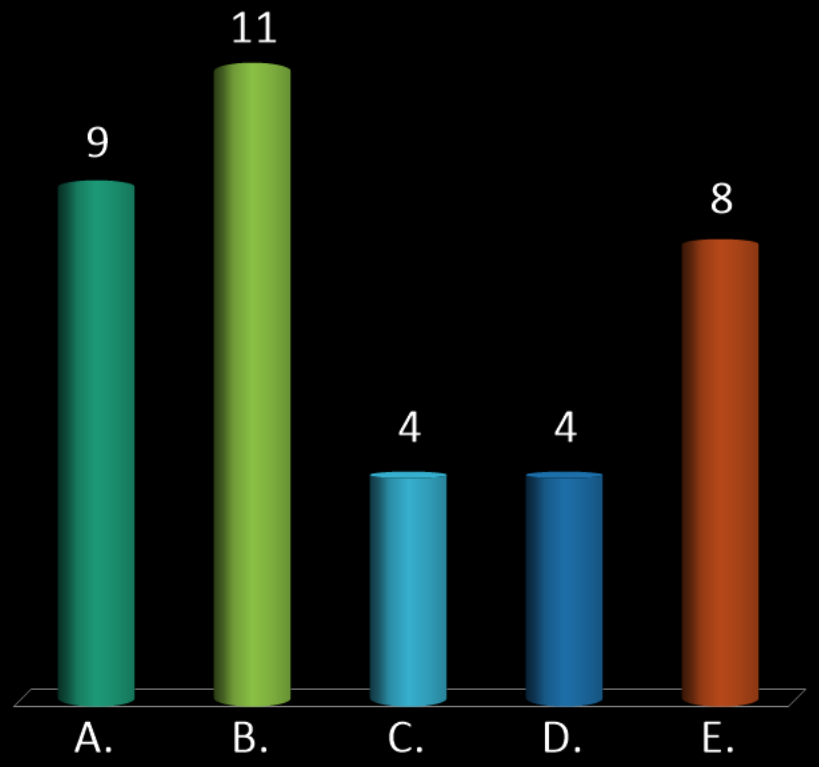
A. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.

B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. This intervention is the first to offer any improvement for patients with this condition.

D. There is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.



© 2020 Institute for Clinical and Economic Review

Population for Questions 8-12: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

12. Are any of the following contextual considerations important in assessing lasmiditan's long-term value for money? (select all that apply)

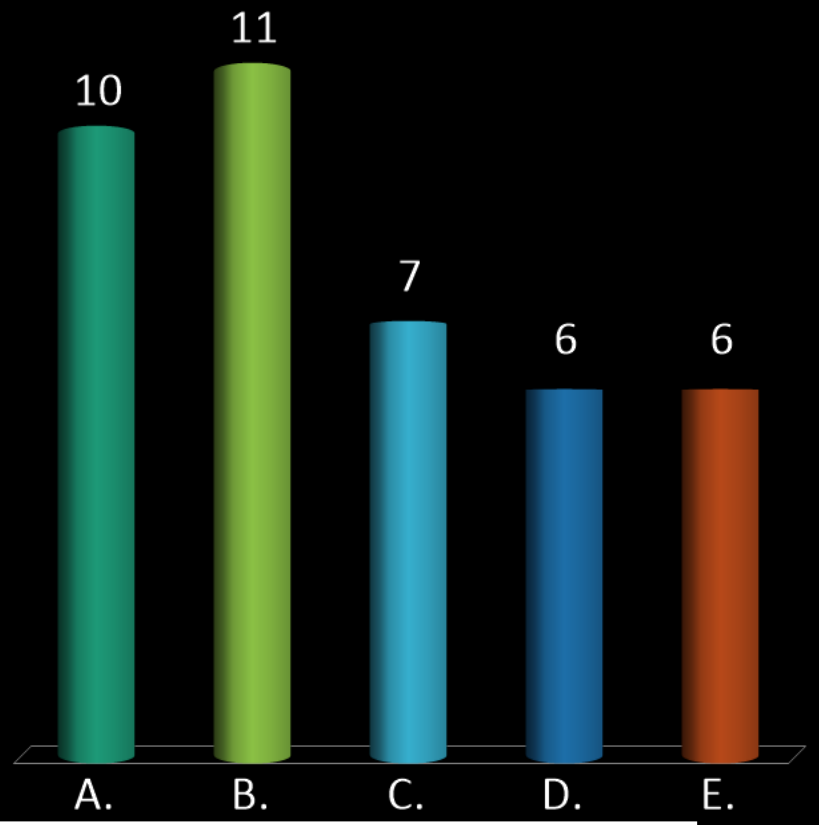
A. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.

B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. This intervention is the first to offer any improvement for patients with this condition.

D. There is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.



© 2020 Institute for Clinical and Economic Review

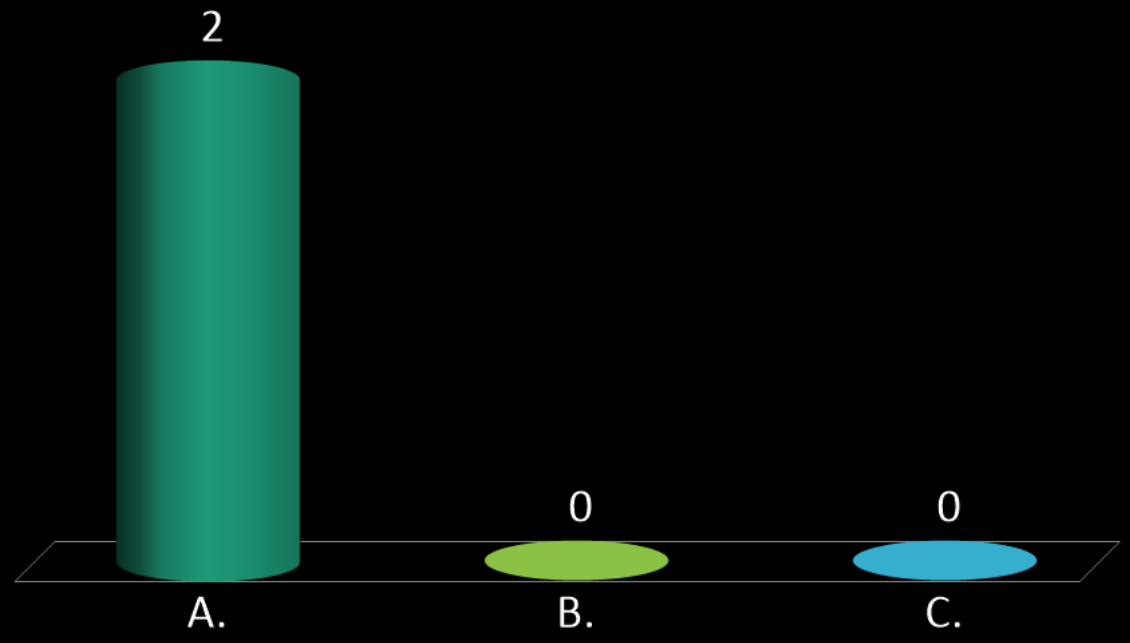
Population for Questions 13-15: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

13. 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 rimegepant versus no treatment?

A. Low long-term value for money at current pricing

B. Intermediate long-term value for money at current pricing

C. High long-term value for money at current pricing



© 2020 Institute for Clinical and Economic Review

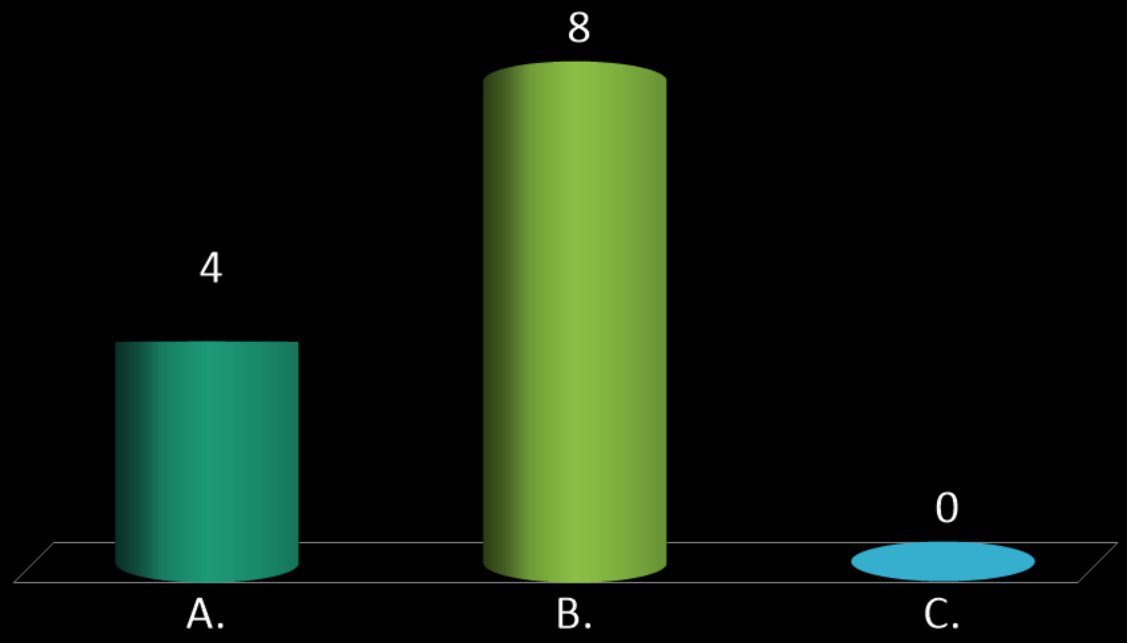
Population for Questions 13-15: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

14. 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 ubrogepant versus no treatment?

A. Low long-term value for money at current pricing

B. Intermediate long-term value for money at current pricing

C. High long-term value for money at current pricing



© 2020 Institute for Clinical and Economic Review

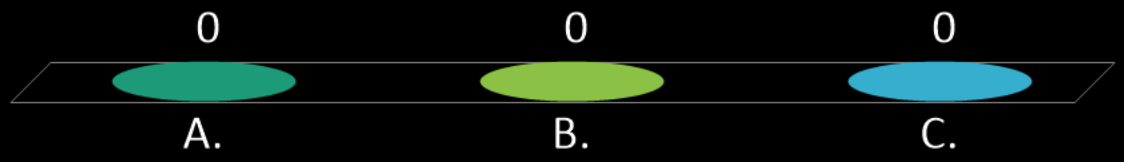
Population for Questions 13-15: Adult patients with a diagnosis of migraine for whom triptans have not been effective, are not tolerated, or are contraindicated.

15. 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 lasmiditan versus no treatment?

A. Low long-term value for money at current pricing

B. Intermediate long-term value for money at current pricing

C. High long-term value for money at current pricing



© 2020 Institute for Clinical and Economic Review

Break

Meeting will resume at 2:30pm

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Policy Roundtable

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Policy Roundtable Participants

Participant	Affiliation	Conflict of Interest
Harold Carter, PharmD	Senior Director, Clinical Solutions	Full Time Employee of Express-Scripts
Erin Doty, MD	Senior Medical Advisor, Migraine and Headache Disorders	Full Time Employee of Eli Lilly
Katie Golden, BA	Director of Patient Relations, Coalition for Headache and Migraine Patients (CHAMP)	Employee at CHAMP
Christopher Gottschalk, MD, FAHS	Director, Headache Medicine; Chief, General Neurology; Yale School of Medicine	Received consulting fees, is an Advisory Board member, and/or is on the Speaker Bureau at: Amgen/Novartis, Alder, Biohaven, Eli Lilly, and Theranica.

© 2020 Institute for Clinical and Economic Review

Policy Roundtable Participants

Participant	Affiliation	Conflict of Interest
Jeffrey Klingman, MD	Chief of Neurology, Kaiser Permanente	None
Gilbert L'italien, PhD	Head of GHEOR and Epidemiology	Full Time Employee of Biohaven Pharmaceuticals
Mitchell Mathis, MD	Vice President, Chief Medical Officer, CNS	Full Time Employee of Allergan
Travis Tacheny, PharmD	Clinical Pharmacy Program Consultant	Employee of HealthPartners
Sarah Wells Kocsis, MBA	Vice President of Public Policy, Society for Women's Health Research	Held senior positions at three diferent health care companies: Amgen, Boston Scientific, and Hologic. Has stock holdings in excess of $10,000 in each of these companies

© 2020 Institute for Clinical and Economic Review

Midwest CEPAC Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around February 13, 2020
  - Includes description of MW CEPAC votes, deliberation, policy roundtable discussion
- Materials available at: https://icer-review.org/topic/acute-migraine/

© 2020 Institute for Clinical and Economic Review

Adjourn

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW