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Acute Treatments for Migraine

Final Evidence Report

February 25, 2020
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Prepared for

MIDWEST CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

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Steven Atlas served as the lead author for the report. Foluso Agboola led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Noemi Fluetsch and Eric Borrelli. Rick Chapman was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Molly Beinfeld authored the section on coverage policies. David Rind and Steve Pearson provided methodologic guidance on the clinical and economic evaluations. Daniel Touchette and Todd Lee led the UIC modeling group and development of the cost-effectiveness model. The UIC team would like to thank Mrinmayee Joshi and Danny Quach for their contributions. The role of the UIC modeling group is limited to the

development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of UIC. None of the authors above disclosed any conflicts of interest.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/acute-migraine-stakeholder-list/

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CHAMP accepts funding from a range of sources, including most medicine and device manufacturers that provide products in the headache, migraine and cluster space. Specifically, CHAMP receives sponsorship support from some of the companies that have products included in this review of Acute Treatments for Migraine.

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NYU has IP rights to the RELAXaHEAD app of which Dr. Minen is the creator.

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List of Acronyms Used in this Report

5-HT	5-hydroxytryptamine
95%CI	95% confidence interval
95%CrI	95% credible interval
AAFP	American Academy of Family Physicians
AAN	American Academy of Neurology
AE	Adverse event
ACS	Acute coronary syndrome
AHRQ	Agency for Healthcare Research and Quality
AHS	American Headache Society
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCBSKC	Blue Cross Blue Shield of Kansas City
BMI	Body mass index
CADTH	Canadian Authority for Drugs and Technologies in Health
CGRP	Calcitonin gene-related peptide
CHAMP	Coalition for Headache and Migraine Patients
CHS	Canadian Headache Society
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CVD	Cardiovascular disease
D/C	Discontinuation
HIV	Human Immunodeficiency Virus
ICER	Institute for Clinical and Economic Review
ICHD	International Classification of Headache Disorders
ITT	Intention-to-treat
ECG	Echocardiogram
ED	Emergency department
Excl.	Excluding
EQ-5D-5L	EuroQol 5-Dimension 5-Level Scale
evLYG	Equal value of life years gained
FDA	Food and Drug Administration
GI	Gastrointestinal
MBS	Most bothersome symptom
mg	Milligram
MI	Myocardial infarction
MIDAS	Migraine Disability Assessment
mITT	Modified intention-to-treat
MQoLQ	Migraine Quality of Life Questionnaire
LCD	Local Coverage Determinations
LY	Life year
n	Number of participants
N	Total number of participants
N/A	Not applicable

NCD	National Coverage Determinations
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
n.s.	Not significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
OLE	Open label extension
OR	Odds ratio
PCE	Personal Consumption Expenditures Price Index
PCI	Percutaneous coronary intervention
PGIC	Patient Global Impression of Change
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, Settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRN	As needed
QALY	Quality-adjusted life year
QOD	Every other day
RCT	Randomized Controlled Trial
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
SUD	Substance use disorder
ULN	Upper Limit Normal
US	United States
USPSTF	US Preventive Services Task Force

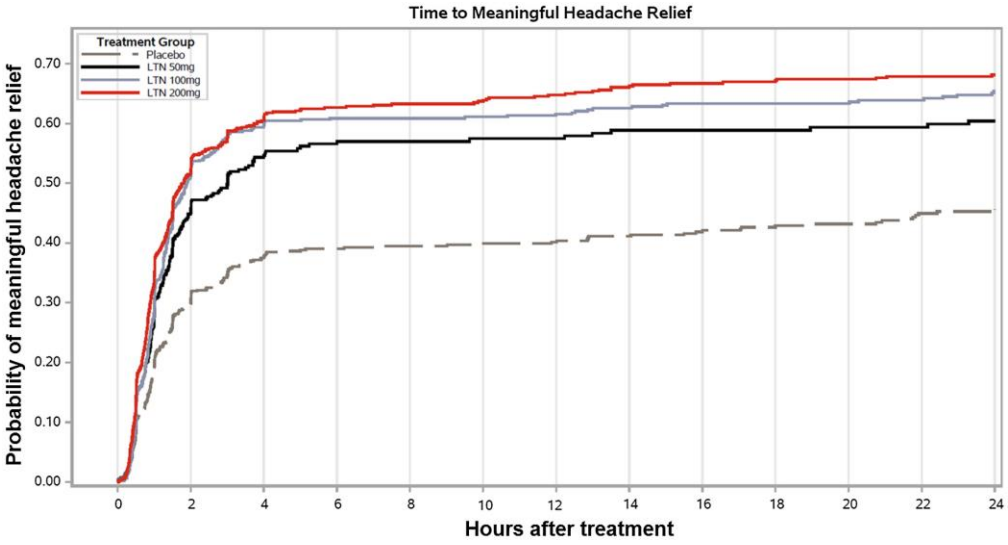
Update (added on May 14, 2020)

The initial Final Evidence Report posted on February 25, 2020 included base case cost-effectiveness findings for ubrogepant and rimegepant based on information on evidence of delayed benefits of treatment with a gepant drug past the two-hour primary outcome assessment in the clinical trials. This evidence on delayed benefits was discussed at the public meeting of the Midwest CEPAC on January 23, 2020, and was incorporated into the primary findings of the Final Evidence Report on February 25, 2020.

ICER had contacted all manufacturers on several occasions asking for data related to potential delayed benefits of treatment but did not receive data from the manufacturer of lasmiditan, Eli Lilly and Company ("Lilly"). However, after publication of the Final Evidence Report on February 25, 2020, Lilly contacted ICER asking to submit new analyses from completed trials that were viewed as relevant to this issue. ICER would not normally consider evaluating new analyses or other evidence after publication of the Final Evidence Report since that may be viewed as offering an unfair advantage to one participant and would not allow full consideration of the evidence by other stakeholders. ICER has decided to make an exception in this case due to an apparent misunderstanding by Lilly of the earlier ICER request for data.

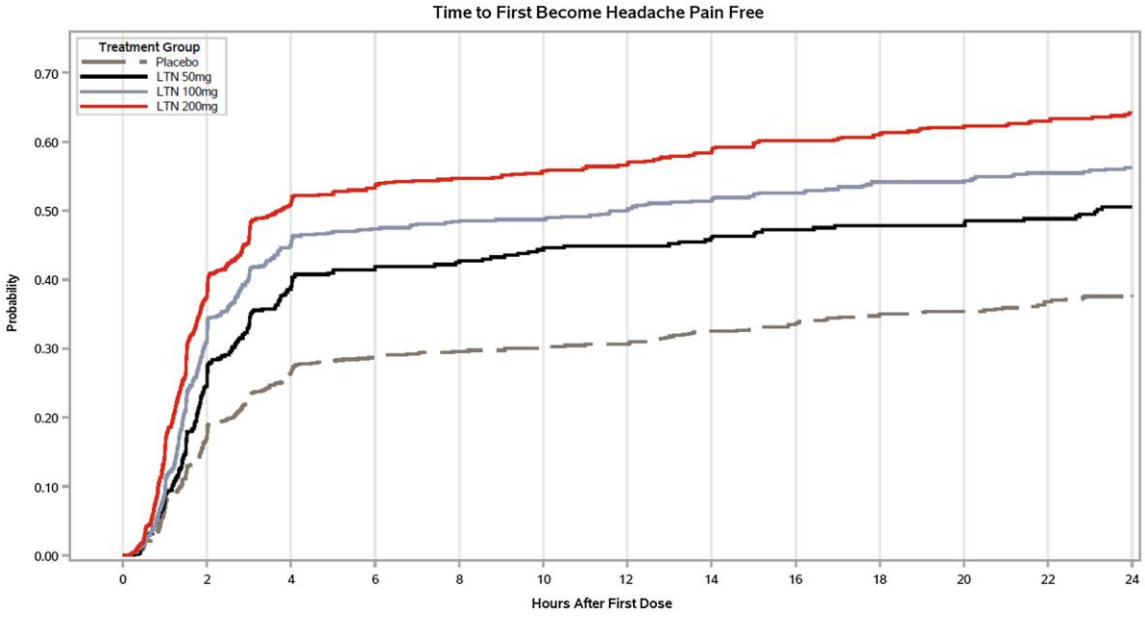
The new evidence provided by Lilly is comprised of pooled data from two trials of lasmiditan (trials 301 and 302) tracking the outcomes of patients who had not achieved pain freedom at two hours, had undergone a second randomization, and had been given placebo. As with the data we had received on ubrogepant, these new analyses provided evidence of some delayed benefit of lasmiditan. The key data point updated in the ICER model is pain freedom among all patients at eight hours (see Figures AD1 and AD2).[1] Importantly, data for all patients in the two trials beyond four hours relied on patient recall at 24 hours of when they had first become pain free. This limitation increases the uncertainty in the results and makes comparison with the data on ubrogepant difficult. Nonetheless, ICER judged the data to be reasonably persuasive and decided to use it to update its cost-effectiveness results.

Figure AD1. Time to Meaningful Headache Relief[1]



Onset of Efficacy Following Oral Treatment With Lasmiditan for the Acute Treatment of Migraine: Integrated Results From 2 Randomized Double-Blind Placebo-Controlled Phase 3 Clinical Studies; Ashina et al, Headache: The Journal of Head and Face Pain, Volume: 59, Issue: 10, Pages: 1788-1801, First published: 17 September 2019.

Figure AD2. Time to First Become Headache Pain Free[1]



Onset of Efficacy Following Oral Treatment With Lasmiditan for the Acute Treatment of Migraine: Integrated Results From 2 Randomized Double-Blind Placebo-Controlled Phase 3 Clinical Studies; Headache: The Journal of Head and Face Pain, Volume: 59, Issue: 10, Pages: 1788-1801, First published: 17 September 2019.

Separate risk ratios for pain relief and for pain freedom were calculated by dividing the difference in response between lasmiditan and placebo at eight hours by the difference at two hours. These risk ratios, which were provided under ICER's academic-in-confidence policy, were used to calculate response among those who had not responded at two hours. The calculated risk ratios were applied to the placebo response rates from Dodick[102] to calculate eight-hour response. Base-case results were only generated for patients for whom triptans had not been effective, were not tolerated, or were contraindicated (Population 1 in the general report).

When applying these risk ratios in the model, the resulting proportion of patients who were pain free or had pain relief at different time points is shown in the table below:

Table AD1. Proportion of Patients with Pain Freedom and Pain Relief

Treatment	Pain Free				Pain Relief			
	2h	8h	24h	48h	2h	8h	24h	48h
Lasmiditan	28.0%	67.2%	74.3%	81.8%	58.0%	96.0%	93.4%	94.2%

Results

Using these new estimates for pain freedom and pain relief, we updated the cost-effectiveness model results for lasmiditan as shown in Table AD2 below. Tables ES7, ES8, ES9, ES13 in the Executive Summary of the report have been updated accordingly to reflect these new results. Tables 4.10, 4.11, 4.12, and 6.1 were also updated within the body of the report.

Table AD2. Base-Case Results for Lasmiditan*

Treatment	Drug Cost (per year)*	Total Cost	QALYs	Life Years	evLYG	Hours of Pain
Lasmiditan	$3,360	$12,000	1.8271	1.95	1.8271	1,650

evLYG: equal value of life years gained, LY: life year, QALY: quality-adjust life year
*Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

The updated incremental cost-effectiveness ratios versus placebo, using the estimated net price for lasmiditan of approximately $3,360 per year, were $151,000 per QALY and per evLYG gained and $4.32 per hour of pain avoided.

Table AD3. Incremental Cost-Effectiveness Ratio for Lasmiditan

Treatment	Comparator	Cost per QALY Gained	Cost per Hour of Pain Avoided
Population 1			
Lasmiditan	Usual Care	$151,800	$4.32

The updated value-based price benchmarks derived from the revised cost-effectiveness results are shown in the table below.

Table AD4. Value-Based Price Benchmarks for Lasmiditan

Treatment	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC Required to Achieve Threshold Prices
Lasmiditan	$4,610	$2,900	$3,350	27%-37%

The changes in these estimates for incremental cost-effectiveness and value-based prices are much smaller than what was seen when a delayed benefit was included for the gepants because the delayed effects of lasmiditan relative to placebo are quite similar to the relative effects at two hours. This can be seen in the slopes of the lines for active treatment and placebo beyond two hours in Figures AD1 and AD2.

Limitations

As discussed above, the eight-hour estimates for pain relief and pain freedom for lasmiditan versus placebo came from patient recall: at 24 hours patients were asked to report when pain relief or pain freedom first occurred. As such, unlike querying patients at eight hours about the status of their pain, these results may not adequately reflect the experience of patients who achieved pain relief or pain freedom prior to eight hours but then had recurrence of pain. A recall question of this sort likely overestimates the effect of lasmiditan on pain at eight hours. This is potentially important as among patients who had pain relief or pain freedom at two hours, among whom loss of response between two hours and 24 hours was measured as a study outcome for all three drugs, loss of response was greater with lasmiditan than with the gepants.

Conclusions

Including a delayed effect for lasmiditan based on the data submitted by Lilly led to small reductions in the incremental cost-effectiveness of lasmiditan and small increases in the value-based price benchmarks.

Note: Base case results related to lasmiditan have been updated in multiple sections of the report. The report indicates where these updates have occurred. In other sections of the report (including sensitivity and scenario analyses), results have not been updated.

Executive Summary

Background

Migraine is a common cause of headache and is characterized by episodic, recurrent attacks that are classically pulsatile or throbbing, frequently involve one side of the head, and are associated with nausea and sensitivity to external stimuli such as light, sound, and smells. Migraine attacks vary in their frequency and intensity, but when severe can be a disabling, chronic condition that can impact all aspects of life including personal relationships and ability to work.[2] An estimated 40 million adults or 12-15% of adults in the United States (US) report migraine or severe headaches.[3 4] Patients with migraine have higher costs of care, decreased work productivity, increased disability claims and account for $11-50 billion in total costs.[5-7,8,9,10]

The precise cause of migraine is not known and there is no specific test to confirm the diagnosis.[11-13] Migraine often starts in early adulthood, is more common in women, runs in families, and attacks can be triggered by a variety of predisposing factors such as stress and certain stimuli, activities and foods.[3,4,14,15] Treatment broadly includes acute therapies to quickly abort episodic symptoms and ongoing therapies to reduce the frequency of attacks.[13] This review examines acute treatments for migraine attacks. Early acute treatment is especially helpful for individuals with aura (focal neurologic symptoms, frequently involving the visual system) that precede the onset of the headache. For those not responding to over-the-counter nonspecific pain medications or with moderate or severe symptoms, the use of specific migraine medications is recommended.

The most commonly used migraine specific medication class for acute treatment are "triptans" (5-hydroxytryptamine (5-HT) 1b/1d receptor agonists) available as pills, nasal sprays, and for injection under the skin.[12] Though effective and safe for patients with migraine, for many patients triptans are not adequately helpful or lose efficacy over time, have intolerable side effects, or have contraindications to their use (e.g., cardiovascular disease).[16,17] The need for new therapeutic options is highlighted by the persistent use of medications, such as barbiturates and opioids that have the potential for misuse, and recognition that frequent use of acute medications can lead to medication overuse headaches.

New therapeutic classes include calcitonin gene-related peptide (CGRP) antagonists and 5-hydroxytryptamine (5-HT) 1f agonists. Interest in CGRP antagonists has been driven by the observation that administration of CGRP can trigger acute headache and delayed migraine-like attacks.[18,19] In addition, monoclonal antibodies targeting the CGRP receptor are being used for migraine prophylaxis.[20] Two new oral CGRP receptor antagonists, ubrogepant (Ubrelvy™, Allergan, FDA approved on December 23, 2019) and rimegepant (under FDA review) have been studied for acute treatment of migraine attacks (class is referred to as "gepants"). Lasmiditan (Reyvow™, Lilly), a selective 5-HT 1f agonist (also referred to as a "ditan") approved on October 11, 2019 by the FDA

for acute treatment of migraine, is thought to work in a similar manner to the triptans. Unlike the triptans, the gepants and lasmiditan do not have vasoconstrictive effects.[17,21,22]

Insights Gained from Discussions with Patients and Patient Groups

Discussions with individual patients and patient advocacy groups identified important insights. We received numerous comments in which patients with migraine describe different personal stories and highlighted common themes that emphasize migraine as an episodic and chronic disease that can profoundly affect all aspects of their lives and the lives of those close to them. Though some have derived benefit from existing therapies, not all respond, headaches can recur as treatment wears off during the acute episode, response can vary from one migraine attack to another, and response can decrease over time with repeated episodic use. For others, side effects have led them to stop therapy or they have contraindications to the use of certain therapies. The net result is that for many patients with moderate or severe migraine headaches there is no single or combined therapy that offers them reliable, long-term control of their acute attacks.

A wide range of deficiencies with currently available acute treatments for migraine were noted.

- Despite a number of non-prescription and prescription medications, used alone or in combination, many patients cannot reliably prevent or abort migraine attacks.
- Available therapies do not provide symptom relief from migraine attacks with minimal side effects for many individuals.
- Triptans are effective in acute therapy for migraines but for many individuals they do not work, have intolerable side effects, or have contraindications to their use.
- For these reasons, patient turn to other medications such as opioids, barbiturates and anti-emetics, but these also have limited benefit, acute side effects or risks with long-term use.

The profound impact of migraine on the lives of patients with migraine was emphasized.

- Migraine often develops in individuals during adolescence and young adulthood; formative educational years, where it can prevent them from reaching their full academic potential.
- Unpredictability of migraine attacks can result in anxiety from not knowing when the next attack will come, impacting individuals even when they do not have migraine symptoms.
- Frequent, severe attacks can have a dramatic impact on quality of life that may not be fully appreciated by the general public and even health professionals.
- As a result, migraine is a chronic condition that affects patients throughout their lives, disrupting personal relationships with friends and family.

The toll on patients with migraine includes important economic consequences.

- If the migraine attack is not aborted quickly and without medication related side effects, ability to work or work productively is profoundly affected.
- Acute treatments for migraine that work quickly and without side effects critically impact the ability to continue to work following a migraine attack.
- Frequent, severe and unpredictable migraine attacks combine to impact the ability to work, productivity when working, and risk of disability.
- The net result can be long-term un/under-employment with major socioeconomic cost that can have a long-term negative economic impact on the patient and her/his family.

Use of opioids and barbiturates for acute migraine is driven by limitations of existing therapies.

- Though recognized as having limited effectiveness, acute side effects, the potential for causing medication overuse headache and misuse, doctors end up prescribing them.
- New therapeutic classes, especially ones without side effects or limitations seen with triptans, may have a broader potential impact on the opioid crisis in the US.

Patient advocacy organizations also raised systematic issues that they felt needed to be addressed.

- Common outcome measures required by the FDA to obtain approval for new drugs may not adequately capture the impact of migraine on overall quality of life.
- Specifically, single dose studies are not designed to assess whether new therapies decrease the frequency of attacks over time or prevent medication overuse headaches.
- Successful migraine treatment may also help patients with other illnesses, such as anxiety and depression, that are impacted by frequent, unpredictable and severe attacks.

Potential Cost-Saving Measures in Migraine

Allergan suggested that opioids represent a low-value service that could be reduced.

Comparative Clinical Effectiveness

We evaluated the comparative clinical effectiveness and safety of lasmiditan, rimegepant and ubrogepant for the acute treatment of patients with migraine. Comparators of interest included: 1) no additional migraine-specific acute treatment (i.e., placebo arms of clinical trials) for patients with migraine attacks not adequately treated with non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated (defined as Population 1), and 2) triptans (eletriptan and sumatriptan) for patients who have migraine attacks that have not adequately responded to non-prescription medicines (defined as Population 2). The specific triptans were chosen because sumatriptan is one of the most widely used triptans in clinical practice and eletriptan was shown in a recent network meta-analysis to be one of the most

efficacious and well tolerated.[16,23] We only examined oral triptan formulations because the new agents under review are all orally available.

We identified three RCTs of lasmiditan (1 Phase II and 2 Phase III),[24-26] four RCTs of rimegepant (1 Phase II and 3 Phase III),[27-30] and three RCTs of ubrogepant (1 Phase II and 2 Phase III)[31-33]. All the RCTs of the interventions are placebo-controlled, except for one Phase II trial of rimegepant that also included sumatriptan as an active control arm.[30] We did not identify any trials comparing lasmiditan or ubrogepant to a triptan. In addition, we identified 23 RCTs of triptans (18 placebo-controlled trials of sumatriptan, three placebo-controlled trials of eletriptan and two head-to-head trials of sumatriptan and eletriptan) that met our inclusion criteria. [34-55]

All the identified studies were large multicenter studies focused on the treatment of a single-migraine attack. The trials enrolled patients who had at least a one-year history of migraine with or without aura as specified by the International Classification of Headache Disorders (ICHD) diagnostic criteria, who experienced two to eight migraine attacks (1 to 6 in triptan trials) of moderate to severe intensity per month, with age of onset before 50 years. Over 80% of the patients were female and the average age was approximately 40 years in each trial. Patients had been living with migraine for approximately 20 years, had an average of three to five migraine attacks per month, and about 20% to 25% of patients in the trials of the interventions were on preventive migraine medication. Characteristics of the treated migraine attack were generally similar across trials, with more patients having moderate than severe headache pain intensity (70% vs. 30%) at baseline. Photophobia was the most common other symptom reported (75% to 90% of patients) and was reported as the most bothersome symptom by 50% to 60% of patients. Approximately 40% to 65% of patients reported nausea, and 55% to 75% of patients reported phonophobia.

We considered all trials sufficiently similar to include in network meta-analyses.

Clinical Benefits

Pain Freedom and Pain Relief at Two Hours

The primary efficacy endpoint in all trials of lasmiditan and CGRP antagonists was freedom from pain at two hours after treatment, before the use of any rescue medication. Pain relief, defined as a decrease in headache pain from moderate or severe at baseline to mild or no pain at two hours after treatment and before taking any rescue medication was measured as a secondary outcome in the trials. Patients with moderate or severe pain who achieve pain freedom would also be counted as having pain relief. Overall, a greater proportion of patients achieved freedom from pain and pain relief at two hours post dose with the interventions compared to placebo (see Table ES1).

Table ES1. Phase III Results of Lasmiditan, Rimegepant and Ubrogepant. Pain Freedom and Pain Relief at 2-Hours

Intervention (Trial)	Arms	Headache Pain Freedom at 2-Hours	Headache Pain Relief at 2-Hours
		n/N (%)	n/N (%)
Lasmiditan (SAMURAI)[25]	Lasmiditan 200mg	167/518 (32.2)	330/555 (59.5)
	Lasmiditan 100mg	142/503 (28.2)	334/562 (59.4)
	Placebo	80/524 (15.3)	234/554 (42.2)
Lasmiditan (SPARTAN)[24]	Lasmiditan 200mg	205/528 (38.8)	367/565 (65.0)
	Lasmiditan 100mg	167/532 (31.4)	370/571 (64.8)
	Placebo	115/540 (21.3)	274/576 (47.7)
Rimegepant (Study 301)[28]	Rimegepant 75mg	104/543 (19.2)	304/543 (56.0)
	Placebo	77/541 (14.2)	247/541 (45.7)
Rimegepant (Study 302)[27]	Rimegepant 75mg	105/537 (19.6)	312/537 (58.1)
	Placebo	64/535 (12.0)	229/535 (42.8)
Rimegepant (Study 303)[29]	Rimegepant 75mg	142/669 (21.2)	397/669 (59.3)
	Placebo	74/682 (10.9)	295/682 (43.3)
Ubrogepant (ACHIEVE I)[32]	Ubrogepant 100mg	95/448 (21.2)	275/448 (61.4)
	Ubrogepant 50mg	81/422 (19.2)	257/422 (60.7)
	Placebo	54/456 (11.8)	224/456 (49.1)
Ubrogepant (ACHIEVE II)[31]	Ubrogepant 50mg	101/464 (21.8)	291/464 (62.7)
	Placebo	65/456 (14.3)	220/456 (48.2)

95% CI: 95% confidence interval, mg: milligrams, n: number of participants, N: total number of participants, vs: versus

Results of the NMA model are presented in terms of the odds ratio (OR) of freedom from pain (or pain relief) for each intervention versus placebo, sumatriptan and eletriptan (Table ES2 and Table 3). ORs above 1 indicate higher odds of pain freedom at two hours with the active intervention versus comparator while ORs below 1 indicate lower odds. Lasmiditan, rimegepant, and ubrogepant all had higher odds of achieving pain freedom at two hours versus placebo. Compared to each other, none of the interventions showed statistically significant differences, though lasmiditan showed a statistically nonsignificant, higher odds of achieving pain freedom. In contrast, all interventions showed lower odds of achieving pain freedom compared to eletriptan and sumatriptan. However, statistical significance was not reached for lasmiditan versus sumatriptan. Similar trends were observed for pain relief at two hours (Table ES3).

Table ES2. NMA results. Interventions and Comparators. Pain Freedom at 2-Hours

Lasmiditan (100/200 mg)					
1.43 (0.97, 2.06)	Rimegepant 75 mg				
1.43 (0.93, 2.14)	1 (0.69, 1.46)	Ubrogepant (50/100 mg)			
0.73 (0.53, 1.06)	**0.51 (0.39, 0.7)**	**0.52 (0.37, 0.74)**	Sumatriptan (50/100 mg)		
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 40 mg	
3.01 (2.2, 4.14)	**2.11 (1.67, 2.72)**	**2.12 (1.58, 2.88)**	**4.09 (3.43, 4.82)**	**5.6 (4.14, 7.23)**	Placebo

mg: milligrams

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.

Table ES3. NMA results. Interventions and Comparators. Pain Relief at 2-Hours

Lasmiditan (100/200 mg)					
1.16 (0.87, 1.52)	Rimegepant 75 mg				
1.15 (0.85, 1.58)	1 (0.75, 1.34)	Ubrogepant (50/100 mg)			
0.84 (0.67, 1.13)	**0.73 (0.58, 0.96)**	0.73 (0.55, 1)	Sumatriptan (50/100 mg)		
0.61 (0.44, 0.88)	**0.52 (0.38, 0.76)**	**0.52 (0.37, 0.78)**	**0.72 (0.58, 0.89)**	Eletriptan 40 mg	
2.53 (2.04, 3.25)	**2.19 (1.8, 2.76)**	**2.19 (1.7, 2.89)**	**2.99 (2.65, 3.34)**	**4.18 (3.32, 5.14)**	Placebo

mg: milligrams

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.

Pain Freedom and Relief between Two and Eight Hours

The randomized trials of the acute therapies for migraine were not designed to assess for delayed benefits from the initial study drug beyond two hours. Though the trials of rimegepant and ubrogepant reported results beyond two hours based on censoring strategies that removed patients who took additional medication after two hours, these censored outcomes have the potential for confounding because they violate the initial intention to treat design. Nevertheless, these censored outcomes (see Figures 3.1 and 3.2) suggested that the primary outcomes at two hours may underestimate the benefit of the study drugs in a time period out to eight hours.

However, the ubrogepant trials permitted examining outcomes out to four hours without breaking the initial intention to treat design. Patients who had not had relief of migraine at two hours and decided to take a second dose of study medication were "randomized" to receive a second dose of placebo. Patients who had initially received ubrogepant were randomized to receive ubrogepant or

placebo. This permitted a comparison between patients who initially received placebo and then received a second dose of placebo and patients who initially received ubrogepant and then received placebo as their second dose. The results of the additional analysis showed an additional delayed benefit with ubrogepant at four hours after the initial dose (see Table 3.6). As shown above in the Update to this report, similar data were received for lasmiditan after the original publication of this report.

Sustained Pain Freedom

Sustained pain freedom refers to individuals who were pain free at two hours and maintained pain freedom with no use of rescue medication or relapse within 24 (sustained pain freedom at 24 hours) or 48 hours (sustained pain freedom at 48 hours) after the initial treatment. The results of the NMA results on 24 hours sustained pain freedom are presented in Table ES4. Similar to the two-hour results, a greater proportion of patients on the interventions achieved sustained pain freedom at 24 hours versus placebo. Although all interventions showed lower odds of achieving sustained pain freedom at 24 hours compared to sumatriptan and eletriptan, these were not statistically significant. Similarly, the interventions were not statistically significantly different from each other.

Table ES4. NMA Results. All Interventions and Comparators. Sustained Pain Freedom at 24-Hours

Lasmiditan (100/200 mg)					
1.16 (0.67, 1.94)	Rimegepant (75 mg)				
1.26 (0.72, 2.11)	1.08 (0.67, 1.74)	Ubrogepant (50/100 mg)			
0.83 (0.5, 1.44)	0.71 (0.48, 1.12)	0.66 (0.41, 1.12)	Sumatriptan		
0.73 (0.34, 1.53)	0.63 (0.32, 1.22)	0.59 (0.28, 1.18)	0.89 (0.44, 1.69)	Eletriptan	
2.92 (1.89, 4.5)	**2.51 (1.89, 3.46)**	**2.32 (1.62, 3.46)**	**3.53 (2.52, 4.77)**	**3.97 (2.24, 7.36)**	Placebo

mg: milligrams

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.

Freedom from Most Bothersome Symptom (MBS)

Absence of the most bothersome migraine associated symptom (i.e. phonophobia, photophobia, or nausea) at two hours after treatment was measured as a co-primary endpoint in the Phase III trials of lasmiditan, rimegepant and ubrogepant. However, none of the triptan studies assessed freedom from MBS as an outcome. The NMA results showed that lasmiditan (1.69, 95% CrI: 1.33, 2.14), rimegepant (1.58, 95% CrI: 1.29, 1.94), and ubrogepant (1.64, 95% CrI: 1.28, 2.12) all had higher

odds of achieving freedom from MBS at two hours post dose compared to placebo. However, compared to each other, none of the interventions showed a statistically significant difference.

Disability

Functional disability assessed at two hours was measured as a secondary outcome in all the Phase III trials of the interventions, but not consistently in the triptan studies. As such we included only the seven Phase III trials in our NMA and compared the interventions to each other and to placebo. The NMA results showed that lasmiditan (1.70, 95% CrI: 1.32, 2.20), rimegepant (1.72, 95% CrI: 1.38, 2.14), and ubrogepant (1.51, 95% CrI: 1.15, 1.96) all had higher odds of achieving no disability at two hours post dose compared to placebo. However, compared to each other, none of the interventions showed a statistically significant difference.

Harms

Harms assessed in the single-attack trials include treatment-emergent adverse events (TEAEs), serious adverse events (AEs), and any AE reported by at least 5% of a trial arm. Overall, the AEs observed in these trials were mild or moderate in intensity. The NMA results showed there were no differences in the odds of any AE and TEAE between rimegepant and ubrogepant versus placebo and triptans in the single-attack trials. However, lasmiditan had higher odds of causing TEAE compared to placebo (5.99, 95% CrI: 3.3, 12.52, Table 3.15), rimegepant (4.00, 95% CrI: 1.38, 12.04), ubrogepant (5.10, 95% CrI: 2.31, 12.95), and sumatriptan (2.57, 95% CrI: 1.3, 6.07). Similar results were seen for any AE.

Nausea was among the most commonly reported AEs in the ubrogepant and rimegepant trials (1% to 3%). In the lasmiditan trials, central nervous system (CNS)-related AEs (e.g., dizziness [16-18%], somnolence [5-6%], paresthesia [2-7%]) were the most frequently reported AEs, with dizziness the most common. Results of the NMA on the incidence of dizziness across trials showed that lasmiditan had higher odds of causing dizziness compared to placebo (8.43, 95% CrI: 4.88, 19.35, see Table 3.16), rimegepant (7.02, 95% CrI: 2.2, 25.63), ubrogepant (4.95, 95% CrI: 1.67, 15.92), sumatriptan (4.09, 95% CrI: 2, 10.6), and eletriptan (3.97, 95% CrI: 1.44, 12.41).

In the open-label extension (OLE) study of lasmiditan, 12.8% of patients discontinued the trial due to adverse events (11.2% of patients in the 100 mg group, and 14.4% in the 200 mg group), and dizziness was reported to be the most common AE leading to discontinuation (2.7% of patients in the 100 mg group, and 4.3% of patients in 200 mg group). There was no incidence of abuse, misuse, or diversion related to the CNS effects of lasmiditan. Due to concerns about somnolence with lasmiditan, the FDA label advises that patients should not drive or operate machinery within 8 hours of taking a dose.[56] Compared to the lasmiditan OLE, rates of discontinuation were lower in the OLEs of rimegepant and ubrogepant (see Table 3.17).

Controversies and Uncertainties

We primarily used indirect quantitative methods (network meta-analyses) to compare lasmiditan, rimegepant and ubrogepant to each other because there were no head-to-head studies, and only one trial compared one of the interventions versus a triptan (rimegepant vs sumatriptan). Such indirect analyses have more uncertainty than had the therapies been compared directly.

The primary outcomes reported included efficacy and side effects of a single dose of each drug compared to placebo at two hours after initial study medication. Though patient and patient advocates highlighted the importance of outcomes after two hours, protocols for use of rescue medications and additional study medication dosing differed markedly among the trials making it difficult to assess the benefits of these drugs after two hours. To address this, we obtained data from the trials of ubrogepant that were designed in a way that could permit a blinded evaluation of the initial study drug out to four hours. However, the magnitude and duration of any delayed benefit of these drugs remains uncertain.

Limitations of current therapies including triptans has led to considerable interest in new therapies for acute treatment of migraine. How helpful these new drugs will be over time for these patients in terms of effectiveness and tolerance is uncertain. Though potentially an option for those with absolute or relative contraindications to triptans, such as heart disease, there is little clinical information on the safety of these new therapies for these individuals.

Since most data presented results of these drugs for treatment of a single migraine attack, it is uncertain about their outcomes when used over time for repeated attacks. Important long-term outcomes such as the effect of these medications on potentially decreasing the frequency of migraine attacks, the occurrence of medication overuse headaches, and the need for other therapies such as opioids and barbiturates are currently not known. It is hoped that having more treatments for migraine can reduce use of opioids and thus the risk for opioid misuse.

Finally, migraine can have a dramatic impact on quality of life and ability to work for those with frequent, severe and unpredictable attacks. It is uncertain if these new therapies may help improve quality of life and work and productivity outcomes over time.

Summary and Comment

Lasmiditan, Rimegepant, and Ubrogepant Versus No Additional Migraine-Specific Acute Treatment (Placebo) or Triptans (Sumatriptan and Eletriptan)

Results from clinical trials and from our NMAs suggest that lasmiditan, rimegepant, and ubrogepant decrease symptoms of migraine attacks and improve function compared to placebo. Few harms were seen in the single-dose trials of lasmiditan, rimegepant and ubrogepant. However, lasmiditan

showed a higher incidence of CNS related AEs (e.g., dizziness, somnolence, paresthesia) in the clinical trials.

Population 1: For adults (18 years and older) with moderate-severe migraine attacks that have not responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated:

- We consider the evidence on lasmiditan, rimegepant and ubrogepant compared to placebo to be "incremental or better" (B+), demonstrating a moderate certainty of a small or substantial health benefit, with a high certainty of at least a small net health benefit.

Population 2: For adults (18 years and older) with migraine attacks that have not responded to non-prescription medicines (and are eligible to use triptans):

- We consider the evidence on lasmiditan, rimegepant and ubrogepant compared to triptans to be "comparable or inferior" (C-), demonstrating moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior. Based on the results of the NMAs, rimegepant and ubrogepant appear to be less efficacious than triptans (sumatriptan and eletriptan) but have comparable short-term adverse events. For lasmiditan, the results of the NMAs suggest it is less efficacious than triptans, but the NMAs do not exclude comparable efficacy compared to sumatriptan. In terms of adverse events, the NMA results suggest a higher incidence with lasmiditan compared to triptans.

For all adults with migraine attacks:

- We consider the evidence on rimegepant and ubrogepant to be "comparable" (C), demonstrating a high certainty of a comparable net health benefit. For lasmiditan, the results of the NMAs suggest it may be slightly more efficacious than rimegepant and ubrogepant. However, the NMAs do not exclude comparable efficacy. Patients treated with lasmiditan had more adverse events and more of them discontinued treatment than patients treated with rimegepant or ubrogepant. In addition, while supplemental post-hoc analyses show a delayed benefit for all three agents compared with placebo, the delayed benefits of the gepants relative to their early benefits appeared larger than the delayed benefits of lasmiditan compared to its early benefits. Thus, we believe any possible greater efficacy of lasmiditan is at best balanced by these adverse events and may be outweighed by them, and thus we consider the evidence on lasmiditan compared to rimegepant and ubrogepant to be "comparable or inferior" (C-).

Long-Term Cost Effectiveness

Model Overview

The primary aim of this analysis was to estimate the cost effectiveness of lasmiditan, rimegepant, and ubrogepant among adults for the acute treatment of migraine using a decision analytic model. In the model, lasmiditan, rimegepant, and ubrogepant were compared with each other and to three comparators in separate analyses across two distinct populations. For the first comparison, we included 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. In this group, we compared lasmiditan, rimegepant, and ubrogepant to each other and to no additional migraine-specific acute treatment. For this analysis, no additional migraine-specific acute treatment was estimated by the placebo arms of the clinical trials, although we recognized that in the real-world, patients may use previously failed or untried over the counter and prescription treatments for acute migraine including analgesics. For the second comparison, we included patients who had migraine attacks that did not respond adequately to non-prescription medicines. In this analysis, we compared lasmiditan, rimegepant, and ubrogepant to each other and to two triptans: sumatriptan and eletriptan. Sumatriptan was chosen because it is one of the most widely used triptans in clinical practice; and eletriptan, a newer triptan, was shown in a recent network meta-analysis to be one of the most efficacious and well tolerated. Since these new agents under review are all available as oral preparations, we focused our comparison of triptans on the oral formulations.

We developed a *de novo* semi-Markov model with time-varying proportions of patients with response to treatment. The outcomes of interest included the incremental cost per quality-adjusted life year (QALY) gained, life-years gained, equal value of life years gained (evLYG), and cost per hour of migraine pain avoided. The model was informed by a network meta-analysis of key clinical trials and prior relevant economic models, systematic literature reviews, and input from stakeholders. The base case used a US health sector perspective with costs and outcomes discounted at 3% annually. The model cycle was 48 hours and the time horizon was two years.

Upon model entry, hypothetical patients entered one of two Markov states, either having a migraine or not having a migraine, based on the average daily rate of migraines. Among patients in the migraine health state, patients were classified as having moderate or severe migraine pain. The treatment response was evaluated at 2, 8, 24 and 48 hours. Patients could have complete resolution of migraine pain (pain freedom), improvement in migraine pain without complete resolution (pain relief) or no improvement. Patients with pain relief at each of the time points were classified as having mild migraine pain. The level of migraine pain was linked to utility values from the EQ-5D. Treatment response was linked with the probability of requiring a provider office visit, emergency department visit or hospitalization due to migraine. Rates of adverse events were

linked to disutility values. Over time, patients could discontinue treatment due to side effects or insufficient effectiveness.

Key Assumptions

The model required several assumptions, which are described below.

Table ES5. Key Model Assumptions

Assumption	Rationale
Mortality is not associated with acute treatment for migraine.	There have been no demonstrated mortality benefits with treatment of migraine pain and other symptoms.
Acute treatment of migraine with lasmiditan, rimegepant, ubrogepant, and triptans does not affect migraine frequency.	Studies evaluating new migraine therapies were either short-term single episode studies or non-controlled open label studies and were not designed to demonstrate changes in migraine frequency with treatment. Longer-term, uncontrolled, open-label studies suffer from a possible placebo effect and a high likelihood that regression to the mean may affect the study's results. Should stronger evidence suggest that migraine frequency and/or characteristics are modified with acute treatments for migraine, this assumption will be reevaluated.
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.	Data describing treatment discontinuation due to lack of effect was obtained from a study in which follow up lasted for 12 months.[57] It is unlikely that the majority of patients receiving no or suboptimal benefit would continue taking a medication beyond 12 months.
Patients who did not respond to acute treatments for migraine were assumed to have moderate or severe pain, in proportion to what was observed at baseline.	Sufficiently detailed data evaluating those who did not respond was not uniformly available from clinical trials. This assumption was necessary to assign utility values to those who did not respond to therapy.
If a migraine treatment resulted in migraine pain of "no pain" or "mild pain" at 2 hours, a person would be able to work.	The impact of migraine on productivity is important to patients. However, clinical trials did not evaluate work productivity. Studies that have evaluated work productivity have assessed the impact of migraine on productivity (primarily absenteeism) but have not assessed the impact of treatment and time to pain and/or symptom relief on productivity. This assumption was necessary to apply results of productivity studies in migraine patients to this model for the scenario analysis evaluating a modified societal perspective.

Model Inputs

Two-hour response to acute treatments for migraine was estimated using data directly from clinical trials included in a network meta-analysis. The proportion of patients who were pain free in clinical trials were considered to have "no pain" at the two-hour time point. The proportion of patients with "mild pain" were those who had pain relief but were not pain free. Those with no response remained in moderate or severe pain in proportion to what was observed at baseline. In clinical trials evaluating lasmiditan, rimegepant, and ubrogepant, some patients who responded at two hours subsequently lost response to treatment between two and 24 hours. The proportion of patients maintaining response at 24 hours was based on estimates from the network meta-analysis of clinical trials. For the patients who lost response, we assumed the maximal proportion lost response at eight hours. After eight hours, patients regained response where the rate of response among this group at 24 hours was equivalent to the placebo response rate. All patients responding at two hours were assumed to have treatment response at 48 hours.

Among patients who did not respond at two hours, the rate of response observed in this group was based on the rate of placebo response at eight, 24, and 48 hours. For Population 1, this observed placebo response was further modified by a relative risk of achieving pain relief or pain freedom for rimegepant and ubrogepant only, to adjust for an observed greater response when compared with placebo after the two-hour time point. Estimates of treatment response at 2, 8, 12, 24, and 48 hours are shown in the full report, Tables 4.3 (Population 1) and 4.4 (Population 2).

The utilities used in the analysis were derived from published literature that estimated migraine-specific utility values using the EQ-5D and stratified by the severity of the migraine. The utility values used in the model were 0.959 for pain free, 0.835 for mild pain, 0.773 for moderate pain and 0.440 for severe pain. Hospitalized patients were assigned a disutility of -0.5 for 48 hours; those admitted to the emergency department were assigned a disutility of -0.5 for 24 hours. We did not include a disutility score for patients suffering from nausea and/or vomiting, photophobia, or phonophobia due to lack of data. Disutility of other adverse events, including drowsiness, dizziness, fatigue and paresthesia, were included in the model.

We used the wholesale acquisition cost (WAC) from Redbook to estimate prices for all drugs with prices available. At the time of publishing this report, the prices for rimegepant was not available. We therefore estimated the price of rimegepant assuming the same price as was announced for ubrogepant. A 27% industry average discount was applied to all WAC prices. Costs for treatments for the usual care arm were estimated using a prevalent mix of treatments and applied WAC prices from Redbook. We used the WAC to price without an applied discount to price triptans, as they are currently available as generic medications.

Table ES6. Drug Cost per Dose

Drug	WAC	Source
Lasmiditan	$80.00	Redbook Online from Micromedex[58]
Rimegepant	WAC not available (used $85)	Assumed same price as for ubrogepant.
Ubrogepant	$85.00	Redbook Online from Micromedex[58]
Sumatriptan, Oral tablets 50 mg 100 mg	$1.04	Redbook Online from Micromedex[58]
Eletriptan 40 mg	$11.95	Redbook Online from Micromedex[58]
Usual Care (mix)	$4.81	Ford 2017[59] Micromedex[58]

mg: milligrams, WAC: wholesale acquisition cost

Base-Case Results

The base-case results using the placeholder prices for lasmiditan, rimegepant, and ubrogepant are reported in Tables ES7 and ES8. (Tables ES7, ES8, and ES9 have been updated based on the results described above in the Update added to this report.)

Table ES7. Base-Case Results for Lasmiditan, Rimegepant, Ubrogepant, and Usual Care for Population 1

Treatment	Drug Cost (per year)*	Total Cost*	QALYs	Life Years	evLYG	Hours of Pain
Lasmiditan	$3,360	$12,000	1.8271	1.95	1.8271	1,650
Rimegepant*	$3,570	$10,660	1.8295	1.95	1.8295	1,570
Ubrogepant	$3,570	$10,660	1.8295	1.95	1.8295	1,580
Usual Care	$280	$10,050	1.8142	1.95	1.8142	2,100

QALY: quality-adjust life year; LY: life year; evLYG: equal value of life years gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

**Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

Table ES8. Base-Case Results for Lasmiditan, Rimegepant, Ubrogepant, Sumatriptan, and Eletriptan for Population 2

Treatment	Drug Cost (per year)**	Total Cost**	QALYs	Life Years	evLYG	Hours of Pain
Lasmiditan	$3,360	$12,000	1.8271	1.95	1.8271	1,650
Rimegepant	$3,570	$13,010	1.8222	1.95	1.8222	1,870
Ubrogepant	$3,570	$13,020	1.8221	1.95	1.8221	1,876
Sumatriptan	$60	$6,630	1.8264	1.95	1.8264	1,610
Eletriptan	$690	$6,790	1.8293	1.95	1.8293	1,480

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)
**Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

The incremental cost-effectiveness results are reported in Table ES9. When evaluating the use of lasmiditan, rimegepant, and ubrogepant using the place-holder prices in Population 1, the ICERs for lasmiditan, rimegepant, and ubrogepant compared with usual care were $151,800, $39,800, and $40,000 per QALY gained, respectively. When compared with each other, rimegepant and ubrogepant dominated lasmiditan, being more effective and less costly. Rimegepant and ubrogepant had nearly identical total costs, QALYs, and cost effectiveness. In Population 2, both sumatriptan and eletriptan produced higher QALYs at a lower total cost, and therefore dominated lasmiditan, rimegepant, and ubrogepant.

Table ES9. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Hour of Pain Avoided
Population 1			
Lasmiditan	Usual Care	$151,800	$4.32
Rimegepant*	Usual Care	$39,800	$1.15
Ubrogepant	Usual Care	$40,000	$1.15
Population 2			
Lasmiditan	Sumatriptan	Dominated	Dominated
Rimegepant*	Sumatriptan	Dominated	Dominated
Ubrogepant	Sumatriptan	Dominated	Dominated
Lasmiditan	Eletriptan	Dominated	Dominated
Rimegepant	Eletriptan	Dominated	Dominated
Ubrogepant	Eletriptan	Dominated	Dominated

QALY: quality-adjusted life years
*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

Sensitivity and Scenario Analyses

We conducted sensitivity analyses and scenario analyses to assess the impact of all model parameters on the estimated cost effectiveness in population 1. The model was sensitive to several of the model inputs. For lasmiditan, the monthly migraine frequency, probability of being hospitalized, probability of having emergency department visits, and proportion with pain relief at 24 hours (in the lasmiditan and/or placebo treatment branches) were considered important variables with the potential to result in incremental cost-effectiveness ratios below $150,000 per QALY gained depending on the input value. For rimegepant and ubrogepant, migraine frequency and probability of hospitalizations had the potential to result in incremental cost-effectiveness ratios above $150,000 per QALY.

Probabilistic sensitivity analyses were also conducted to assess the variation across all parameters with 1,000 Monte Carlo simulations. Table ES10 shows the proportion of simulations for which each treatment had the highest net mean benefit at different cost-effectiveness thresholds for lasmiditan, rimegepant, ubrogepant, and usual care. When conducting probabilistic sensitivity analyses on the base case in Population 1, rimegepant and ubrogepant were the most cost-effective options at the $50,000 per QALY gained threshold 36.8% and 47.6% of the time, respectively.

Lasmiditan was not considered the most cost-effective option in four-way comparisons at any of the threshold prices.

Table ES10. Probabilistic Sensitivity Analysis Results Proportion of ICERs below specified Thresholds for Lasmiditan, Rimegepant, Ubrogepant Compared with Usual Care (Placebo)

Treatment Compared with Usual Care	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Lasmiditan	0.0%	0.0%	0.0%
Rimegepant*	36.8%	45.7%	46.5%
Ubrogepant	47.6%	53.5%	53.5%

QALY: quality-adjusted life year
*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

Scenario Analyses

The modified societal perspective included potential labor benefits for reduced migraine pain in the analysis for Population 1. In this scenario, the ICERs for lasmiditan compared to usual care was $57,500, while rimegepant and ubrogepant dominated (i.e. lower cost and higher QALYs gained) usual care.

Threshold Analyses Results

Average annual prices that would result in willingness-to-pay thresholds of $50,000 to $150,000 per QALY gained for Population 1 are shown in table ES11 below.

Table ES11. Threshold Analysis Results for Population 1 (Patients Who Cannot Take Triptans)

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Lasmiditan	$2,450	$2,900	$3,350
Rimegepant	$3,670	$4,160	$4,640
Ubrogepant	$3,670	$4,150	$4,630

QALY: quality-adjusted life year

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). Model calculations were verified, and model input parameters were varied to evaluate face validity of changes in results. We also conducted sensitivity analyses with null input values to

ensure the model was producing findings consistent with expectations. Model validation was also conducted in terms of comparisons to other model findings.

Summary and Comment

In our analysis of the cost effectiveness of lasmiditan, rimegepant, and ubrogepant, we found that for patients for whom triptans are not effective, not tolerated, or are contraindicated (Population 1), rimegepant (assuming similar pricing to ubrogepant) and ubrogepant are cost effective at commonly used thresholds. Lasmiditan slightly exceeds the $150,000 per QALY gained threshold in this population. For patients able to take triptans (Population 2), sumatriptan and eletriptan are both more effective and less expensive than these newer agents. Due to clinical trial designs, there is considerable uncertainty in some estimates used in the base case, such as the impact of the treatments on emergency visits and hospitalizations, pain relief at time points beyond two hours, and repeated medication use on migraine frequency. More evidence is required to obtain better precision in cost-effectiveness estimates for lasmiditan, rimegepant, and ubrogepant when compared with usual care.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES12. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Similar to most triptans, lasmiditan, rimegepant and ubrogepant are orally available medications and would not be expected to increase the complexity of care. The favorable side effects seen to date with rimegepant and ubrogepant, similar to those seen with placebo, may make these medications attractive to patients and clinicians. The restriction on driving after taking lasmiditan is a potential disadvantage of that therapy.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	Not applicable
This intervention will significantly reduce caregiver or broader family burden.	New therapies for acute treatment of migraine may reduce caregiver and family burden if outcomes are improved for those in whom existing therapies do not effectively and safely control symptoms.
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.	These new therapies reflect translational research in which improved understanding of the mechanisms of disease has led to new therapeutics. Lasmiditan, approved for migraine attacks, targets the 5HT1F (5-hydroxytryptamine 1F) receptor, and unlike the triptans does not induce vasoconstriction. The gepants, target CGRP, a peptide neural transmitter found in the pathways that play an important role in migraine. Ubrogepant is the first approved small molecule gepant and rimegepant is under review.
This intervention will have a significant impact on improving return to work and/or overall productivity.	The availability of new treatments for migraine is likely to allow some patients to remain at work in situations where they would otherwise have needed to miss or leave work. The restriction on driving after taking lasmiditan may negatively impact work/productivity outcomes.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Patients and advocates expressed the hope that these new therapies for patients with migraine may provide an effective and safe alternative for individuals who may turn to opioids and barbiturates because of limitations of existing therapies.

Contextual Considerations

Table ES12. Potential Contextual Considerations

Contextual Consideration	Description
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.	For patients with frequent and severe migraine attacks that have not responded to other therapies or have had intolerable side effects or contraindications to their use, these new therapies may offer a new treatment option.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	For some individuals with migraine, it is a frequent, unpredictable and disabling condition that impacts all aspects of life.
This intervention is the first to offer any improvement for patients with this condition.	There are currently available over the counter and FDA approved medications for patients with migraine attacks.
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	For patients who improve with lasmiditan, rimegepant or ubrogepant and have tolerable side effects, it is expected that prolonged use for migraine attacks will be recommended. Questions remain about the development of new side effects and the risk of medication overuse headaches with frequent use over time.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	For new medications that have mainly been evaluated in single dose comparative trials or non-comparative open-label studies of up to a year, their long-term benefits are uncertain relative to other therapies that have years of experience.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Lasmiditan, rimegepant and ubrogepant have not been shown to cause vasoconstriction, but whether they are free of cardiovascular adverse effects, particularly in those with cardiovascular disease or at high risk, remains to be proven.

Value-Based Price Benchmarks

Annual value-based price benchmarks (VBPBs) of these drugs (vs. usual care) are presented in Table 6.1. The VBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. The results in this section have been updated based on the above Update to this Report.

For lasmiditan, price discounts of 27% from the assumed list price would be required to reach the $150,000 per QALY threshold price (Table 6.1). Price discounts of approximately 37% from assumed list prices would be required to reach the $100,000 per QALY threshold price range. For ubrogepant, price discounts of 5% and 15% would be required to reach the $150,000 and $100,000 threshold prices, respectively. The WAC is not currently available for rimegepant. We have

estimated required price discounts in Table ES13, given the assumption that rimegepant will be priced the same as ubrogepant when a WAC becomes available.

As there is no mortality effect in the model, cost per LY gained is not relevant, and the cost per evLYG is essentially the same as the cost per QALY gained. We therefore do not report VBPBs for these in the table below.

Table ES13. Value-Based Price Benchmark Ranges for Lasmiditan, Rimegepant, and Ubrogepant versus Usual Care in Population 1 (Patients Who Cannot Take Triptans)

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC Required to Achieve Threshold Prices
Lasmiditan	$4,610	$2,900	$3,350	27%-37%
Rimegepant*	Not available (Estimated at $4,896)	$4,160	$4,640	5%-15%
Ubrogepant	$4,896	$4,150	$4,630	5%-15%

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Rimegepant price estimated using ubrogepant WAC. The WAC has not been released for rimegepant.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of each drug (lasmiditan, rimegepant, and ubrogepant) added to usual care for prevalent individuals in the United States (US) aged 18 years and over experiencing migraines requiring acute treatment, with or without aura. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. We used the WAC, assumed net price, and three threshold prices for lasmiditan and ubrogepant in our estimates of budget impact. As the price for rimegepant was not available, we assumed the same WAC and net price as for ubrogepant. We also included a scenario analysis where the frequency of migraines is assumed to decrease over time. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

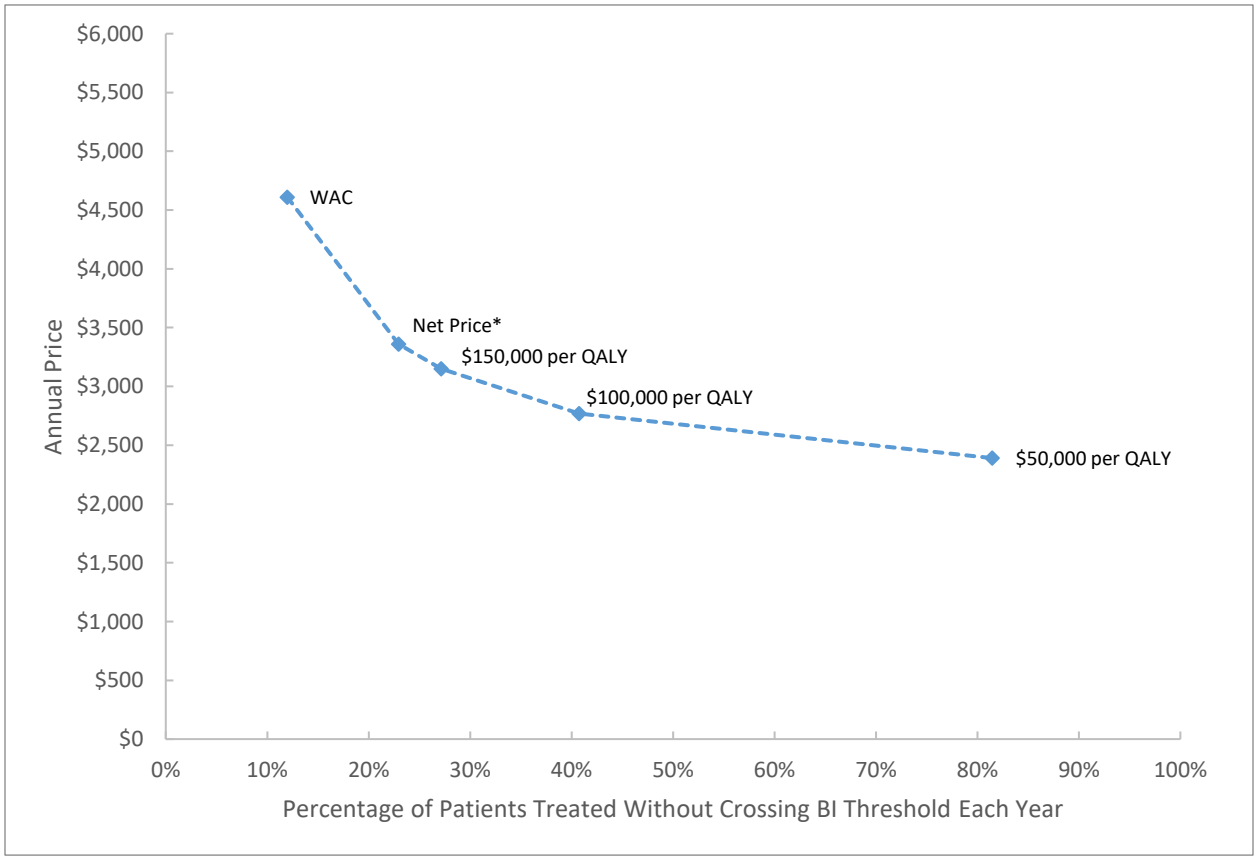
This potential budget impact analysis does not include the population cohort of patients with migraines who are eligible for treatment with triptans, as sumatriptan and eletriptan dominated these drugs in our cost-effectiveness analysis. This potential budget impact analysis includes the cohort of patients 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. Using data from the literature, we estimate the size of the potential candidate population for treatment in

the average 2020-2024 estimated US adult population as approximately 6.4 million patients, or approximately 1.3 million patients each year over five years.

Base-Case Results

Results have not been updated based on the above Update added to this report. For lasmiditan, as shown in Figure ES1, approximately 12% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC. Approximately 23% of eligible patients could be treated without crossing the budget impact threshold at its assumed net price. Approximately 27% of eligible patients could be treated at the price to reach the cost-effectiveness threshold of $150,000 per QALY, increasing to approximately 82% at the $50,000 threshold price.

Figure ES1. Potential Budget Impact Scenarios of Lasmiditan versus Usual Care at Different Acquisition Prices

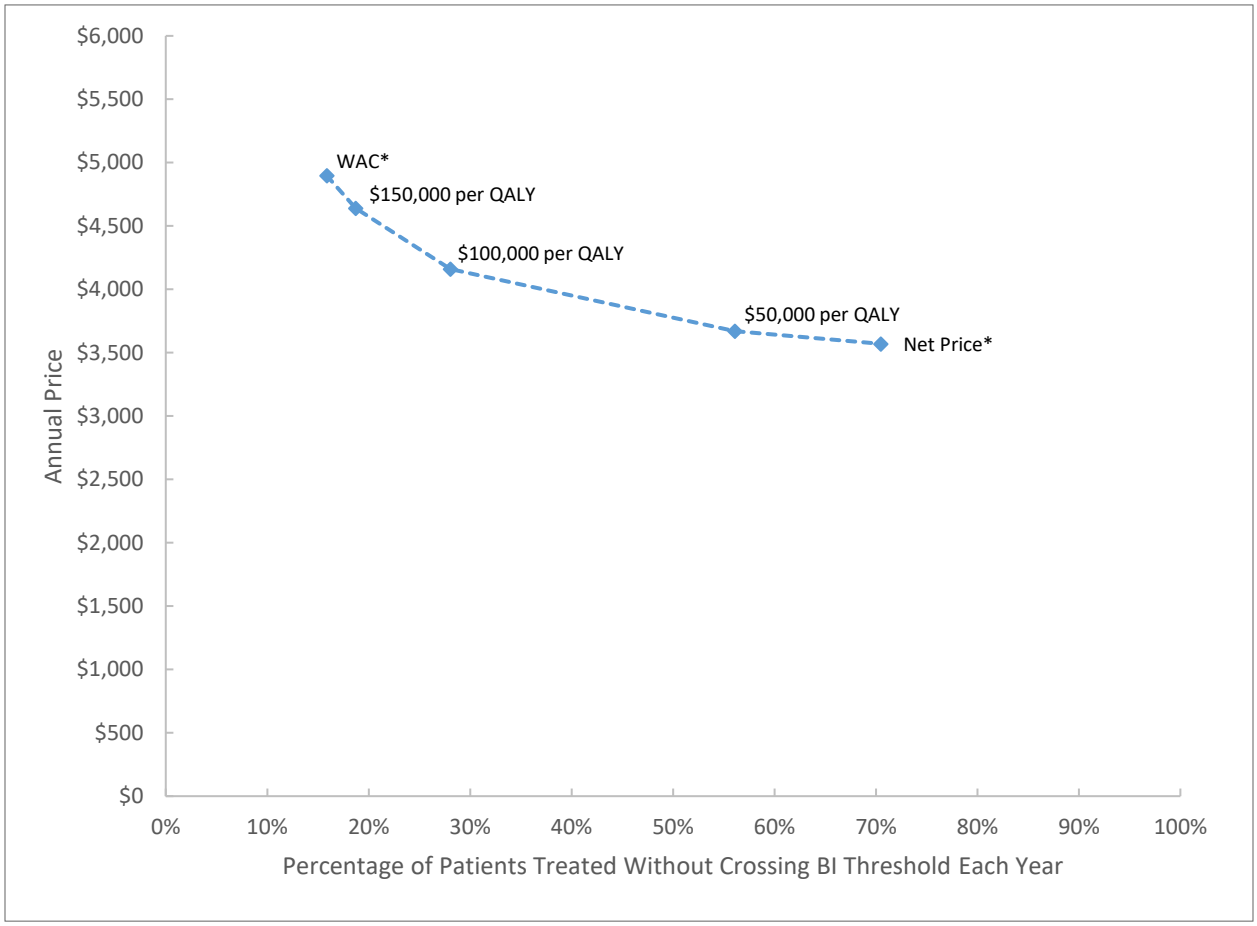


*Assumed 27% discount.
BI: budget impact, QALY: quality-adjusted life year

For rimegepant, as shown in Figure ES2, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at rimegepant's assumed WAC. Approximately 19% of eligible patients could be treated without crossing the

budget impact threshold at the $150,000 threshold price, increasing to approximately 56% at the price to reach $50,000 per QALY. Approximately 71% of eligible patients could be treated at the assumed net price.

Figure ES2. Potential Budget Impact Scenarios of Rimegepant versus Usual Care at Different Acquisition Prices

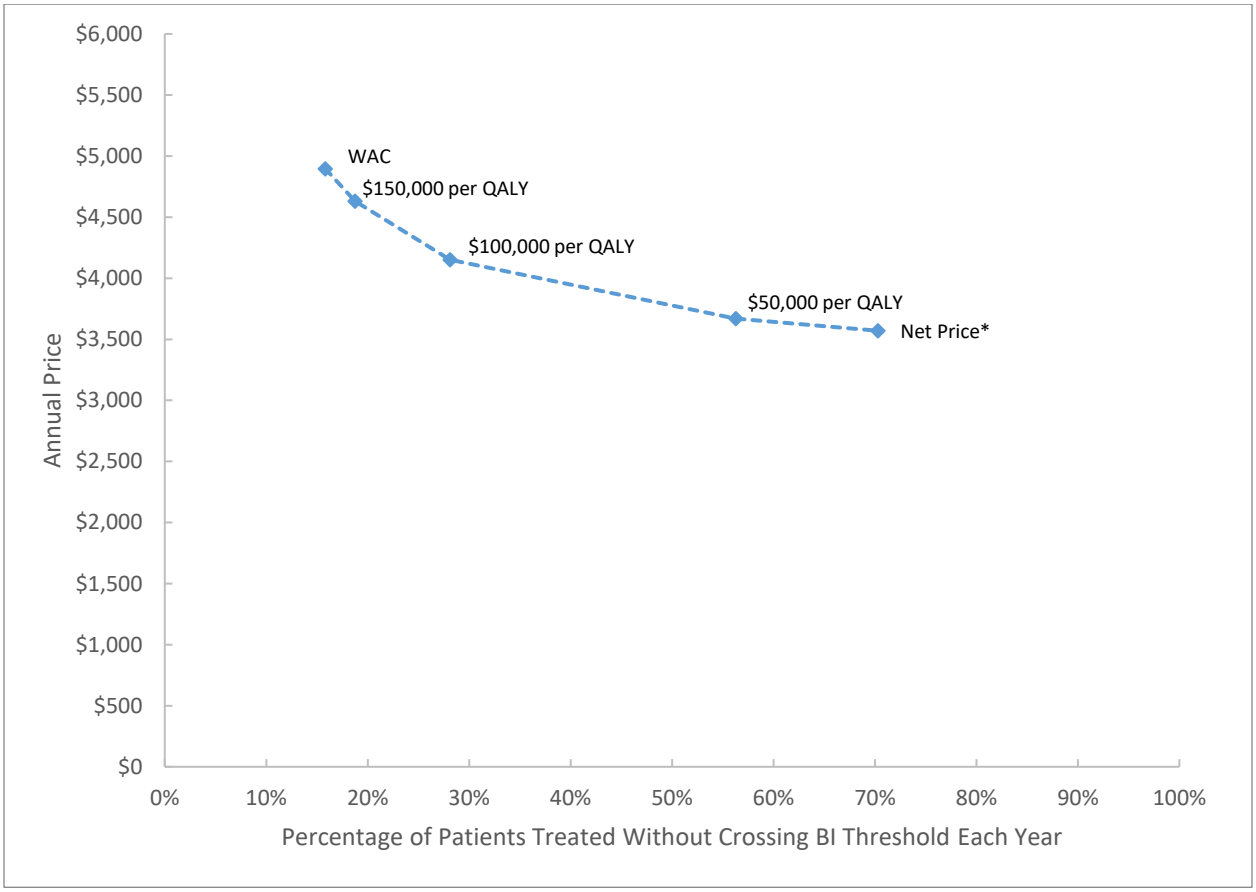


*Assumed placeholder WAC and net price equal to ubrogepant's WAC and assumed net price (27% discount from WAC).

BI: budget impact, QALY: quality-adjusted life year

For ubrogepant, as shown in Figure ES3, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at ubrogepant's WAC. Approximately 19% of eligible patients could be treated without crossing the budget impact threshold at the $150,000 threshold price, increasing to approximately 56% at the price to reach $50,000 per QALY. Approximately 70% of eligible patients could be treated at the assumed net price.

Figure ES3. Potential Budget Impact Scenarios of Ubrogepant versus Usual Care at Different Acquisition Prices



*Assumed 27% discount

BI: budget impact, QALY: quality-adjusted life year

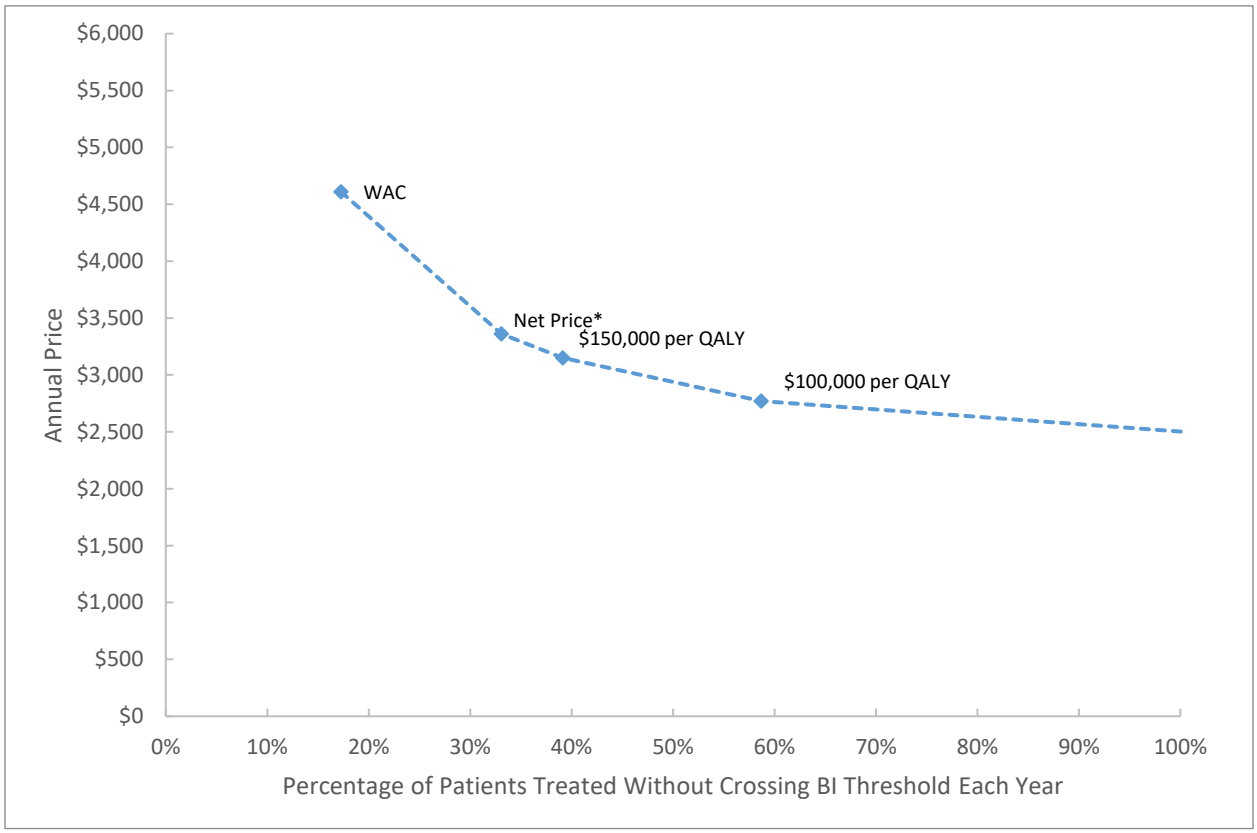
Scenario Results

Data from a long-term open label safety study suggests that the frequency of migraines decreased over time. While this single-arm trial was not designed to evaluate whether the same effect was observed in a control population, decreasing migraine frequency over time could have a significant impact on budget impact analyses. We therefore created a scenario analysis where we modeled the potential budget impact of these treatments if migraine frequency decreases over time.

For lasmiditan in this scenario, as shown in Figure ES4, approximately 17% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at lasmiditan's WAC. Approximately 33% of eligible patients could be treated without crossing the budget impact threshold at its assumed net price. Approximately 39% of eligible patients could be treated at the price to reach the cost-effectiveness threshold of $150,000 per QALY, increasing to approximately 59% at the $100,000 threshold price. All eligible patients could be treated at the

$50,000 per QALY threshold price, with estimated potential budget impact of approximately 85% of the threshold.

Figure ES4. Potential Budget Impact Scenarios of Lasmiditan versus Usual Care at Different Acquisition Prices: Decreased Frequency Scenario

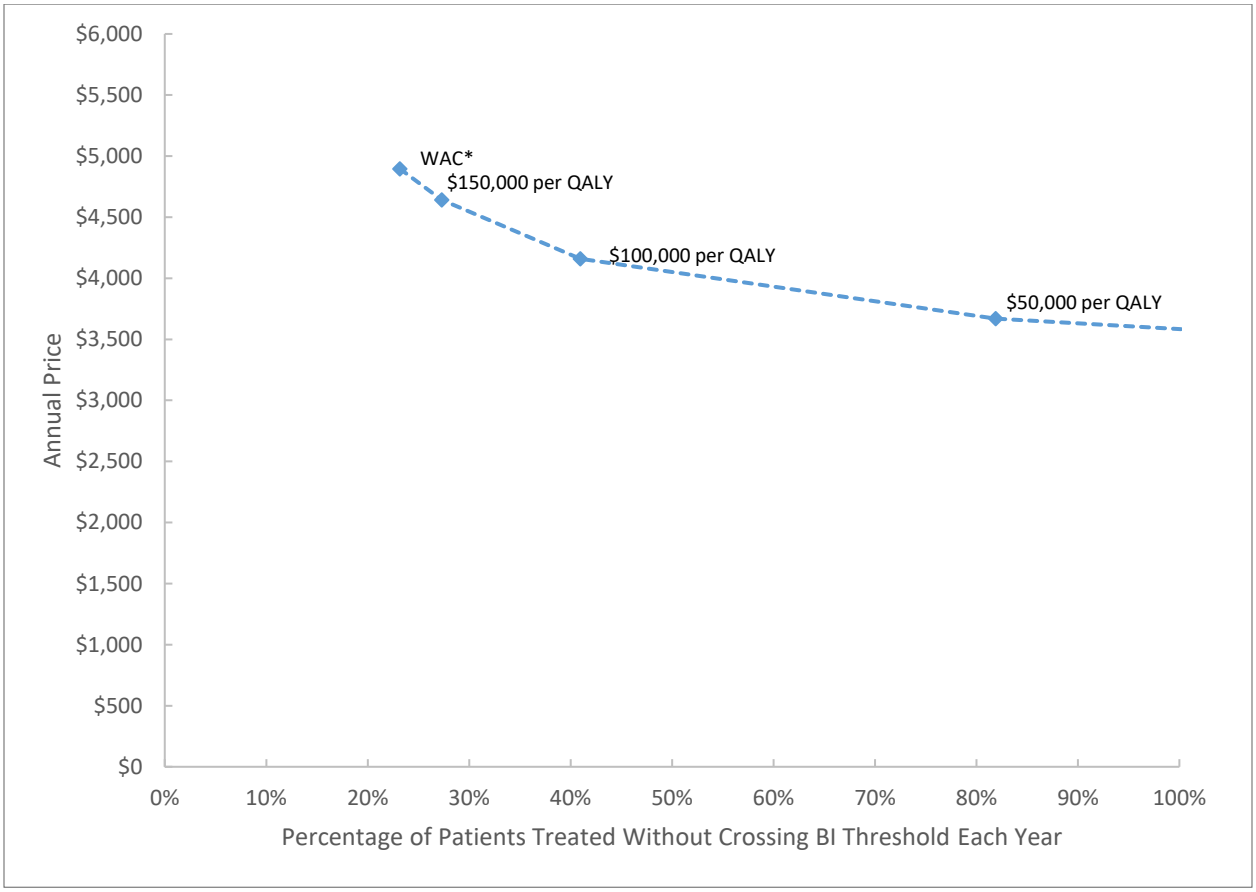


*Assumed 27% discount.

BI: budget impact, QALY: quality-adjusted life year

For rimegepant in this decreased frequency scenario, approximately 23% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at rimegepant's assumed WAC. Approximately 27% of eligible patients could be treated without crossing the budget impact threshold at the $150,000 threshold price, increasing to approximately 82% at the price to reach $50,000 per QALY. All eligible patients could be treated at the assumed net price, with estimated potential budget impact of approximately 97% of the threshold.

Figure ES5. Potential Budget Impact Scenarios of Rimegepant versus Usual Care at Different Acquisition Prices: Decreased Frequency Scenario

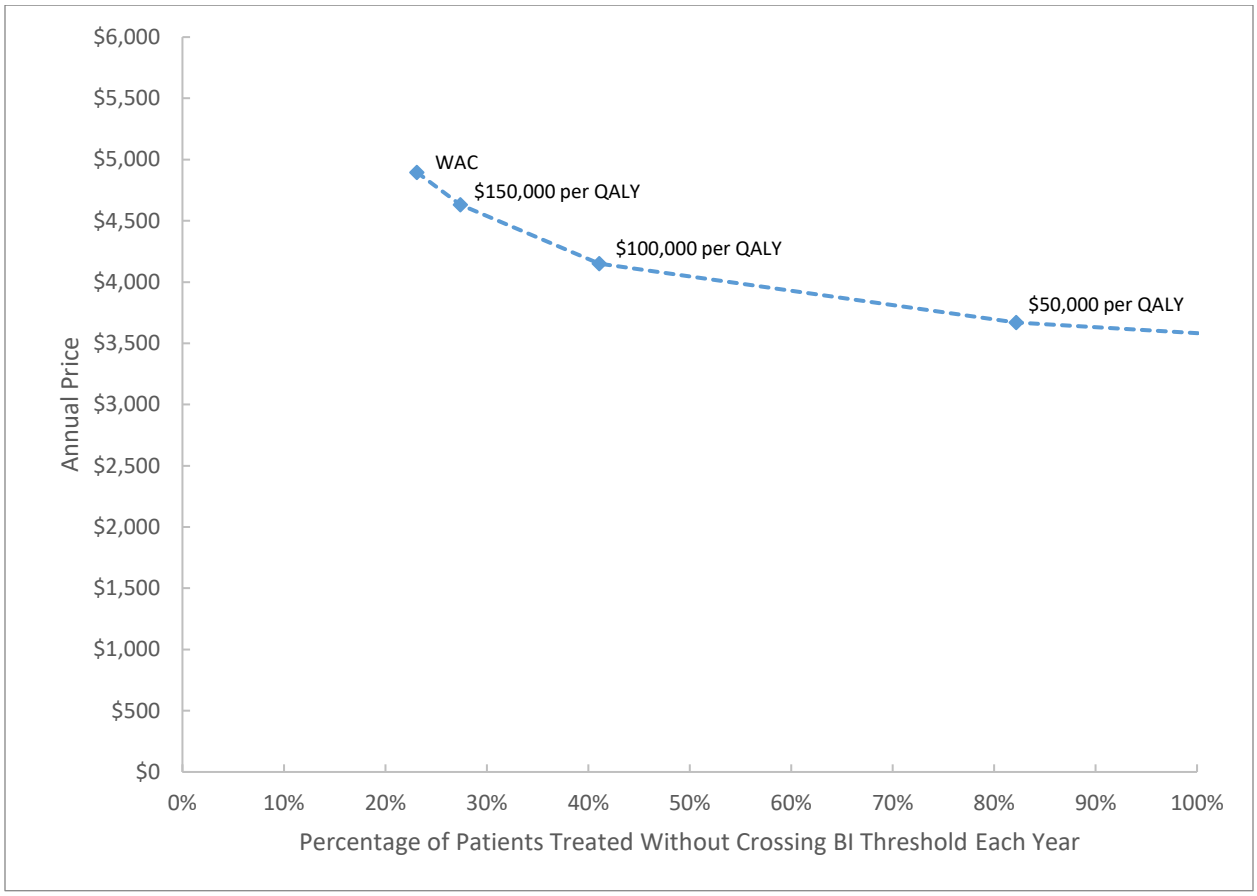


*Assumed placeholder WAC and net price equal to ubrogepant's WAC and assumed net price (27% discount from WAC).

BI: budget impact, QALY: quality-adjusted life year

For ubrogepant in this scenario, approximately 23% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at ubrogepant's WAC (Figure ES6). Approximately 27% of eligible patients could be treated without crossing the budget impact threshold at its price to reach the cost-effectiveness threshold of $150,000, increasing to approximately 82% at the price to reach $50,000 per QALY. All eligible patients could be treated at the assumed net price, with estimated potential budget impact of approximately 97% of the threshold.

Figure ES6. Potential Budget Impact Scenarios of Ubrogepant versus Usual Care at Different Acquisition Prices: Decreased Frequency Scenario



*Assumed 27% discount.
BI: budget impact, QALY: quality-adjusted life year

Midwest CEPAC Voting Results

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on January 23, 2020. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Population for Questions 1-7: *All adults patients with a diagnosis of migraine.*

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

Yes: 12 votes	No: 0 votes

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

Yes: 12 votes	No: 0 votes

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

Yes: 12 votes	No: 0 votes

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

Yes: 0 votes	***No: 12 votes***

If yes:

4a. Which therapy, rimegepant or ubrogepant, has the greater net health benefit?

No vote taken

5. Is the evidence adequate to demonstrate that the **gepants** have a superior net health benefit compared to **triptans**?

Yes: 0 votes	***No: 12 votes***

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

Yes: 0 votes	***No: 12 votes***

7. Is the evidence adequate to distinguish the net health benefits between the **gepants** and **lasmiditan**?

Yes: 1 vote	***No: 11 votes***

If yes:

7a. Which therapy, **gepants** or **lasmiditan**, has the greater net health benefit?

No vote taken

Potential Other Benefits or Disadvantages and Contextual Considerations

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)

This intervention will significantly reduce caregiver or broader family burden.	**11/12**
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.	**12/12**
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	**11/12**
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention.	**See Section 8.2**

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

This intervention will significantly reduce caregiver or broader family burden.	**10/12**
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.	**11/12**
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	**9/12**
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention.	**See Section 8.2**

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

This intervention offers reduced complexity that will significantly improve patient outcomes.	**9/12**
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention.	6/12

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

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.	**9/12**
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	**11/12**
This intervention is the first to offer any improvement for patients with this condition.	**12/12**
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	4/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	**8/12**

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

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.	**10/12**
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	**11/12**
This intervention is the first to offer any improvement for patients with this condition.	**12/12**
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	6/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	6/12

Long-Term Value for Money

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?

No vote taken

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?

    **Note: This vote was based on information presented at the public meeting. Supplemental post-hoc analyses suggest that there is a delayed benefit for the gepants, and the base case cost-effectiveness model was modified to reflect this. As a result, the revised models suggest that the gepants are cost effective based on the WAC cost for ubrogepant.*

Low: 4 votes	***Intermediate: 8 votes***	High: 0 votes

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?

No vote taken

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of lasmiditan, rimegepant, and ubrogepant among adults for the acute treatment of migraine. The policy roundtable members included two patient advocates, two clinical experts, one payer, and four representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Payers

(1) Given that the evidence does not demonstrate superiority of the newer agents to existing less-expensive treatment options, it is reasonable for insurers and other payers to develop prior authorization criteria for lasmiditan, rimegepant and ubrogepant to ensure prudent use of these new therapies.

(2) For ubrogepant and rimegepant, given their similar mechanisms of action and available evidence suggesting no major differences in safety or effectiveness, it is not unreasonable for payers to negotiate lower prices by offering preferential formulary status to one or the other drug, including the possibility of exclusion of one of the drugs. If only one drug is covered,

however, clinicians and patients should have the ability to appeal for coverage for the other gepant drug should a trial of the favored drug not produce adequate success.

(3) Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policies are discussed in Section 8.3.

Providers

(1) With the advent of these new treatment options, specialists in migraine treatment should seek new avenues to educate primary care clinicians on the appropriate use of triptans and other acute treatment options in order to maximize the appropriate care of the substantial population of patients with migraine while helping to control costs.

(2) Migraine specialists and specialty societies should update guideline recommendations to address the role of these new medications for acute treatments for migraine.

Manufacturers and Researchers

(1) Manufacturers and researchers should develop long term comparative trials of acute treatments for migraine that assess outcomes over the entire course of a migraine attack.

(2) Manufacturers and researchers should develop comparative trials of acute treatments for migraine that assess whether new medications have a lower risk for medication overuse headache and can reduce the frequency of migraine attacks over time.

(3) Manufacturers and researchers should conduct real-world comparative studies of acute treatments for migraine that assess important outcomes including quality of life, work, productivity and disability.

Regulators

(1) The patient population which may be considered for treatment with lasmiditan, rimegepant and ubrogepant is very large. Regulators have an important role to play in how new therapeutics enter clinical practice and therefore should require post-approval, long-term comparative outcomes studies for new acute treatments for migraine that are initially evaluated and approved in single-dose randomized trials.

1. Introduction

1.1 Background

Migraine is a common, typically episodic cause of disabling headache often associated with nausea and sensitivity to light and sound. Approximately 40 million adults (12-15%) in the United States (US) have reported migraine or severe headaches.[3,4] The hallmark of migraine is recurrent attacks characterized by headache that is often but not always one-sided and described as pulsatile or throbbing. In addition to headache, other symptoms may start right before or occur with the headache including nausea with or without vomiting, and sensitivity to external stimuli such as light, sound, and smells. The frequency of attacks and the intensity of symptoms vary widely, but when frequent and severe, migraine can be a disabling, chronic condition that can impact all aspects of life including personal relationships and ability to work.[2] Patients with migraine have increased use of health care resources including visits to health care providers and emergency departments.[5,6] Overall cost of health care for those with migraine are estimated to be $11-50 billion dollars in the US.[5,7] Direct health care costs as well as indirect costs associated with decreased productivity, work loss and disability claims are higher for those with migraine,[8-10] and migraine is one of the most common causes of disability worldwide.[60]

Diagnosis of migraine is based upon patient-reported symptoms, history, and physical examination findings; there is no test available that confirms the diagnosis.[11] This may partly explain why many individuals with migraine may be incorrectly diagnosed.[13 13] Clinical criteria broadly include the frequency and nature of the headache and the presence or absence of aura. Aura refers to a gradual onset of sensory or motor symptoms either before the onset of headache or as part of the headache. Though some patients do not have aura, the most common are visual symptoms such as seeing bright lines, shapes, or objects.[13] Headache features associated with a diagnosis of migraine include location on one side of the head, pulsating quality, moderate or severe pain intensity, and known triggers. Migraine is more common in women than men,[14] and in those aged 18 to 44 years.[3,4] A genetic predisposition to migraines is thought to account for their tendency to run in families. The precise cause of migraines is not known, but hypersensitivity of the brain to external stimuli and internal factors lead to activation of the trigeminovascular system of nerves that result in blood vessel and pain responses.[12] Predisposing factors associated with migraine attacks include emotional stress, menstruation, visual stimuli, changes in weather, and certain foods and activities.[15]

Treatment of migraine broadly focuses on two strategies: preventive therapy to reduce the frequency of attacks or acute therapy meant to quickly abort episodic symptoms, which is usually more effective the sooner it is given.[13] Acute treatments are referred to by a number of other terms including “abortive treatment,” and “symptomatic treatment”; we will use the term “acute

treatment" in this document. Early acute treatment is especially helpful for individuals with aura that precedes the onset of the headache. The choice of therapy is based upon symptom frequency, severity, and the presence of nausea and vomiting. For individuals with mild symptoms, first-line over-the-counter nonspecific pain medications include aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen, and acetaminophen. There are also combination preparations with caffeine, but caffeine withdrawal headaches can occur with frequent use. Other strategies such as lying down in a quiet and dark room are also helpful, and a nap or sleep sometimes lead to relief.

For individuals with moderate or severe symptoms or lack of response to nonspecific pain medications, the use of specific migraine medications is recommended. The most commonly used migraine specific medication class targets the 5-hydroxytryptamine (5-HT) or serotonin receptor. Seven 5-HT 1b/1d agonists or "triptans" are US Food and Drug Administration (FDA) approved for acute treatment of migraine attacks.[12] Triptans are available as pills, nasal sprays, and for injection under the skin, with non-oral routes of administration typically for those with severe headache accompanied by nausea and/or vomiting. Though effective and safe for many patients with migraine, triptans are labeled as contraindicated in patients with known cardiovascular disease because of their vasoconstrictive effects, but observational studies have not identified major cardiovascular risk as used in clinical practice.[61] Similarly, despite a reported possibility of serotonin syndrome in patients who combine triptans with selective serotonin and serotonin-norepinephrine reuptake inhibitors, the actual risk appears to be extremely low.[62,63]

Ergotamine preparations also represent migraine-specific treatment, but side effects and limited efficacy have resulted in their being much less commonly used since the introduction of triptans. Non-specific pain medications, such as barbiturates and opioids, have similar limitations as well as the potential for tolerance and misuse, and have led to their being reserved for patients unresponsive to other therapies. For patients with associated nausea and vomiting, antiemetics are used but generally in addition to other medications. For most individuals with migraine, treatment focuses on episodic intervention. However, for the one-quarter to one-third of patients with severe and frequent attacks, medications to prevent migraine attacks are recommended.[13] This is important because medication overuse headache can result from frequent administration of acute medications for migraine attack, especially with nonspecific pain medications such as opioids, barbiturates, and combination agents. However, the prevalence of medication overuse headaches varies widely based upon differences in definitions and the population assessed.[64,65]

Interventions: Calcitonin gene-related peptide (CGRP) antagonists (rimegepant, ubrogepant) and 5-hydroxytryptamine (5-HT) 1f agonist (lasmiditan)

Many individuals do not adequately respond to multiple different medications for acute treatment, demonstrating a need for new therapeutic options. For example, studies of triptans often demonstrate response rates of 40-75%,[16] and decreased response over time can also be seen in some individuals.[17] One new target for therapy is calcitonin gene-related peptide (CGRP). Interest in agents that target CGRP is based upon it being expressed in trigeminal ganglia nerves involved in the vasodilatory component of neurogenic inflammation, and administration of CGRP can trigger acute headache and delayed migraine-like attacks.[18,19] Injectable monoclonal antibodies targeting the CGRP receptor recently began being used for migraine prophylaxis, and there are two new oral CGRP receptor antagonists for acute treatment of migraine attacks: ubrogepant (Ubrelvy™, Allergan), approved on December 23, 2019 by the FDA, and rimegepant, under review by the FDA.[20,66] This new class of medications has been referred to as "gepants." Another new acute treatment for migraine is lasmiditan (Reyvow™, Lilly), a selective 5-HT 1f agonist (also referred to as a "ditan"), that was approved on October 11, 2019 by the FDA. Unlike triptans that cause vasoconstrictive effects on cranial and coronary blood vessels via the 5-HT 1b receptor, the gepants and lasmiditan have not been shown to cause vasoconstriction but maintain activity for acute treatment of migraine.[17,21,22]

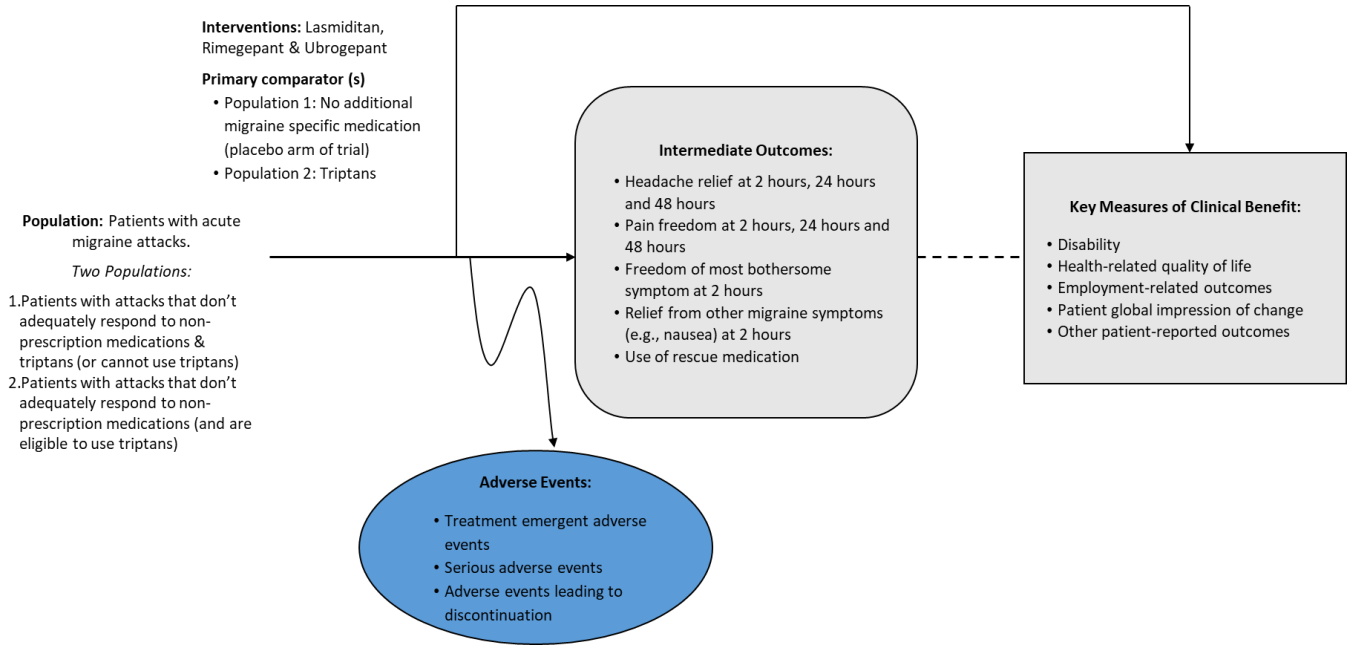
1.2 Scope of the Assessment

This review evaluates the comparative clinical effectiveness and economic impacts of lasmiditan, rimegepant, and ubrogepant for acute treatment of migraine. Evidence was collected from available randomized controlled trials, non-randomized clinical trials, comparative observational studies, as well as high-quality systematic reviews. We limited our review to those studies that captured the outcomes of interest. We included all randomized controlled trials (RCTs) and sought evidence on lasmiditan, rimegepant, and ubrogepant from non-randomized controlled trials and observational studies. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). We sought head-to-head studies of lasmiditan, rimegepant, and ubrogepant and comparators to evaluate the feasibility of a network meta-analyses of selected outcomes.

Analytic Framework

The general analytic framework for assessment of acute therapies for migraine is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Acute Therapies for Migraine



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in blood pressure), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.[67]

Populations

The population of focus for this review was adults ages 18 years and older with a diagnosis of migraine, with or without aura as specified by the ICHD diagnostic criteria. We evaluated two populations of patients with migraine:

1. Patients who have migraine attacks that have not adequately responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated.
2. Patients who have migraine attacks that have not adequately responded to non-prescription medicines (and are eligible to use triptans).

For both populations, we also sought evidence on subgroups of interest, such as: a) patients considered to have chronic migraine (>15 headache days per month); b) patients currently receiving preventive migraine medication.

Interventions

The following new therapies were evaluated:

- Lasmiditan
- Rimegepant
- Ubrogepant

Comparators

For Population 1, we compared lasmiditan, rimegepant, and ubrogepant to each other and to no additional migraine-specific acute treatment. For the purpose of this review, no additional migraine-specific acute treatment was estimated by the placebo arms of the clinical trials, although we recognized that in the real-world patients may use failed over-the-counter analgesics including analgesics marketed as effective for acute treatment of migraine.

For Population 2, we compared lasmiditan, rimegepant, and ubrogepant to each other and to two triptans: sumatriptan and eletriptan. Sumatriptan was chosen because it is one of the most widely used triptans in clinical practice; and eletriptan, a newer triptan, was shown in a recent network meta-analysis to be one of the most efficacious and well tolerated.[16,23] Since these new agents under review are all orally available, we focused our comparison of triptans on the oral formulations.

Outcomes

We looked for evidence on the following outcomes of interest.

Efficacy Outcomes:

- Headache relief at two hours
- Sustained headache relief (at 24 hours and 48 hours)
- Pain freedom at two hours
- Sustained pain freedom (at 24 and 48 hours)
- Freedom from most bothersome symptom (MBS) at two hours
- Relief from other migraine symptoms (e.g., photophobia, phonophobia, nausea, vomiting) at two hours
- Headache relief and pain freedom at 24 and 48 hours
- Patient global impression of change
- Use of rescue medication
- Disability
- Health-related quality of life

- Other patient-reported outcomes (e.g., depression, anxiety, and difficulties in interpersonal relationships)
- Employment-related outcomes (e.g., unemployment, work productivity loss, absenteeism)

Safety Outcomes:

- Serious adverse events
- Adverse events leading to discontinuation
- Treatment-emergent adverse events (e.g.)
    - Dizziness
    - Nausea
    - Paresthesia
    - Somnolence
- Medication overuse headache

Timing

Evidence on intervention effectiveness and safety was derived from studies of any duration, as long as they met the study design criteria set forth above and measure the outcomes of interest.

Settings

All relevant settings were considered, with a focus on outpatient settings in the United States.

1.3 Definitions

Clinical Outcome Measures

Outcomes of clinical trials of acute treatment of migraine commonly include relief of symptoms including pain, nausea/vomiting, photophobia and phonophobia. Pain freedom is defined as a reduction in severity of headache from mild, moderate or severe pain at baseline to none at a given follow-up time point. Freedom from most bothersome symptoms (MBS) refers to total absence of nausea/vomiting, photophonia or phonophobia at a given follow-up time point. Pain relief is defined as having mild to no pain at a given follow-up time point. The primary efficacy time point for phase 3 trials of lasmiditan, rimegepant and ubrogepant was at two hours after the first dose of the study drug. Sustained symptom response after two-hours refers to those with an initial response that is sustained at subsequent follow-up time points without the use of repeat dosing or rescue medications. Censored outcomes after two hours that exclude those with repeat dosing or rescue medications are meant to maintain initial randomization to study drug or placebo but are less useful when estimating outcomes for an entire population at varying time points. As a result, uncensored outcomes after two hours were examined with the recognition that such outcomes may

include the benefit of rescue medications or simply the passage of time. Finally, even uncensored outcomes over time using Kaplan-Meier methods do not account for changes in symptoms after the initial outcome response.

Patients' Global Impression of Change (PGIC)

The PGIC is a seven-point scale reflecting patients' rating of overall improvement. It ranges from 1 ("very much worse") to 7 ("very much better").

Migraine Disability Assessment Test (MIDAS)

The Migraine Disability Assessment (MIDAS) is a brief, 7-item, self-administered questionnaire designed to quantify headache-related disability.[68] Respondents answer five questions about activity limitations in the past three months due to migraine including (1) missed work or school days, (2) missed household chores days, (3) missed non-work activity days, and days at work or school (4) plus days of household chores (5) where productivity was reduced by half or more. Two additional questions about the number of headaches and average pain level associated with headaches over the past three months are not used in deriving the MIDAS score, but they are for use by the respondent's clinician. The MIDAS score is the sum of the number of days reported for each of the five questions. Respondents with a MIDAS score of 0-5 are rated as having little or no disability, 6-10 as having mild disability, 11-20 as having moderate disability, and 21 or greater as having severe disability.

1.4 Insights Gained from Discussions with Patients and Patient Groups

In developing and executing this report, we received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. We received public comments on our draft scoping document from the following patient advocacy organizations: the Coalition for Headache And Migraine Patients (CHAMP), the Headache & Migraine Policy Forum, and the Institute for Patient Access. We also conducted scoping calls with the Alliance for Patient Access, American Headache Foundation, American Migraine Foundation, CHAMP, Golden Graine Blog, Headache & Migraine Policy Forum, Miles for Migraine, and the National Headache Foundation. Below we summarize the key insights derived from this input.

Patients with migraine describe different personal stories, but they identified common themes that emphasize migraine as an episodic and chronic disease that can profoundly affect all aspects of their lives and the lives of those close to them. Though some have derived benefit from existing therapies, not all respond and response to individual attacks can be variable. For others, side effects have led them to have to stop therapy. Patients also report recurrence of headaches as medications wear off during the acute episode or medication overuse headaches from frequent

dosing for acute attacks. The net result is that for many patients with moderate or severe migraine headaches there is no single or combined therapy that offers them control of their acute attacks.

Patients and patient advocacy groups highlighted the deficiencies with currently available acute treatments for migraine. Despite a wide range of medications, both non-prescription and prescription, used alone or in combination, many patients are not able to reliably prevent or abort migraine attacks, either because therapies do not work, lose efficacy or have intolerable side effects. The result is that currently available therapies do not provide symptom relief from migraine attacks with minimal side effects for many individuals. Patients and advocacy groups noted that triptans represented a major advance in acute therapy for migraines when introduced over 20 years ago. However, many individuals cannot use triptans either because they do not work, have intolerable side effects such as flushing, numbness or chest pain, or have contraindications to their use such as existing cardiovascular disease. Because of limitations with triptans, patient often turn to other medications such as anti-emetics, barbiturates and opioids, but these also have limited benefit, acute side effects and important risks associated with long-term use.

A patient with episodic migraine describes her experience with available therapies in her public comments on the ICER draft evidence report: "I eagerly tried sumatriptan when it first hit the market in the 90s. I had a severe adverse reaction to it including severe tachycardia, shortness of breath, and my headache got much, much worse. Over the years I have tried various triptans again as new ones have hit the market or because my doctor wanted to rule them out again. I have always had the same reaction to the medications. DHE has not helped in years either. It used to work if I treated an attack when it was starting, but it no longer helps, and I often wake with a migraine attack already in progress anyway. For acute treatment, I've tried opiates and NSAIDS as well. 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."

The profound impact of migraine on the lives of patients with moderate and severe migraine was also emphasized. Migraine often develops in individuals during adolescence and young adulthood. Frequent, severe attacks can have a dramatic impact on quality of life that may not be fully appreciated by the general public and even health professionals. Stakeholders indicated that migraine attacks, especially when severe, recurrent and poorly controlled can be disabling. One patient commented: "Two years after being diagnosed with chronic, intractable migraine, I had to stop working in a career that I truly loved and for a company that was incredibly supportive of my illness. I also was in my second year of grad school at Georgetown University. The migraine thief took all of that away from me." As mentioned in this patient's story, when migraine attacks occur during formative educational years, it can prevent individuals from reaching their full academic potential. Patients also highlighted that the unpredictability of migraine attacks can result in anxiety from not knowing when the next attack will come, thus affecting individuals even when

they do not have migraine symptoms. The net effect is that migraine is an episodic and chronic condition that affects patients throughout their lives, disrupting personal relationships with friends and family, and their ability to work. The toll on patients with migraine also includes important economic consequences. For many individuals with migraine, attack severity disrupts daily life, often unpredictably. If the migraine attack is not aborted quickly and without medication related side effects, ability to work or work productively is profoundly affected. The combination of frequent, severe and unpredictable migraine attacks impacts ability to work, increases the risk of disability, and can have a long-term negative economic impact on the patient and her/his family. Patients and patient advocates recognize the critical importance of acute treatments for migraine that work quickly and without side effects on the ability to continue to work on the day of a migraine attack. Whether patients cannot work at all, work intermittently or part-time, or were less productive at work because of symptoms of migraine or side effects of therapies, the net result can be long-term un/under-employment with major socioeconomic costs.

Patients and advocates emphasized that because many patients do not find triptans effective or have side effects or contraindications to their use, doctors end up prescribing barbiturates and opioids. Though recognized as having limited effectiveness, acute side effects, the potential for causing medication overuse headaches, and a misuse potential, desperate patients frequently end up being prescribed these medications (for a small percentage of patients with difficult to treat migraine, barbiturates and opioids may be appropriate). The importance of new therapeutic classes, especially ones without side effects or limitations to use as seen with triptans, is important for managing patients with migraine attacks and may also have a broader potential impact on the opioid crisis in the US.

Finally, patient advocacy organizations also raised systematic issues that they felt needed to be addressed. They highlighted that common outcome measures required by the FDA to obtain approval for new drugs may not adequately capture the impact of migraine on things that affect the overall quality of life of migraine patients including relationships, work, and family issues. For example, outcomes of single dose efficacy studies are not designed to assess whether new therapies can decrease the frequency of migraine attacks over time or prevent medication overuse headaches. They felt this to be particularly important for patients with frequent and severe migraine attacks who have not responded to, are intolerant of, or unable to take triptans. Moreover, patients with migraine may have other illnesses, such as anxiety and depression, that are impacted by frequent, unpredictable and severe migraine symptoms. Successful treatment of migraine attacks may also help with these other conditions.

1.5. Potential Cost-Saving Measures in Migraine

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for migraine (e.g., reduction in ED visits), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of migraine beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with migraine that could be reduced, eliminated, or made more efficient.

For this review, we received one such suggestion: Allergan and some patient groups noted that opioids for acute treatment of migraines are discouraged by guidelines and yet remain overused. Allergan suggested that opioids represent a low-value service that could be reduced.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for acute treatments of migraine relevant to this review, we reviewed National and Local Coverage Determinations (NCDs and LCDs) from the Centers for Medicare and Medicaid Services (CMS), and publicly available coverage policies from representative national plans (Aetna and Cigna), national and regional private payers (HealthPartners and Blue Cross Blue Shield of Kansas City) and state Medicaid plans (MO Healthnet and IL Health and Family Services). We surveyed the coverage policies for lasmiditan, rimegepant, ubrogepant, and oral triptans (with special focus on sumatriptan and eletriptan). No coverage policies, nor any NCDs or LCDs, for lasmiditan and oral CGRP antagonists rimegepant and ubrogepant were yet available at the time of this report. The FDA recently approved lasmiditan on October 11, 2019 for acute treatment of migraine. Approval is pending for rimegepant and ubrogepant.

On the national level, generic sumatriptan and eletriptan tablets are on the preferred drug list as step 1, tier 2 or high cost generic formulary without prior authorization, however quantity limits apply (between 9 and 12 tablets per month). Brand name versions are typically non-preferred and require prior authorization[69,70] or are step 2.[71]

2.2 Clinical Guidelines

American Headache Society (AHS)

The American Headache Society (AHS) 2015 guideline for acute treatment of migraine labeled several medications as Level A (established as effective for acute migraines based on available evidence): almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan (oral, nasal spray, patch and subcutaneous), zolmitriptan (oral and nasal spray), acetaminophen, ergots, NSAIDS, butorphanol nasal spray and acetaminophen/aspirin/caffeine and sumatriptan/naproxen combination therapies.[72] The society acknowledged that there are many acute migraine treatments with strong evidence to support their efficacy, but that clinicians should also consider potential side effects and adverse events when prescribing medications for acute migraine. Further the society indicated that opioids, such as butorphanol, codeine and tramadol, though probably effective, are not recommended for regular use.

American Academy of Family Physicians (AAFP)

The American Academy of Family Physicians (AAFP) issued a 2012 guideline on the acute treatment of migraines in the emergency setting.[73] They concluded there is moderate evidence to support the use of neuroleptics, NSAIDS and injectable sumatriptan for the ability to achieve pain-free status in 1-2 hours, moderate evidence to support neuroleptics and injectable sumatriptan for the ability to provide headache relief at 1-2 hours, and moderate evidence to support the use of neuroleptics, metoclopramide, opioids and injectable sumatriptan for the ability to reduce pain intensity.

American Academy of Neurology (AAN) - Choosing Wisely

In 2013 the American Academy of Neurology (AAN) and Choosing Wisely issued a joint statement recommending that the use of opioids or butalbital for acute treatment of migraine be avoided except as a last resort because other more effective treatments are available and frequent use can worsen headache. Opioids should be reserved only for those patients who fail other treatments or cannot take migraine-specific treatments.[74]

Canadian Headache Society (CHS)

A 2013 Canadian Headache Society (CHS) guideline gave twelve medications a strong recommendation for use in acute migraine: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, aspirin, ibuprofen, naproxen sodium, diclofenac potassium and acetaminophen. Four received a weak recommendation: dihydroergotamine, ergotamine, codeine-containing combination analgesics and tramadol-containing combination analgesics.[75] Ergotamine, butorphanol, codeine, butalbital and tramadol-containing medications were not recommended or were strongly recommended against. The society acknowledged that several trials of acute treatments might be required before finding the right approach for a specific patient and that a rescue plan should be in place if acute treatment is insufficient. The society recommends triptans for the acute treatment of migraine attacks that are likely to become moderate or severe and if a patient does not respond well to one triptan or tolerates it poorly, other triptans should be tried (after 24 hours). If response to sumatriptan is inadequate, the society suggests considering adding an NSAID simultaneously with the triptan. Finally, patients with moderate to severe migraine attacks should take triptans as early in the attack as possible.

Canadian Authority for Drugs and Technologies in Health (CADTH)

In a 2012 systematic review of the safety of triptans, the Canadian Authority for Drugs and Technologies in Health (CADTH) found no consistent differences in the occurrence of adverse events (AEs) between triptans, although a dose-response relationship for oral sumatriptan was observed.[76] AEs for sumatriptan include dizziness, drowsiness, paresthesia, nausea and fatigue, but are generally mild and self-limiting. Overall incidence of withdrawal due to AEs for all doses of sumatriptan was 1.6% compared to 0.68% for placebo.

A 2007 CADTH review assessed the cost effectiveness of triptans for acute treatment of migraines. They found no evidence that one triptan was more effective than another and concluded that more research is needed to establish differences in benefits and harms between triptans.[77] The cost-effectiveness studies included in the review mostly only included drug costs, making them difficult to interpret from a broader system or societal perspective.

National Institute for Health and Care Excellence (NICE)

We reviewed clinical guidelines for migraine from the National Institute for Health and Care Excellence (NICE), last updated in 2015.[78] For acute treatment of migraine, NICE recommends oral triptans in combination with NSAIDs, aspirin or paracetamol. NICE suggests starting with the lowest cost triptan, followed by other triptans if treatment is ineffective. Furthermore, NICE recommends an anti-emetic drug in addition to acute treatment, even in the absence of nausea but recommends against non-migraine specific pain medications such as ergots or opioids.

NICE currently has three reviews of injectable CGRP antagonists for preventing migraine: erenumab (publication TBD), fremanezumab (April 15 2020) and galcanezumab (publication TBD).[79-81] Preliminary recommendations from NICE state that erenumab is not a recommended first-line treatment for preventing migraines.[82] If a patient does not respond to beta-blockers, antidepressants, and anti-epileptics, another oral preventive drug or Botox should be offered first. Erenumab is an option when at least three treatments have failed to prevent migraine.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our review of the comparative clinical effectiveness of lasmiditan, rimegepant, and ubrogepant for acute treatment of migraine, we systematically identified and synthesized the existing evidence from available clinical studies. Full PICOTS criteria were described in Section 1.2. In brief, we compared the efficacy, safety, and effectiveness of lasmiditan, rimegepant, and ubrogepant to each other. In addition, we compared all three interventions to no additional migraine-specific acute treatment (placebo) and triptans (sumatriptan and eletriptan). Our review focused on clinical benefits, as well as potential harms. We sought evidence on all outcomes listed in Section 1.2. Methods and findings of our review of the clinical evidence are described in the sections that follow.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on lasmiditan, rimegepant, and ubrogepant for acute treatment of migraine followed established best methods.[83,84] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[85] The PRISMA guidelines include a list of 27 checklist items, which are listed in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, and Study Design elements described in Section 1.2.

We identified a recent systematic review and network meta-analysis of triptans which followed a similar scope to the one planned for this review, with literature search end date of 2016.[23] RCTs of sumatriptan and eletriptan that met our criteria from the systematic review were identified. In addition, we searched for new evidence on sumatriptan and eletriptan that has emerged since 2016 by conducting an updated systematic literature search. However, we conducted a de novo search for lasmiditan, rimegepant, and ubrogepant. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2 – A5. The date of the most recent search is August 21, 2019.

To supplement the database searches, we performed manual checks of the reference lists of included trials and recent systematic reviews of the intervention and individual comparators and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

Study Selection

After removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels. Three reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada) and disagreements were resolved through consensus.

Studies that did not meet the PICOTS criteria defined above, were excluded. No study was excluded at abstract level screening due to insufficient information. Citations accepted during abstract-level screening were reviewed as full text. Reasons for exclusion were categorized according to the PICOTS elements.

Data Extraction and Quality Assessment

Two reviewers extracted data from the full set of included studies into an excel spreadsheet. Extracted data were independently verified by another researcher. Data elements included a description of patient populations, sample size, duration of follow-up, study design features (e.g., RCT or open label), interventions (drug, dosage), outcome assessments (e.g., timing and definitions), results, and quality assessment for each study. We used criteria employed by the US Preventive Services Task Force (USPSTF) that included presence of comparable groups, non-differential loss to follow-up, use of blinding, clear definition of interventions and outcomes, and appropriate handling of missing data to assess the quality of clinical trials and classify into categories "good," "fair," or "poor."[86] For more information on data extraction and quality assessment, refer to Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[87]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for "lasmiditan", "rimegepant", and "ubrogepant" using the ClinicalTrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that has not subsequently been published.

Data Synthesis and Statistical Analyses

Data on outcome results were abstracted in evidence tables (see Appendix Tables D1-D14) and synthesized quantitatively and qualitatively in the body of the review. Data from OLEs and studies were described narratively only and not included in the quantitative syntheses. Using the available trial data, we conducted network meta-analyses (NMAs) for each outcome of interest when data existed on all the interventions of interest from at least three trials that were sufficiently similar in population, interventions, outcome definition, time point, and other characteristics. Based in part on availability of data from sufficiently similar trials, we conducted NMAs on the following outcomes: pain freedom, pain relief, freedom from the most bothersome symptom, disability, adverse events, and treatment-emergent adverse events. For the NMA, we used the 2- and 24-hour timepoints as available in each of the studies that reported on these outcomes. Due to inconsistent or limited reporting of data across studies, freedom from other migraine symptoms, use of rescue medication and patient global impression of change are described only in a narrative fashion.

All NMAs were conducted in a Bayesian framework with random effects on the treatment parameters using the *gemtc* package in R.[88] The outcomes were all binary and were analysed using a binomial likelihood and logit link.[89] We conducted network meta-regression to adjust for differences in placebo group response rate in the NMAs. Goodness of fit of the analyses with and without adjustment for differences in placebo arm response were assessed, and we present the results of the adjusted NMA model where it provided a better fit of the data. Tabular results below were presented for the treatment effects (odds ratio [OR]) of each intervention versus placebo along with 95% credible intervals (95% CrI). The expected proportion of patients experiencing the outcome were also presented when anchoring to the average placebo effect observed across the trials. Additional details regarding the analysis methods, network diagrams, as well as the results of unadjusted NMAs are provided in Appendix D.

3.3 Results

Study Selection

Our literature search identified a total of 323 potentially relevant references (see Appendix A Figure A1). We included 40 references, of which 37 references were on comparative clinical trials and three were open label extension studies (OLEs). These references consisted of 31 publications and nine conference abstracts. Primary reasons for study exclusion included use of interventions or comparators outside of our scope (e.g., subcutaneous sumatriptan), wrong study population (e.g., pediatric population), and conference abstracts with duplicate data as the full-text publications. In addition, because the trials of lasmiditan, rimegepant and ubrogepant included patients with moderate to severe acute migraine, we excluded studies of triptans that evaluated only mild cases of acute migraine.

The 37 references of comparative trials correspond to 33 trials, of which 10 trials (15 references) assessed lasmiditan or the CGRP antagonists, and 23 trials (22 references) assessed one or more of the comparators of interest. We identified only one head-to-head trial of one of the interventions versus a comparator of interest (rimegepant vs sumatriptan). Below, we describe the trials and efficacy results, followed by a discussion of the tolerability and harms.

Quality of Individual Studies

We highlighted the information on the quality of all trials (published and unpublished) using criteria from the US Preventive Services Task Force (USPSTF) in Appendix Table D4. The trials of lasmiditan, rimegepant and ubrogepant had comparable arms at baseline, did not have differential attrition, were patient and physician/investigator blinded, had clear definitions of intervention and outcomes, and used an intent-to-treat analysis or a modified version. As such, we rated all three lasmiditan trials, the three published rimegepant trials, and all three ubrogepant trials to be of good quality. We did not assign an overall quality rating to the unpublished rimegepant trial (Study 301) obtained from grey literature sources (i.e. conference proceedings).

The triptan trials had ratings of good (19 trials) or fair (4 trials). Reasons for lower ratings include a lack of clear reporting on the comparability of the arms at baseline or the use of per-protocol as the primary method of analysis. Detailed information on the ratings can be found in Appendix Tables D4.

Overview of Studies

Lasmiditan, Rimegepant and Ubrogepant versus No Additional Migraine-Specific Acute Treatment (Placebo-controlled studies)

We identified three RCTs of lasmiditan (1 Phase II and 2 Phase III),[24-26] four RCTs of rimegepant (1 Phase II and 3 Phase III),[27-30] and three RCTs of ubrogepant (1 Phase II and 2 Phase III)[31,32 33] versus placebo. Currently, one of the Phase III trials of rimegepant is unpublished and data for this study was obtained from conference abstracts.

All the identified studies were large multicenter studies, conducted predominantly in the United States, and were all focused on the treatment of a single-migraine attack. The trials enrolled patients who had at least a one-year history of migraine with or without aura as specified by the International Classification of Headache Disorders (ICHD) diagnostic criteria, who experienced two to eight migraine attacks of moderate to severe intensity per month, with age of onset before 50 years. Patients who met the eligibility criteria were randomized to intervention or placebo group and were asked to treat a single migraine attack of moderate or severe intensity within a maximum of four hours of onset. Patients and investigators were blinded to treatment assignment. Patients used an electronic diary to record their baseline migraine severity, other migraine-associated symptoms (e.g., photophobia, nausea, phonophobia), and response at different time intervals after taking the study drug over a 48-hour period. The trials reported results based on modified intention to treat populations, eliminating patients who did not experience a moderate to severe migraine event during the study period, so the number of participants included in the effect estimates for the outcomes in each trial were often less than the number of patients randomized.

All trials provided for the use of additional, rescue treatment for patients not responding to the initial study drug at two hours or having recurrent symptoms after initial benefit. However, there were important differences in the rescue treatments permitted and their timing and combinations (Table 3.11). The lasmiditan and ubrogepant trials permitted the use of an optional second dose (randomized in the lasmiditan trials and open label in the ubrogepant trials). In terms of rescue medications allowed, the ubrogepant trials permitted patients to take their usual acute care treatment (including triptans and ergots), while the lasmiditan and rimegepant trials only allowed the use of non-specific migraine medication such as NSAIDS. The use of other medications was permitted between two and 24 hours after initial dosing in the lasmiditan trials and between two and 48 hours after initial dosing in the ubrogepant and rimegepant trials, if needed.

Appendix Tables D1 and D2 contains the key study design and baseline characteristics of each RCT. A summary is presented in Table 3.1. Over 80% of the patients were female and the average age was approximately 40 years in each trial. Patients had been living with migraine for approximately 20 years, had an average of three to five migraine attacks per month, and about 20% to 25% of patients in the trials were on preventive migraine medication. Characteristics of the treated

migraine attack were generally similar across trials, with a distribution of approximately 30% and 70% for severe and moderate headache pain intensity, respectively. Photophobia was the most common other symptom reported (75% to 90% of patients) and was reported as the most bothersome symptom by 50% to 60% of patients. Approximately 40% to 65% of patients reported nausea, and 55% to 75% of patients reported phonophobia.

All trials excluded patients who had more than 15 days of headache per month, and patients who had clinically significant, unstable or recently diagnosed cardiovascular disease (e.g., coronary artery disease, uncontrolled hypertension) were excluded. Patients who initiated or changed preventative medication within 3 months were excluded from the lasmiditan trials.

The primary efficacy endpoint in all trials was freedom from pain at two hours after treatment, before the use of any rescue medication. Pain intensity was measured on a four-point Likert scale (0=none, 1=mild, 2=moderate. 3=severe). Most trials assessed freedom from the most bothersome symptom associated with migraine (MBS) (i.e. phonophobia, photophobia or nausea) at two hours as a co-primary endpoint. MBS was measured using a binary scale (0=absent, 1=present). The main secondary efficacy endpoints assessed in the trials included: 1) those assessed at two hours: headache pain relief (defined as reduction in pain severity from moderate or severe to mild or none), photophobia, phonophobia, nausea, ability to function normally, 2) those assessed at 24 and 48 hours: sustained freedom from pain, sustained freedom from MBS, and sustained pain relief. Sustained response was in those with a response at 2 hours who did not experience subsequent recurrence or use of rescue medications.

Lasmiditan, Rimegepant and Ubrogepant versus Triptans (Sumatriptan and Eletriptan)

We identified one placebo-controlled Phase II trial of rimegepant that included sumatriptan as an active control arm .[30] However, the trial did not report any statistical comparison between rimegepant and sumatriptan. We did not identify any trials comparing lasmiditan or ubrogepant to a triptan. As such, our assessment of these interventions versus triptans (sumatriptan and eletriptan) is informed by indirect comparisons (i.e. network meta-analysis). In all, we included 33 trials (23 triptan RCTs and 10 RCTs of the interventions including the Phase II trial of rimegepant with an active sumatriptan arm) to inform the indirect comparison. The 23 triptan RCTs [34-55] had comparable baseline characteristics to the other trials of the interventions described above. Of the 23 triptan studies, 18 were placebo-controlled trials of sumatriptan, three were placebo-controlled trials of eletriptan and two were head-to-head trials of sumatriptan and eletriptan with placebo arms.

As with the lasmiditan and the CGRP receptor antagonist trials, the majority of the included triptan studies were large multicenter studies, conducted in a variety of countries around the world and were focused on the treatment of a single-migraine attack. However, we included one trial that evaluated multiple migraine attacks (Pfaffenrath 1998) because it presented data on the first

migraine attack separately.[46] Patients and investigators were blinded to treatment assignment, and most of the trials permitted the use of rescue medication between 2 and 24 hours after initial dosing, if needed. The studies included patients who met the ICHD diagnostic criteria and had inclusion and exclusion criteria sufficiently comparable to the trials of lasmiditan and CGRP antagonist. The majority of studies included patients with a history of one to six migraine attacks of moderate to severe intensity per month. Most trials excluded patients with cardiovascular disease (e.g., cardiac ischemia, atherosclerosis, cardiac arrhythmia or uncontrolled hypertension).

Similar to the lasmiditan and CGRP antagonist trials, the majority of patients were female, the average age was approximately 40 years in each trial, and patients had been living with migraine for approximately 20 years. Patients in the eletriptan studies had an average of three to eight migraine attacks per month. Patients in the sumatriptan studies reported a range of one to eight attacks per month. Where reported, the distribution of treated migraine ranged from approximately 30% to 70% for severe headache pain intensity. Appendix Tables D1 and D2 contain the baseline characteristics of all the included triptan studies. A summary is presented in Table 3.1.

21 triptan trials evaluated pain relief at two hours post dose. Sixteen triptan trials reported freedom from pain at two hours post dose. None of the trials assessed freedom from the most bothersome symptom as an outcome. Other secondary outcomes evaluated in the triptan studies include sustained freedom from pain at 24 hours (6 trials) and sustained pain relief at 24 hours (10 trials).

Table 3.1. Overview of the Randomized Controlled Trials

Drug	Trials	N	Characteristics of Attacks	
			Pain Intensity	Baseline Symptoms
Lasmiditan vs. Placebo	3 trials: SAMURAI SPARTAN Farkkila 2012	4, 291	Severe: 30 – 40% About 1-4% mild attacks and the remaining were moderate pain intensity attacks.	Nausea: 40 -65% Phonophobia: 60 -65% Photophobia: 75 -80%
Rimegepant vs. Placebo	4 trials: Study 301 Study 302 Study 303 Marcus 2014*	3, 869	Severe & Moderate: 100% (distribution not reported). No mild intensity attacks.	Nausea: 60% Phonophobia: 70% Photophobia: 80 - 90%
Ubrogepant vs. Placebo	3 trials: ACHIEVE I ACHIEVE II Voss 2016	3,105	Severe: 30 – 40% The remaining were moderate pain intensity attacks. No mild intensity attacks.	Nausea: 55% Phonophobia: 75% Photophobia: 90%
Triptan studies included in the NMA				
Sumatriptan vs. Placebo	18 trials	8,489	In 11 trials Severe: 30 – 70% Two trials included 5% to 10% mild intensity attacks. The remaining were moderate pain intensity attacks In 7 trials, Severe & moderate: 100% (distribution not reported).	Nausea: 50 – 70% Phonophobia: 70-75% Photophobia: 80-90%
Eletriptan vs. Placebo	3 trials	1,085	Severe: 50% The remaining were moderate pain intensity attacks. No mild intensity attacks.	Nausea: 50 – 65% Phonophobia: 70% Photophobia: 75-80%
Eletriptan vs. Sumatriptan	2 trials†	2,479	Severe: 40-45% The remaining were moderate pain intensity attacks. No mild intensity attacks.	Nausea: 50-65% Phonophobia: 65% Photophobia: 75%

N: total number of participants, NMA: network meta-analysis, vs.: versus
*Marcus 2014 includes an active comparator arm (sumatriptan)
†Includes a placebo comparator arm

Long-Term Studies of Lasmiditan, Rimegepant and Ubrogepant

We identified three ongoing 12-month open label extension studies (OLEs) of repeated use of acute medication for migraine over the study period, one on each intervention of interest. In the lasmiditan OLE study (GLADIATOR), interested patients who had completed either of the two-single attack Phase III RCTs with lasmiditan were randomized to receive either 100 mg lasmiditan or 200 mg lasmiditan.[57] Similar to the RCTs, patients enrolled in GLADIATOR were asked to treat moderate or severe attacks and were allowed to use a second dose of the medication after two hours. The rimegepant long term OLE study (Lipton 2019) evaluated the use of once daily rimegepant taken as needed (PRN) versus scheduled dosing (every other day) plus as needed use.[90] In the ubrogepant OLE (Ailani 2019), patients who had completed the two Phase III RCTs of ubrogepant were re-randomized to receive usual care or one of two doses of ubrogepant (50 mg or 100 mg).[91] Patients were instructed to treat up to eight attacks of any severity every four weeks and could use a second dose of the medication for non-response or recurrence. The trials primarily assessed the long-term safety and tolerability of the interventions. In addition, efficacy outcomes related to potential preventive effects of these medications (e.g., reduction in migraine days per month) were also reported in these trials.

Clinical Benefits

As described in Section 1.2 of this report, we sought evidence on the following intermediate outcomes: pain freedom, freedom from most bothersome symptom (i.e. phonophobia, photophobia, and nausea), headache relief, and use of rescue medication. We found data to on all the intermediate outcomes for the three interventions of interest. We also sought evidence on the key measures of clinical benefit including disability, health-related quality of life, employment-related outcomes, and other patient reported outcomes. We found data on disability and patient reported global impression of change but did not find any data on the other outcomes. In addition, we also describe the available evidence on reduction in migraine days per month available in the identified trials, although we did not perform a systematic review specifically to evaluate this outcome.

For the interventions that evaluated more than one dose in the clinical trials (lasmiditan and ubrogepant), we describe the results observed in all arms of the trials. However, for the purpose of the NMAs, we pooled the two highest doses into one i.e. 100 mg and 200 mg arms of the lasmiditan trials were pooled into one arm (lasmiditan 100/200 mg), and 50 mg and 100 mg arms of the ubrogepant trials were pooled into one arm (ubrogepant 50/100 mg). The lower doses (50 mg lasmiditan and 25 mg ubrogepant) were not included in the NMA because these doses were not consistently evaluated in the Phase III trials and were not included in the long-term open label extension studies.

Freedom from Pain at Two Hours

This was defined as the presence of no pain at two hours after treatment in a person who had mild, moderate or severe pain and before the use of any rescue medication. In the individual Phase III clinical trials of the interventions presented in Table 3.2, lasmiditan (50 mg, 100 mg, or 200 mg), rimegepant (75 mg) and ubrogepant (25 mg, 50 mg or 100 mg) all resulted in a greater proportion of patients being free from pain at two hours post dose compared with patients receiving placebo (Table 3.2). A similar pattern was observed in the Phase II studies of the interventions and the triptan studies.

In total, 26 trials (3 lasmiditan trials,[24-26] 4 rimegepant trials including 1 trial that included sumatriptan as an active comparator arm,[27-30] 3 ubrogepant trials,[31-33] and 16 triptan studies[34-39,43-45,47-49,51-53]) reported on the proportion of patients with pain freedom at two hours. We considered all 26 trials sufficiently similar to include in the NMA. Appendix Table D5 provides the data for the NMA, including the sample size and the number of patients who reported pain freedom.

The NMA model that adjusted for placebo response provided a better fit and the results are presented in Table 3.3 and Table 3.5 (unadjusted NMA results are provided in Appendix D). The results are presented in terms of the odds ratio (OR) of freedom from pain for each intervention versus placebo, sumatriptan and eletriptan. ORs above 1 indicate higher odds of pain freedom at two hours with the active intervention versus comparator while ORs below 1 indicate lower odds. Lasmiditan (OR: 3.01; 95% CrI: 2.2 to 4.14), rimegepant (OR: 2.11; 95% CrI: 1.67 to 2.72), and ubrogepant (OR: 2.12; 95% CrI: 1.58 to 2.88) all had higher odds of achieving pain freedom at two hours versus placebo. Compared to each other, none of the interventions showed statistically significant differences, though lasmiditan showed a statistically non-significant, higher odds of achieving pain freedom. In contrast, all interventions showed lower odds of achieving pain freedom at two hours compared to sumatriptan (lasmiditan: 0.73, rimegepant: 0.51, ubrogepant: 0.52) and eletriptan (lasmiditan: 0.54, rimegepant: 0.38, ubrogepant: 0.38). Of note, statistical significance was not reached for lasmiditan versus sumatriptan.

Based on the estimated odds ratios, the expected proportion of patients achieving pain freedom at two hours was 28% for lasmiditan, 21% for rimegepant, 21% for ubrogepant, 35% for sumatriptan and 42% for eletriptan (Table 3.5).

Pain Relief at Two Hours

Pain relief was defined as a decrease in headache pain from moderate or severe at baseline to mild or no pain at two hours after treatment and before taking any rescue medication. Patients with moderate or severe pain who achieve pain freedom would also be counted as having pain relief. In the individual Phase III clinical trials of the interventions, lasmiditan (50 mg, 100 mg, or 200 mg), rimegepant (75 mg) and ubrogepant (25 mg, 50 mg or 100 mg) all resulted in a greater proportion

of patients experiencing pain relief at two hours post dose compared with patients on placebo (Table 3.2).

We included 31 trials in the NMA (3 lasmiditan trials,[24-26] 4 rimegepant trials including 1 trial that included sumatriptan as an active comparator arm,[27-30] 3 ubrogepant trials,[31-33] and 21 triptan studies[34-53]). Appendix Table D5 provides the trial data included in the NMA, which are the sample size and the number of patients who reported pain relief.

The NMA model adjusted for placebo response provided a better fit and the results are presented in Table 3.4 and Table 3.5 (unadjusted NMA results are provided in Appendix D). The results of the NMA are presented in terms of the odds ratio (OR) of relief from pain for each intervention versus placebo, sumatriptan and eletriptan. Lasmiditan (OR: 2.53; 95% CrI: 2.04 to 3.25), rimegepant (OR: 2.19; 95% CrI: 1.8 to 2.76), and ubrogepant (OR: 2.19; 95% CrI: 1.7 to 2.89) all had higher odds of achieving pain freedom at two hours versus placebo. Compared to each other, none of the interventions showed a statistically significant difference, though lasmiditan showed a statistically non-significant, higher odds of achieving pain relief. Compared to sumatriptan, all interventions showed lower odds of achieving pain relief, however, only rimegepant was statistically significantly worse (OR: 0.73; 95% CrI: 0.58 to 0.96). Results compared to eletriptan also showed lower odds of achieving pain relief at two hours for the three interventions, and all were statistically significant (lasmiditan: 0.61, rimegepant: 0.52, ubrogepant: 0.52).

Based on the estimated odds ratios, the expected proportion of patients achieving pain relief at two hours was 58% for lasmiditan, 54% for rimegepant, 54% for ubrogepant, 62% for sumatriptan and 69% for eletriptan (Table 3.5).

Table 3.2. Phase III Results of Lasmiditan, Rimegepant and Ubrogepant. Pain Freedom and Pain Relief at 2-Hours.

Intervention (Trial)	Arms	Headache Pain Freedom at 2-Hours		Headache Pain Relief at 2-Hours	
		n/N (%)	Odds Ratio vs. Placebo (95%CI), p-value	n/N (%)	Odds Ratio vs. Placebo (95%CI), p-value
Lasmiditan (SAMURAI)[25]	Lasmiditan 200mg	167/518 (32.2)	2.6 (2.0, 3.6), <0.001	330/555 (59.5)	2.5 (1.9, 3.3), <0.001
	Lasmiditan 100mg	142/503 (28.2)	2.2 (1.6, 3.0), <0.001	334/562 (59.4)	2.4 (1.8, 3.1), <0.001
	Placebo	80/524 (15.3)	---	234/554 (42.2)	---
Lasmiditan (SPARTAN)[24]	Lasmiditan 200mg	205/528 (38.8)	2.3 (1.8, 3.1), <0.001	367/565 (65.0)	2.4 (1.8, 3.1), <0.001
	Lasmiditan 100mg	167/532 (31.4)	1.7 (1.3, 2.2), <0.001	370/571 (64.8)	2.3 (1.7, 2.9), <0.001
	Lasmiditan 50mg	159/556 (28.6)	1.5 (1.1, 1.9), 0.003	353/598 (59.0)	1.7 (1.3, 2.2), <0.001
	Placebo	115/540 (21.3)	---	274/576 (47.7)	---
Rimegepant (Study 301)[28]	Rimegepant 75mg	104/543 (19.2)	1.4 (1.0, 2.0), 0.03	304/543 (56.0)	1.5 (1.2, 1.9), <0.001
	Placebo	77/541 (14.2)		247/541 (45.7)	
Rimegepant (Study 302)[27]	Rimegepant 75mg	105/537 (19.6)	1.8 (1.3, 2.5), <0.001	312/537 (58.1)	1.9 (1.5, 1.3), <0.0001
	Placebo	64/535 (12.0)		229/535 (42.8)	
Rimegepant (Study 303)[29]	Rimegepant 75mg	142/669 (21.2)	2.2 (1.6, 3.0), <0.0001	397/669 (59.3)	1.9 (1.5, 2.4), <0.0001
	Placebo	74/682 (10.9)		295/682 (43.3)	
Ubrogepant (ACHIEVE I)[32]	Ubrogepant 100mg	95/448 (21.2)	2.0 (1.4, 3.0), 0.0003	275/448 (61.4)	1.7 (1.3, 2.2), 0.0023
	Ubrogepant 50mg	81/422 (19.2)	1.8 (1.3, 2.7), 0.0023	257/422 (60.7)	1.7 (1.3, 2.2), 0.0023
	Placebo	54/456 (11.8)	---	224/456 (49.1)	---
Ubrogepant (ACHIEVE II)[31]	Ubrogepant 50mg	101/464 (21.8)	1.6 (1.1, 2.3), 0.01	291/464 (62.7)	1.8 (1.4, 2.3), 0.01
	Ubrogepant 25mg	90/435 (20.7)	1.6 (1.1, 2.2), 0.03	263/435 (60.5)	1.7 (1.3, 2.2), 0.07
	Placebo	65/456 (14.3)	---	220/456 (48.2)	---

95% CI: 95% confidence interval, mg: milligrams, n: number of participants, N: total number of participants, vs.: versus

Table 3.3. NMA results. Interventions and Comparators. Pain Freedom at 2-Hours

Lasmiditan (100/200 mg)					
1.43 (0.97, 2.06)	Rimegepant 75 mg				
1.43 (0.93, 2.14)	1 (0.69, 1.46)	Ubrogepant (50/100 mg)			
0.73 (0.53, 1.06)	**0.51 (0.39, 0.7)**	**0.52 (0.37, 0.74)**	Sumatriptan (50/100 mg)		
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 40 mg	
3.01 (2.2, 4.14)	**2.11 (1.67, 2.72)**	**2.12 (1.58, 2.88)**	**4.09 (3.43, 4.82)**	**5.6 (4.14, 7.23)**	Placebo

mg: milligrams

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.

Table 3.4. NMA results. Interventions and Comparators. Pain Relief at 2-Hours

Lasmiditan (100/200 mg)					
1.16 (0.87, 1.52)	Rimegepant 75 mg				
1.15 (0.85, 1.58)	1 (0.75, 1.34)	Ubrogepant (50/100 mg)			
0.84 (0.67, 1.13)	**0.73 (0.58, 0.96)**	0.73 (0.55, 1)	Sumatriptan (50/100 mg)		
0.61 (0.44, 0.88)	**0.52 (0.38, 0.76)**	**0.52 (0.37, 0.78)**	**0.72 (0.58, 0.89)**	Eletriptan 40 mg	
2.53 (2.04, 3.25)	**2.19 (1.8, 2.76)**	**2.19 (1.7, 2.89)**	**2.99 (2.65, 3.34)**	**4.18 (3.32, 5.14)**	Placebo

mg: milligrams

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.

Table 3.5. NMA results versus Placebo. Pain Freedom and Pain Relief at 2-Hours

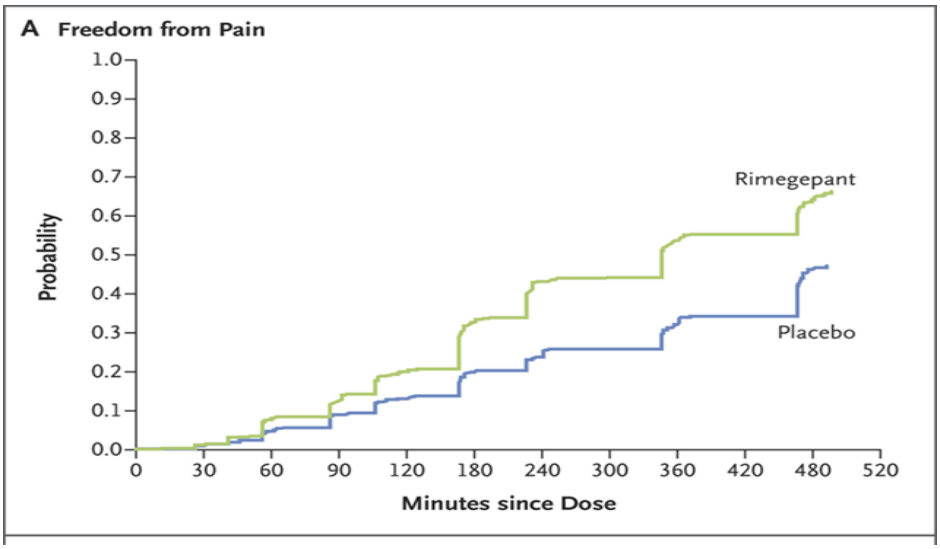
	Pain Freedom at 2-Hours		Pain Relief at 2-Hours	
	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion with Pain Freedom (95% CrI)	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion with Pain Relief (95% CrI)
Placebo	Reference	0.11	Reference	0.35
Lasmiditan (100/200 mg)	3.01 (2.2, 4.14)	0.28 (0.22, 0.35)	2.53 (2.04, 3.25)	0.58 (0.52, 0.63)
Rimegepant (75 mg)	2.11 (1.67, 2.72)	0.21 (0.18, 0.26)	2.19 (1.8, 2.76)	0.54 (0.49, 0.6)
Ubrogepant (50/100 mg)	2.12 (1.58, 2.88)	0.21 (0.17, 0.27)	2.19 (1.7, 2.89)	0.54 (0.48, 0.61)
Sumatriptan (50/100 mg)	4.09 (3.43, 4.82)	0.35 (0.31, 0.38)	2.99 (2.65, 3.34)	0.62 (0.59, 0.64)
Eletriptan (40 mg)	5.6 (4.14, 7.23)	0.42 (0.35, 0.48)	4.18 (3.32, 5.14)	0.69 (0.64, 0.73)

95% CrI: 95% credible interval, mg: milligrams, vs.: versus

Pain Freedom and Relief between Two and Eight Hours

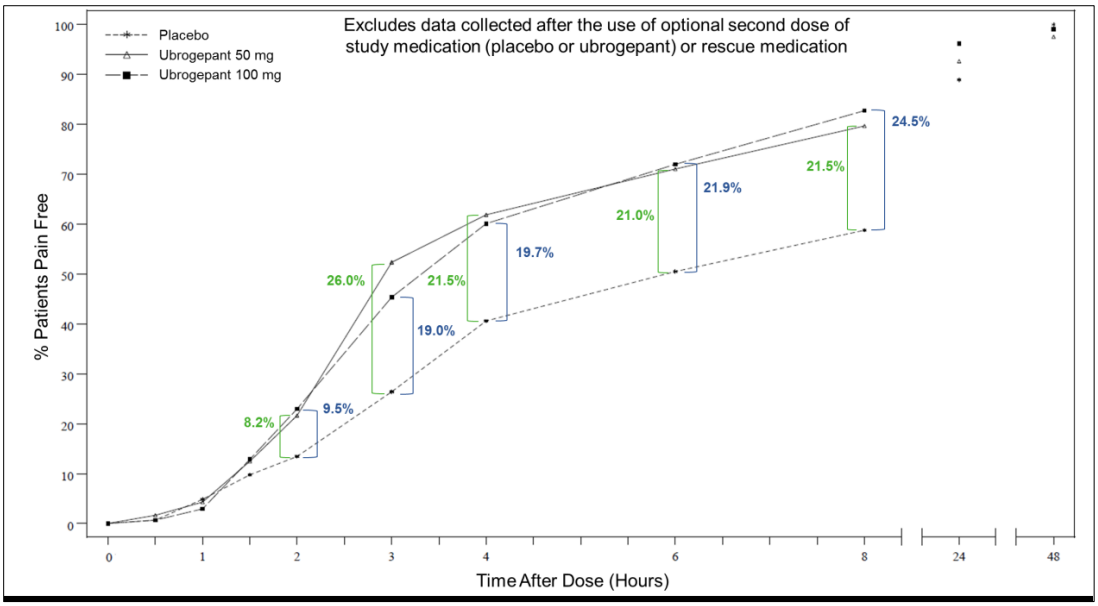
The randomized trials of the acute therapies for migraine were designed to assess the primary outcomes at two hours. As previously described, all trials provided or allowed the use of additional, rescue treatment for patients not responding to the initial study drug at two hours. While the trials were designed to assess recurrence of pain after two hours in initial responders, they were not designed to assess for delayed benefits from the initial study drug beyond two hours. The trials of both rimegepant and ubrogepant reported on relative results compared with placebo beyond two hours based on censoring strategies that removed patients who took second doses of the randomized medication or rescue medication after two hours. Published results showed a continued separation of rimegepant and ubrogepant from placebo beyond two hours, with maximal efficacy observed between three to eight hours (see Figure 3.1 and 3.2). This suggested that focusing on the primary outcomes at two hours may underestimate the benefit of the study drug in a time period out to eight hours. As shown above in the Update to this report, similar data were received for lasmiditan after the publication of this report.

Figure 3.1. Rimegepant: Time to Pain freedom 8 Hours After Initial dose



Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine, Lipton RB, Croop R, Stock EG, et al. N Engl J Med. 2019 Jul 11;381(2):142-149.Copyright © (2020) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 3.2. Ubrogepant: Time to Pain freedom 48 Hours After Initial dose



Ubrogepant for the Acute Treatment of Migraine: Efficacy, Safety, Tolerability, and Functional Impact Outcomes from a Single Attack Phase III Study, ACHIEVE I, Dodick WD, Lipton RB, Ailani J, et al., Presented at the 2018 American Headache Society Annual Scientific Meeting

However, these censored outcomes were presented as exploratory analyses because of the potential for confounding by the choice to take or not take additional medication and violate the initial intention to treat design of the trials. The ability to assign delayed benefit to the initial study drug or to the rescue treatment is uncertain. In an attempt to identify the delayed benefit of the initial study drug, we sought additional information from the manufacturer of ubrogepant because of unique design features of their clinical trials. The trials of ubrogepant involved a second randomization for patients who had not had relief of migraine at two hours and decided to take a second dose of study medication rather than a different rescue medication. As a result, some patients who had initially received placebo decided to take additional medicine for their symptoms and were "randomized" to receive a second dose of placebo (in a manner that maintained blinding). Patients who had initially received ubrogepant were randomized to receive one of two doses of ubrogepant or to receive placebo. Patients who decided to take additional study drug were instructed not to take any other rescue medication until four hours (two hours after the second dose of medication).

The net effect of this blinded second dose of study drug results is a comparison between patients who initially received placebo and chose to receive a second dose of medication (always placebo) and patients who initially received ubrogepant and who received placebo as their second dose. Examining these patients permits an unbiased comparison potentially demonstrating delayed efficacy of the initial dose of ubrogepant. This is not a measure of the actual broad efficacy of ubrogepant versus placebo at four hours since it excludes patients who had initial benefit and patients who take rescue medication, but is capable of answering whether ubrogepant has delayed

efficacy past two hours in an unbiased manner. This analysis was performed based on a specific request from ICER to the manufacturer and while it was performed post hoc, the goal was to better identify delayed benefit of initial study drug. The results of the additional analysis showed that there is an additional delayed benefit with ubrogepant at four hours after the initial dose (see Table 3.6). As shown above in the Update to this report, similar data were received for lasmiditan after the original publication of this report.

Table 3.6. Pain Freedom and Relief by time point – pooled ACHIEVE I & II

	Placebo + Placebo	Ubrogepant + placebo	Difference	Risk ratio
Pain Freedom				
2 hours	20 (4.9)	15 (5.7)	0.8	1.16
4 hours	60 (14.7)	55 (20.8)	6.2	1.42
Pain Relief				
2 hours	152 (37.2)	115 (43.6)	6.4	1.17
4 hours	201 (49.1)	186 (70.5)	21.3	1.43

Sustained Pain Freedom

Sustained pain freedom was defined as the percentage of subjects who were pain free at two hours and maintained pain freedom with no use of rescue medication or relapse within 24 (sustained pain freedom at 24 hours) or 48 hours (sustained pain freedom at 48 hours) after the initial treatment. In the individual Phase III clinical trials of the interventions, lasmiditan (50 mg, 100 mg, or 200 mg), rimegepant (75 mg) and 100 mg ubrogepant all resulted in a greater proportion of patients experiencing sustained pain freedom at 24 hours and 48 hours compared with placebo (Table 3.7). The other two doses of ubrogepant (25 mg and 50 mg) were not statistically significantly different from placebo on sustained pain freedom at 24 hours (Table 3.7).

Mainly because of data availability, we conducted NMA only for the 24 hours sustained pain freedom outcome. In total, we identified 15 trials (2 lasmiditan,[24,25] 4 rimegepant trials including 1 head-to head versus sumatriptan,[27-30] 3 ubrogepant,[31-33] and 6 triptan studies[35,37,47-49]) sufficiently similar to include in the NMA. Appendix Table D6 provides the data for the NMA, including the sample size and the number of patients who reported sustained pain freedom.

The NMA model adjusted for placebo response provided a better fit and the results are presented in Table 3.8 and Table 3.9 (unadjusted NMA results are provided in Appendix D). Consistent with the trials, the NMA results showed that lasmiditan (OR: 2.92; 95% CI: 1.89 to 4.5), rimegepant (OR: 2.51; 95% CI: 1.89 to 3.46), and ubrogepant (OR: 2.32; 95% CI: 1.62 to 3.46) all had higher odds of achieving sustained pain freedom at 24 hours versus placebo. Compared to the triptans, although all interventions showed lower odds of achieving sustained pain freedom at 24 hours compared to sumatriptan (lasmiditan: 0.83, rimegepant: 0.71, ubrogepant: 0.66) and eletriptan (lasmiditan: 0.73,

rimegepant: 0.63, ubrogepant: 0.59), these were not statistically significant. Similarly, the interventions were not statistically significantly different from each other (Table 3.8).

Based on the estimated odds ratio, the expected proportion of patients achieving sustained pain freedom at 24 hours was 19% for lasmiditan, 17% for rimegepant, 16% for ubrogepant, 22% for sumatriptan and 24% for eletriptan (Table 3.9). Of note, because of recurrent symptoms after two hours, the number of patients with sustained pain freedom at 24 hours was less than those achieving pain freedom at two hours (see Table 3.9).

Sustained relief is based on a concept similar to sustained pain freedom. It was defined as the percentage of subjects who had pain relief at two hours with no use of rescue medication or relapse at follow-up after the initial treatment. We found no data on sustained pain relief for lasmiditan. In total, we included the four rimegepant trials, the three ubrogepant trials and 10 triptan trials for the NMA on sustained pain relief (see Appendix Table D6). The results of the NMA on sustained pain relief followed a similar pattern as the 24 hours sustained pain freedom (see Appendix Table D15).

Table 3.7: Phase III Results of Lasmiditan, Rimegepant and Ubrogepant. Sustained Pain Freedom at 24- and 48-Hours

Intervention (Trial)	Arms	Sustained Pain Freedom at 24-Hours		Sustained Pain Freedom at 48-Hours	
		n/N (%)	Odds Ratio vs. Placebo (95%CI), p-value	n/N (%)	Odds Ratio vs. Placebo (95%CI), p-value
Lasmiditan (SAMURAI)[25]	Lasmiditan 200mg	103/555 (18.6)	2.8 (1.9, 4.1), <0.001	91/555 (16.4)	2.4 (1.6, 3.5), <0.001
	Lasmiditan 100mg	83/562 (14.8)	2.1 (1.4, 3.1), <0.001	84/562 (14.9)	2.1 (1.5, 3.2), <0.001
	Placebo	42/554 (7.6)	---	42/554 (7.6)	---
Lasmiditan (SPARTAN)[24]	Lasmiditan 200mg	128/565 (22.7)	1.9 (1.4, 2.6), <0.001	111/565 (19.6)	1.8 (1.3, 2.5), <0.001
	Lasmiditan 100mg	102/571 (17.9)	1.4 (1.0, 1.9), 0.021	86/571 (15.1)	1.3 (0.9, 1.9), 0.058
	Lasmiditan 50mg	103/598 (17.2)	1.3 (1.0, 1.9), 0.036	89/598 (14.9)	1.3 (0.9, 1.8), 0.065
	Placebo	77/576 (13.4)	---	68/576 (11.8)	---
Rimegepant (Study 301)[28]	Rimegepant 75mg	76/543 (14.0)	1.8 (1.2, 2.7), 0.002*	63/543 (11.6)	1.7 (1.1, 2.6), 0.013*
	Placebo	44/541 (8.1)		39/541 (7.2)	
Rimegepant (Study 302)[27]	Rimegepant 75mg	66/537 (12.3)	1.8 (1.2, 2.8), 0.004*	53/537 (9.9)	1.7 (1.1, 2.7), 0.02*
	Placebo	38/535 (7.1)		32/535 (6.0)	
Rimegepant (Study 303)[29]	Rimegepant 75mg	105/669 (15.7)	3.2 (2.1, 4.7), <0.0001*	90/669 (13.5)	2.7 (1.8, 4.1), <0.0001*
	Placebo	38/682 (5.6)		37/682 (5.4)	
Ubrogepant (ACHIEVE I)[92]	Ubrogepant 100mg	68/441 (15.4)	2.0 (1.3, 3.0), 0.0037	NR	
	Ubrogepant 50mg	53/418 (12.7)	1.6 (1.0, 2.4), n.s.		
	Placebo	39/452 (8.6)	---		
Ubrogepant (ACHIEVE II)[31]	Ubrogepant 50mg	66/457 (14.4)	1.9 (1.2, 2.8), 0.01	NR	
	Ubrogepant 25mg	55/432 (12.7)	1.6 (1.0, 1.8), n.s.		
	Placebo	37/451 (8.2)	---		

*Odds ratio estimated

95%CI: 95% confidence interval, mg: milligrams, n: number of participants, N: total number of participants, NR: not reported, vs.: versus

Table 3.8. NMA Results. All Interventions and Comparators. Sustained Pain Freedom at 24-Hours

Lasmiditan (100/200 mg)					
1.16 (0.67, 1.94)	Rimegepant (75 mg)				
1.26 (0.72, 2.11)	1.08 (0.67, 1.74)	Ubrogepant (50/100 mg)			
0.83 (0.5, 1.44)	0.71 (0.48, 1.12)	0.66 (0.41, 1.12)	Sumatriptan		
0.73 (0.34, 1.53)	0.63 (0.32, 1.22)	0.59 (0.28, 1.18)	0.89 (0.44, 1.69)	Eletriptan	
2.92 (1.89, 4.5)	**2.51 (1.89, 3.46)**	**2.32 (1.62, 3.46)**	**3.53 (2.52, 4.77)**	**3.97 (2.24, 7.36)**	Placebo

mg: milligrams

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.

Table 3.9. NMA Results versus Placebo. Sustained Pain Freedom at 24-Hours Compared to Pain Freedom Achieved at 2-Hours

	Sustained Pain Freedom at 24-hours		Pain Freedom at 2-hours	
	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion with Sustained Pain Freedom (95% CrI)	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion with Pain Freedom (95% CrI)
Placebo	Reference	0.07	Reference	0.11
Lasmiditan 100/200 mg	2.92 (1.89, 4.5)	0.19 (0.13, 0.26)	3.01 (2.2, 4.14)	0.28 (0.22, 0.35)
Rimegepant 75 mg	2.51 (1.89, 3.46)	0.17 (0.13, 0.22)	2.11 (1.67, 2.72)	0.21 (0.18, 0.26)
Ubrogepant 50/100 mg	2.32 (1.62, 3.46)	0.16 (0.11, 0.22)	2.12 (1.58, 2.88)	0.21 (0.17, 0.27)
Sumatriptan 50/100 mg	3.53 (2.52, 4.77)	0.22 (0.17, 0.27)	4.09 (3.43, 4.82)	0.35 (0.31, 0.38)
Eletriptan 40 mg	3.97 (2.24, 7.36)	0.24 (0.15, 0.37)	5.6 (4.14, 7.23)	0.42 (0.35, 0.48)

95% CrI: 95% credible interval, mg: milligrams, NA: not available, vs.: versus

Freedom from Most Bothersome Symptom (MBS)

Absence of the most bothersome migraine associated symptom (i.e. phonophobia, photophobia, or nausea) at two hours after treatment was measured as a co-primary endpoint in the Phase III trials of lasmiditan, rimegepant and ubrogepant. None of the Phase II studies of the interventions or the triptan studies assessed freedom from MBS as an outcome. As such we included only the seven Phase III trials in our NMA and compared the interventions to each other and to placebo.[24,25,27-29,31,32,93]

Table 3.10 presents the results of the Phase III trials. A greater proportion of patients on lasmiditan (50 mg, 100 mg, or 200 mg), rimegepant (75 mg) or ubrogepant (25 mg, 50 mg or 100 mg) experienced freedom from MBS at two hours post dose compared with patients on placebo. The unadjusted NMA comparing the interventions to each other provided a better fit and the results are presented in Table 3.11. The results showed that lasmiditan (OR: 1.99; 95% CI: 1.03 to 3.9), rimegepant (OR: 2.57; 95% CI: 1.61 to 4.26), and ubrogepant (OR: 2.09; 95% CI: 1.19 to 3.9) all had higher odds of achieving freedom from MBS at two hours post dose compared to placebo. However, compared to each other, none of the interventions showed a statistically significant difference. Based on the estimated odds ratio, the expected proportion of patients achieving freedom from MBS at two hours was 40% for lasmiditan, 38% for rimegepant, and 39% for ubrogepant.

Table 3.10: Phase III Results of Lasmiditan, Rimegepant and Ubrogepant. MBS Freedom at 2-Hours

Intervention (Trial)	Arms	Freedom From Most Bothersome Symptom at 2-Hours	
		n/N (%)	Odds Ratio vs. Placebo (95%CI), p-value
Lasmiditan (SAMURAI)[25]	Lasmiditan 200mg	196/481 (40.7)	1.6 (1.3, 2.1), <0.001
	Lasmiditan 100mg	192/469 (40.9)	1.7 (1.3, 2.2), <0.001
	Placebo	144/488 (29.5)	---
Lasmiditan (SPARTAN)[24]	Lasmiditan 200mg	235/483 (48.7)	1.9 (1.4, 2.4), <0.001
	Lasmiditan 100mg	221/500 (44.2)	1.6 (1.2, 2.0), <0.001
	Lasmiditan 50mg	209/512 (40.8)	1.4 (1.1, 1.8), 0.009
	Placebo	172/514 (33.5)	---
Rimegepant (Study 301)[28]	Rimegepant 75mg	199/543 (36.6)	1.5 (1.2, 2.0), 0.002
	Placebo	150/541 (27.7)	
Rimegepant (Study 302)[27]	Rimegepant 75mg	202/537 (37.6)	1.8 (1.4, 2.3), <0.0001
	Placebo	135/535 (25.2)	
Rimegepant (Study 303)[29]	Rimegepant 75mg	235/669 (35.1)	1.5 (1.2, 1.9), 0.001
	Placebo	183/682 (26.8)	
Ubrogepant (ACHIEVE I)[92]	Ubrogepant 100mg	169/448 (37.7)	1.6 (1.2, 2.2), 0.0023
	Ubrogepant 50mg	163/420 (38.6)	1.7 (1.3, 2.3), 0.0023
	Placebo	127/454 (27.8)	---
Ubrogepant (ACHIEVE II)[31]	Ubrogepant 50mg	180/463 (38.9)	1.7 (1.3, 2.2), 0.01
	Ubrogepant 25mg	148/434 (34.1)	1.4 (1.0, 1.8), 0.07
	Placebo	125/456 (27.4)	---

mg: milligrams, n: number of participants, N: total number of participants, NR: not reported, vs: versus

Table 3.11. NMA Results. Interventions and Comparators. Freedom from MBS at 2-Hours

Lasmiditan (100/200 mg)			
1.07 (0.78, 1.46)	Rimegepant (75 mg)		
1.03 (0.73, 1.45)	0.96 (0.69, 1.33)	Ubrogepant (50/100 mg)	
1.69 (1.33, 2.14)	**1.58 (1.29, 1.94)**	**1.64 (1.28, 2.12)**	Placebo

mg: milligrams

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.

Freedom from Other Migraine Symptoms (phonophobia, photophobia and nausea)

Freedom from phonophobia, photophobia, and nausea were assessed as secondary outcomes in the trials of lasmiditan, rimegepant and ubrogepant. However, there was a lack of consistency in how these outcomes were analyzed across trials. In the rimegepant trials, freedom from migraine associated symptoms were evaluated correctly among patients who exhibited these symptoms at baseline, while the trials of lasmiditan and ubrogepant evaluated these outcomes among all patients, irrespective of their baseline symptoms. As such we did not quantitatively compare the drugs to each other on these outcomes.

Regardless of how the trials evaluated these outcomes, all three interventions were not different from placebo in achieving freedom from nausea at two hours in any of the Phase III trials. All interventions had higher odds of achieving freedom from phonophobia and freedom from photophobia at two hours post dose compared to placebo (Appendix Table D8).

Use of Rescue Medication

Due to differences in the design of the trials related to the use of rescue medication (e.g. open label second dose vs. randomized; NSAID vs. usual acute migraine treatment), we could not quantitatively compare the interventions to each other on this outcome (see Table 3.12). In general, patients who were randomized to the interventions were less likely to use a second dose or another medication for rescue compared to patients on placebo.

Table 3.12. Use of Rescue Medication after 2 Hours

	Lasmiditan Phase III Trials	Rimegepant Phase III Trials	Ubrogepant Phase III Trials
Timing and Indication for Rescue Medication			
Initial Response	Rescue medication could be used within 24 hours if pain freedom not achieved at 2 hours.	Rescue medication could be used within 48 hours if pain relief not achieved at 2 hours.	Rescue medication could be used within 48 hours if pain relief not achieved at 2 hours.
Recurrence	Patients could take a rescue medication for recurrence within 24 hours	Patients could take a rescue medication for recurrence within 48 hours	Patients could take a rescue medication for recurrence within 48 hours
Rescue Medication Allowed			
Second dose of study Medication	Patients were re-randomized to an optional second dose of placebo or lasmiditan. Second dose only taken if another rescue medication has not been used.	Patients were not given an optional second dose	Patients were given an optional second dose (those on placebo were given placebo and others were re-randomized to placebo or ubrogepant). Second dose only taken if another rescue medication has not been used.
Other Medications	Triptans, ergots, opioids and barbiturates were not allowed. Patients could take other over the counter medications of choice.	Triptans, ergots, opioids and barbiturates were not allowed within 48 hours. Patients could take aspirin, NSAIDs, acetaminophen, antiemetics, or baclofen.	Patients could take triptans, ergots, NSAIDs, acetaminophen, opioids, or other over the counter medications.

In the Phase III trials of lasmiditan, all patients were randomly allocated to an optional second dose of the study drug. Patient with persistent or recurrent pain wanting to take additional treatment could take the optional second dose or their own rescue medication within two to 48 hours after the initial dose. The second dose was used between two and 24 hours in 32% to 39% of the lasmiditan group (200/100 mg) versus 60% of the placebo group in the SPARTAN trial; and 20% to 35% of the lasmiditan group (200/100/50 mg) versus 40% of the placebo in the SAMURAI trial.[24,25] Of these second doses, approximately 95% were taken as rescue medication, while the remaining were taken for pain recurrence.

The rimegepant trials did not provide patients with an optional second dose of study medication but allowed the use of rescue medications. Across the four rimegepant trials, 14% to 21% of patients on rimegepant used a rescue therapy compared to 30% to 37% for patients on placebo.[27-30]

In the Phase III trials of ubrogepant, patients were re-randomized to an optional second dose of ubrogepant. Patient with persistent or recurrent pain wanting to take additional treatment could opt to take the optional second dose or their own rescue medication within two to 48 hours after the initial dose. In the pooled ubrogepant group, 38% of patients used an optional second dose compared with 43% in the placebo group. Rates of rescue medication use after the first dose was approximately 15% in the ubrogepant group versus 21% to 29% in the placebo group.

Disability

Functional disability was measured as a secondary outcome in all the Phase III trials of the interventions. This was assessed at two hours after initial treatment, before the use of rescue medication with a four-point functional disability scale (0=no disability [i.e. ability to function normally]; 1=mild disability [i.e. ability to perform all activities of daily living but with some difficulty]; 2=moderate disability [unable to perform certain activities of daily living]; 3=severe disability [i.e. unable to perform most to all activities of daily living or requiring bed rest]). This outcome was not consistently evaluated in the included triptan studies. As such we included only the seven Phase III trials in our NMA and compared the interventions to each other and to placebo.[24,25,27-29,92,93]

Table 3.13 presents the results of the Phase III trials. A greater proportion of patients on lasmiditan (50 mg, 100 mg, or 200 mg), rimegepant (75 mg) and ubrogepant (25 mg, 50 mg or 100 mg) were able to function normally at two hours post dose compared with patients on placebo. The unadjusted NMA comparing the interventions to each other provided a better fit and the results are presented in Table 3.13. The NMA showed that lasmiditan (OR:1.7; 95% CI:1.32 to 2.20), rimegepant (OR:1.72; 95% CI: 1.38 to 2.14), and ubrogepant (OR: 1.51; 95% CI: 1.15 to 1.96) all had higher odds of achieving no disability at two hours post dose compared to placebo. However, compared to each other, none of the interventions showed a statistically significant difference (Table 3.14). Based on the estimated odds ratio, the expected proportion of patients who could function normally at two hours post dose was 38% for lasmiditan, 38% for rimegepant, and 35% for ubrogepant.

Table 3.13. Phase III results of Lasmiditan, Rimegepant and Ubrogepant. Ability to Function Normally at 2-Hours

Intervention (Trial)	Arms	Ability to Function Normally at 2-Hours	
		n/N (%)	p-value vs. Placebo
Lasmiditan (SAMURAI)[25]	Lasmiditan 200mg	180/555 (32.4)	<0.001
	Lasmiditan 100mg	181/562 (32.2)	<0.001
	Placebo	119/554 (21.5)	Reference
Lasmiditan (SPARTAN)[24]	Lasmiditan 200mg	209/565 (37.0)	<0.001
	Lasmiditan 100mg	193/571 (33.8)	<0.001
	Lasmiditan 50mg	187/598 (31.3)	0.019
	Placebo	143/576 (24.8)	Reference
Rimegepant (Study 301)[28]	Rimegepant 75mg	181/543 (33.3)	<0.0001
	Placebo	118/541 (21.8)	
Rimegepant (Study 302)[27]	Rimegepant 75mg	175/537 (32.6)	NR
	Placebo	125/535 (23.4)	
Rimegepant (Study 303)[29]	Rimegepant 75mg	255/669 (38.1)	NR
	Placebo	176/682 (25.8)	
Ubrogepant (ACHIEVE I)[92]	Ubrogepant 100mg	193/423 (42.9)	<0.01
	Ubrogepant 50mg	172/448 (40.6)	<0.01
	Placebo	136/456 (29.8)	Reference
Ubrogepant (ACHIEVE II)[31]	Ubrogepant 50mg	188/464 (40.5)	<0.01
	Ubrogepant 25mg	185/435 (42.6)	<0.01
	Placebo	156/456 (34.2)	Reference

mg: milligrams, n: number of participants, N: total number of participants, NR: not reported, vs.: versus

Table 3.14. NMA results. Interventions and Comparators. Ability to Function Normally at 2-Hours

Lasmiditan (100/200 mg)			
0.99 (0.71, 1.39)	**Rimegepant (75 mg)**		
1.13 (0.78, 1.64)	1.14 (0.81, 1.62)	**Ubrogepant (50/100 mg)**	
1.7 (1.32, 2.2)	**1.72 (1.38, 2.14)**	**1.51 (1.15, 1.96)**	**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.

mg: milligrams

Patient Global Impression of Change

Patient global impression of change (PGIC) was measured as a secondary outcome in the Phase III trials of lasmiditan and ubrogepant. This was assessed at two hours after initial treatment, before the use of rescue medication with a seven-point scale (1=very much worse; 2=much worse; 3=a little worse; 4=no change; 5= a little better; 6=much better; 7=very much better). The results of the trials showed that a higher proportion of ubrogepant or lasmiditan-treated patients indicated their migraine was much better/very much better at two hours post dose compared with placebo-treated patients (Table 3.14). We did not identify any PGIC data on rimegepant.

Table 3.15. Phase III Results of Lasmiditan and Ubrogepant. PGIC at 2-Hours.

Trial	Arms	N	PGIC (% That Achieved "Very Much Better and Much Better")	p-value vs. Placebo
SAMURAI[25]	Lasmiditan 200mg	555	37.9	<0.001
	Lasmiditan 100mg	562	37.2	<0.001
	Placebo	554	21.8	Reference
SPARTAN[24]	Lasmiditan 200mg	565	42.5	<0.001
	Lasmiditan 100mg	571	41.2	<0.001
	Lasmiditan 50mg	598	36.6	<0.001
	Placebo	576	28.0	Reference
ACHIEVE I[92]	Ubrogepant 50mg	297	34.3	<0.001
	Ubrogepant 100mg	299	34.4	<0.001
	Placebo	313	22.0	Reference
ACHIEVE II[31]	Ubrogepant 50mg	392	33.4	<0.001
	Ubrogepant 25mg	435	34.1	<0.001
	Placebo	376	20.7	Reference

mg: milligrams, N: total number of participants, PGIC: Patient Global Impression of Change, vs.: versus

Reduction in Migraine Days per Month

Stakeholders identified that decreased frequency and severity of migraine attacks was a potential benefit of lasmiditan, rimegepant and ubrogepant when used over time, something that had not been shown with the use of triptans. We did not perform a systematic review specifically to address this issue, however we examined this potential benefit and our interpretation of the evidence.

The available Phase III RCTs on the interventions of interest are short-term single dose studies, and so were not designed to provide information on changes in migraine frequency or severity over time. Evidence related to this outcome was all from long-term open label extension (OLE) studies that were uncontrolled. Specifically, we identified two OLE studies (GLADIATOR and Lipton 2019) that evaluated this outcome.[57,90]

In GLADIATOR, two lasmiditan doses (100 mg and 200 mg) taken as needed were evaluated in 2,037 patients over one year, but only 847 patients completed the study.[57] Overall, the mean number of migraine days per month was reported to have decreased from a baseline rate of 15.5 days per month to 8.2 days per month in the 200 mg lasmiditan group (mean change -7.3 migraine days/month) and to 8.8 days per month in the 100 mg lasmiditan group (mean change -6.7 migraine days/month) at one year. In addition, the migraine disability assessment (MIDAS) score was reported to be reduced by approximately 50% in both groups by the end of the first year.

Lipton 2019 evaluated 75 mg rimegepant taken as needed (PRN group, n=1,498) or on schedule (taken every other day) plus as needed (QOD+PRN group, n=286) over one year, but patient follow-up over time was not reported.[90] At three months, the trial reported a mean reduction of 4 migraine days per month among patients observed to have 14 or more migraine days/month at baseline (in both rimegepant group). For patients in the QOD+PRN group, approximately half reported a ≥50% reduction from baseline in the frequency of monthly migraine days of moderate to severe pain intensity at three months, regardless of baseline migraine days.

While the results of these studies reported a decreasing frequency of migraine attacks over time, we were concerned about study design and reporting issues that may bias these results. We felt that patients with a high frequency of attacks at baseline may experience decreases over time simply due to regression to the mean. Because these were uncontrolled studies without a placebo arm, it is not possible to differentiate regression to the mean from placebo effect or from an actual benefit. We were also concerned that patients who may have had the greatest migraine burden and were not benefitting from therapy might drop out over time, leaving patients at later follow-up points who were having fewer migraines at baseline and thus overestimating any decrease in migraine frequency or severity.

Several lines of evidence support our concerns about regression to the mean as playing a prominent role in the reported data from OLE trials. First, it is notable that therapies with very different mechanisms of action (lasmiditan and rimegepant) should both show reductions in headache frequency over time when prior acute migraine therapies have not done so in controlled trials. Moreover, it is unexpected that lasmiditan, which works through a mechanism closely related to triptans, would show this benefit when triptans are not believed to have such a benefit. To explore this issue further, we reviewed a trial comparing telcagepant (a gepant) with rizatriptan (a triptan) in more than 1000 patients.[94] We reproduce below a figure showing similar reduction in headache frequency over time including in the triptan arm, as would be expected with regression to the mean (Figure 3.3).

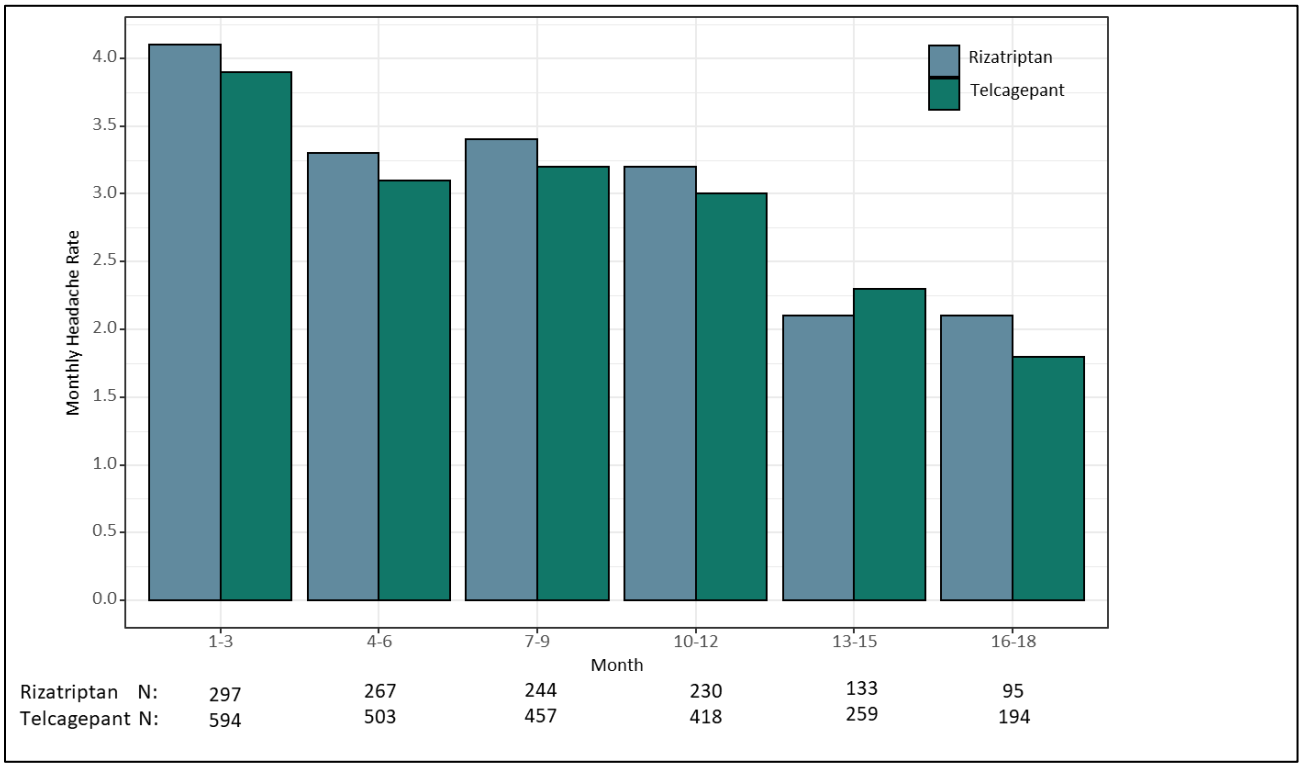
Loss of follow-up over time in the GLADIATOR trial was large (51.7%) and suggests that using the larger denominator at baseline but a smaller one at follow-up may affect the reported results. The most common reason for discontinuation was “patient request’ (21.8%), which likely referred to those patients who discontinued the medication for lack of effect. In the rimegepant OLE trial,

information was obtained from a conference abstract, so information on dropout is unclear. Based on the data in the poster, only 17.6% of patients that were evaluated at 12 weeks were included in the reported analysis.

Finally, regarding placebo effect, we note that the response rate in the placebo arms of the single dose RCTs ranged from 25% to 51%, and that in ICER's prior report on migraine prevention, the placebo response rate for prophylactic therapy ranged from 10% to 62%. In addition, the mean decrease in migraine-specific days and migraine-specific medication consumption per month was considerably smaller in RCTs of CGRP monoclonal antibodies for prevention of migraine attacks.[66]

Given these concerns, we do not feel that current evidence supports a conclusion that treatment with lasmiditan, rimegepant, or ubrogepant decreases migraine frequency over time. A placebo-controlled trial would likely be needed to explore this issue, and in the absence of such a trial, we do not think patients or clinicians should select one of these medications based upon such a treatment-specific benefit.

Figure 3.3. Mean monthly headache rate. Adapted from "Long-Term Tolerability of Telcagepant for Acute Treatment of Migraine in a Randomized Trial," by Connor KM, Aurora SK, Loeys T, et al. Headache. 2011 Jan;51(1):73-84



N: total number of participants

Harms

Randomized Controlled Trials

The majority of adverse events observed in the single-attack trials were mild or moderate in intensity. Adverse events (AEs) with incidence ≥5% in any of the treatment arm are presented in Appendix Table D10. In the lasmiditan trials, central nervous system (CNS)-related AEs (e.g., dizziness, somnolence, paresthesia) were the most frequently reported AE, with dizziness the most common. Nausea was among the most commonly reported AE in the ubrogepant and rimegepant trials (1% to 3%). In general, there was a low incidence of serious adverse events in these trials. There was a low or no incidence of cardiovascular related AEs in the trials.

Table 3.16 presents the data on AEs, treatment-emergent AEs (TEAEs), and most frequent AEs from the Phase III trials of the interventions. In the Phase III trials, TEAEs among patients on placebo ranged from 1% to 3%, while they ranged from 6% to 12% in patients on CGRP antagonists and 32% to 38% among those on lasmiditan. In total, 24 trials (including the Phase II trials and the triptan studies) reported on the number of patients who experienced any type of adverse event (any AE)[24,25,27-29,33,34,36-38,40,41,43,45,46,48,49,51-54,92,93] and 16 trials (including the Phase II trials and the triptan studies) reported on the number of patients who experienced any treatment emergent adverse event (any TEAE).[24,26,28,29,33,34,37,41,47,51,52,54,55,92,93] We considered all the trials sufficiently similar to include in the NMA. Appendix Table D7 provides the data for the NMA, including the sample size and the number of patients who reported pain freedom.

The unadjusted NMAs on any AE and TEAE provided a better fit and the results are presented in Table 3.15 and Appendix Table D16-D18. The NMA results are expressed as ORs, where values greater than one indicate a higher odd of any AE or TEAE for the active therapy versus placebo. Lasmiditan had higher odds of any AE compared to placebo (3.91, 95% CrI: 2.45, 6.25, Table 3.16), rimegepant (3.13, 95% CrI: 1.69, 5.82), ubrogepant (3.51, 95% CrI: 1.86, 6.61), sumatriptan (2.16, 95% CrI: 1.27, 3.56), and eletriptan (3.66, 95% CrI: 2.03, 6.51) (Appendix Table D16). Compared to placebo, both rimegepant and ubrogepant had point estimates with higher odds of any AE, but these were not statistically significant. There was also no statistically significant difference between rimegepant and ubrogepant, and these agents versus the triptans. Based on the estimated odds ratio, the expected proportion of patients achieving any AE was 50% for lasmiditan, 24% for rimegepant, 22% for ubrogepant, 31% for sumatriptan and 21% for eletriptan (Table 3.16).

In terms of TEAEs, lasmiditan had higher odds of TEAE compared to placebo (5.99, 95% CrI: 3.3, 12.52, Table 3.15), rimegepant (4.00, 95% CrI: 1.38, 12.04), ubrogepant (5.10, 95% CrI: 2.31, 12.95), and sumatriptan (2.57, 95% CrI: 1.3, 6.07). The point estimate compared to eletriptan was 3.27, however it was not statistically significant (95% CrI: 1, 11.83). Both rimegepant and ubrogepant were not statistically significantly different from placebo, sumatriptan, and eletriptan (Appendix Table D17). However, both rimegepant and ubrogepant had point estimates with lower odds of

TEAEs compared to sumatriptan and eletriptan. Based on the estimated odds ratio, the expected proportion of patients achieving any AE was 42% for lasmiditan, 15% for rimegepant, 12% for ubrogepant, 22% for sumatriptan and 18% for eletriptan (Table 3.16).

We also quantitatively compared the incidence of dizziness, the most frequent AE that was consistently reported in the trials. Lasmiditan had higher odds of causing dizziness compared to placebo (8.43, 95% CrI: 4.88, 19.35, Table 3.18), rimegepant (7.02, 95% CrI: 2.2, 25.63), ubrogepant (4.95, 95% CrI: 1.67, 15.92), sumatriptan (4.09, 95% CrI: 2, 10.6), and eletriptan (3.97, 95% CrI: 1.44, 12.41) (Appendix Table D18). Based on the estimated odds ratios, the expected proportion of patients experiencing dizziness was 14% for lasmiditan, 2% for rimegepant, 3% for ubrogepant, 4% for sumatriptan and 4% for eletriptan (Table 3.18).

Table 3.16. Adverse Events. Phase III Single-Attack Trials of Lasmiditan, Rimegepant, and Ubrogepant

Intervention (Trial)	Arms	N	SAEs, n (%)	Any AEs, n (%)	TEAEs, n (%)	Dizziness, n (%)	Somnolence, n (%)	Paresthesia, n (%)	Nausea, n (%)
Lasmiditan (SAMURAI)[25]	Lasmiditan 200mg	609	2 (0.3)	260 (42.7)	237 (38.9)	99 (16.3)	33 (5.4)	48 (7.9)	32 (5.3)
	Lasmiditan 100mg	630	0 (0)	229 (36.3)	205 (32.5)	79 (12.5)	36 (5.7)	36 (5.7)	19 (3.0)
	Placebo	617	1 (0.2)	101 (16.4)	78 (12.6)	21 (3.4)	14 (2.3)	13 (2.1)	12 (1.9)
Lasmiditan (SPARTAN)[24]	Lasmiditan 200mg	649	1 (0.2)	253 (39.0)	NR	117 (18.0)	42 (6.5)	43 (6.6)	17 (2.6)
	Lasmiditan 100mg	635	1 (0.2)	230 (36.2)	NR	115 (18.1)	29 (4.6)	37 (5.8)	21 (3.3)
	Lasmiditan 50mg	654	0 (0)	167 (25.5)	NR	56 (8.6)	35 (5.4)	16 (2.4)	18 (2.8)
	Placebo	645	0 (0)	75 (11.6)	NR	16 (2.5)	13 (2.0)	6 (0.9)	8 (1.2)
Rimegepant (Study 301)[28]	Rimegepant 75mg	546	2 (0.4)	69 (12.6)	3 (0.5)	4 (0.7)	NR	NR	5 (0.9)
	Placebo	549	1 (0.2)	59 (10.7)	1 (0.2)	2 (0.4)	NR	NR	6 (1.1)
Rimegepant (Study 302)[27]	Rimegepant 75mg	537	1 (0.2)	93 (17.3)	NR	NR	NR	NR	10 (1.8)
	Placebo	535	2 (0.4)	77 (14.4)	NR	NR	NR	NR	6 (1.1)
Rimegepant (Study 303)[29]	Rimegepant 75mg	682	0 (0)	90 (13.5)	47 (6.9)	6 (0.9)	NR	NR	11 (1.6)
	Placebo	693	0 (0)	73 (10.5)	36 (5.2)	7 (1.0)	NR	NR	3 (0.4)
Ubrogepant (ACHIEVE I)[92]	Ubrogepant 100mg	485	2 (0.4)	79 (16.3)	58 (12.0)	7 (1.4)	12 (2.5)	NR	20 (4.1)
	Ubrogepant 50mg	466	3 (0.6)	44 (9.4)	27 (5.8)	4 (0.9)	3 (0.6)	NR	8 (1.7)
	Placebo	485	0 (0)	62 (12.8)	41 (8.5)	3 (0.6)	4 (0.8)	NR	8 (1.6)
Ubrogepant (ACHIEVE II)[31]	Ubrogepant 50mg	488	0 (0)	63 (12.9)	42 (8.6)	7 (1.4)	4 (0.8)	NR	10 (2.0)
	Ubrogepant 25mg	478	0 (0)	44 (9.2)	30 (6.3)	10 (2.1)	4 (0.8)	NR	12 (2.5)
	Placebo	499	0 (0)	51 (10.2)	30 (6.0)	8 (1.6)	2 (0.4)	NR	10 (2.0)

AEs: adverse events, mg: milligrams, n: number of participants, N: total number of participants, NR: not reported, SAEs: serious adverse events, TEAEs: treatment-emergent adverse events

Table 3.17. NMA results. Any Adverse Event and Treatment Emergent Adverse Event (Single-Attack RCTs)

	Any Adverse Event (AE)		Treatment Emergent Adverse Event (TEAE)	
	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion with Any AE (95% CrI)	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion with TEAEs (95% CrI)
Placebo	Reference	0.20	Reference	0.13
Lasmiditan	3.91 (2.45, 6.25)	0.5 (0.38, 0.61)	5.99 (3.3, 12.52)	0.42 (0.29, 0.6)
Rimegepant	1.25 (0.83, 1.87)	0.24 (0.17, 0.32)	1.5 (0.67, 3.71)	0.15 (0.08, 0.31)
Ubrogepant	1.11 (0.73, 1.71)	0.22 (0.16, 0.3)	1.17 (0.68, 2.03)	0.12 (0.08, 0.2)
Sumatriptan	1.82 (1.48, 2.27)	0.31 (0.27, 0.36)	2.33 (1.58, 3.29)	0.22 (0.16, 0.29)
Eletriptan	1.07 (0.76, 1.52)	0.21 (0.16, 0.28)	1.83 (0.65, 5.24)	0.18 (0.07, 0.39)

95% CrI: 95% credible interval, vs.: versus

Table 3.18. NMA Results. Dizziness (Single-Attack RCTs)

	Odds Ratio vs. Placebo (95% CrI)	Expected Proportion With Dizziness (95% CrI)
Placebo	NA	0.02
Lasmiditan	8.43 (4.88, 19.35)	0.14 (0.09, 0.27)
Rimegepant	1.22 (0.44, 3.48)	0.02 (0.01, 0.06)
Ubrogepant	1.73 (0.73, 4.52)	0.03 (0.01, 0.08)
Sumatriptan	2.07 (1.3, 3.34)	0.04 (0.02, 0.06)
Eletriptan	2.14 (0.96, 5.11)	0.04 (0.02, 0.09)

95% CrI: 95% credible interval, NA: not available, vs.: versus

Long-Term Studies

We present data on any AE and discontinuation due to AEs from the interim analysis of the OLEs of the interventions in Table 3.19. The majority of AEs observed in these trials were mild or moderate in intensity. Similar to the RCTs, most of the AEs observed in the OLE of lasmiditan after 12 months of follow up were CNS-related, with the most frequently reported event being dizziness (21.3% of patients in the 100 mg group, and 15.8% in the 200 mg group). Somnolence occurred in 8-9% of patients and paresthesia occurred in 5-8% of patients.

In total, 12.8% of patients discontinued the trial due to adverse events (11.2% of patients in the 100 mg group, and 14.4% in the 200 mg group), and dizziness was reported to be the most common AE leading to discontinuation (2.7% of patients in the 100 mg group, and 4.3% of patients in 200 mg group). There was no incidence of abuse, misuse, or diversion related to the CNS effects of lasmiditan. Of note, one patient on lasmiditan experienced a road traffic accident during the OLE, although dosing was reported to have occurred two days before the accident, and the patient was also on concomitant medications that have CNS-related effect (lithium and quetiapine). Due to concerns about somnolence with lasmiditan, the FDA label advises that patients should not drive or

operate machinery within 8 hours of taking a dose.[56] Compared to the lasmiditan OLE, rates of discontinuation were lower in the OLEs of rimegepant and ubrogepant (Table 3.19).

Table 3.19. Adverse Events and Discontinuation due to Adverse Events. Results of 12-months OLEs

Intervention (Trial)	Arms	N	Discontinuation due to AE, n (%)	SAEs, n (%)	Any AE, n (%)	Dizziness, n (%)
Lasmiditan (GLADIATOR)[57]	Lasmiditan 200mg	1015	146 (14.4)	32 (3.2)	731 (72.0)	217 (21.3)
	Lasmiditan 100mg	963	108 (11.2)	28 (2.9)	636 (66.0)	153 (15.8)
Rimegepant (Study 201)[90]	Rimegepant 75mg	1784	48 (2.7)	45 (2.5)	1062 (59.5)	39 (2.2)
Ubrogepant (NCT02873221)[91,95,96]	Ubrogepant 100mg	409	11 (2.7)	12 (2.9)	297 (72.6)	12 (2.9)
	Ubrogepant 50mg	417	9 (2.2)	9 (2.2)	268 (66.3)	5 (1.2)

AE: adverse event, mg: milligrams, n: number of participants, N: total number of participants, SAEs: serious adverse events

Subgroup Analyses

Prior Use of Triptans:

We identified two subgroup analyses that evaluated outcomes among patients in the lasmiditan and ubrogepant trials based upon their prior use of triptans (Knivel 2018 and Blumenfeld 2019).

Knivel 2018 was a pooled analysis of the Phase III trials of lasmiditan (SAMURAI and SPARTAN). At baseline, patients had rated themselves as good, poor, or nonresponders based on three months historical triptan use. The analysis included only patients that were randomized to receive either lasmiditan 100 mg or 200 mg, or placebo in the RCTs. The results showed no significant difference in the benefit of lasmiditan 200 mg versus placebo (on headache pain freedom, MBS freedom, and headache pain relief) in the different triptan responder subgroups.[97]

Blumenfeld 2019 was a pooled analysis of the Phase III trials of ubrogepant (ACHIEVE I and II). At baseline, patients were categorized as triptan-responder, triptan-insufficient responder (includes lack of efficacy, tolerability or contraindications), or triptan-naïve, based on historical experience. Although, higher response rates were observed for ubrogepant 50mg versus placebo in the triptan-responder (2-hour pain freedom OR 2.03; 95%CI: 1.32, 3.11) and triptan-insufficient responder subgroups (2-hour pain freedom OR 2.16; 95%CI: 1.19, 3.95) compared to triptan-naive subgroup (2-hour pain freedom OR 1.37; 95%CI: 0.94, 2.01), the benefit of ubrogepant 50 mg versus placebo was not significantly different (on 2-hours pain freedom [p=0.29), 2-hours freedom from MBS

[p=0.70]) among the three triptan subgroups, indicating comparable treatment effect regardless of historical triptan experience.[98]

Patients Receiving Migraine Preventive Medications

Monoclonal CGRP antagonists for prevention were not permitted in the lasmiditan trials, use was not permitted within 3 months of enrollment in the ubrogepant trials, and their use is not specifically mentioned in the rimegepant trials. We identified two subgroup analyses that evaluated patients on migraine preventive medications in the trials of lasmiditan and rimegepant (Loo 2019 and Dodick 2019).

Loo 2019 was a pooled analysis of the Phase III trials of lasmiditan (SAMURAI and SPARTAN). The two RCTs allowed patients to continue migraine preventives as long as doses were stable for three months prior to screening and were unchanged during the study. Approximately 18% of patients were on migraine preventive treatments (n=698). The results of the analysis showed that 200 mg lasmiditan was more effective than placebo in achieving pain freedom at two hours for the subgroup using (OR 3.3; 95%CI: 1.9 to 5.7) and not using (OR 2.3: 95%CI: 1.9 -2.9) migraine preventive medications. There was no significant difference in the benefit of all lasmiditan doses versus placebo between patients using or not using migraine preventives (all interaction p-values >=0.1). Rates of adverse events were also similar for patients using and not using preventive medications.[99]

Dodick 2019 was a pooled analysis of the Phase III trials of rimegepant (Study 301, 302, and 303). In total, approximately 16% of the total patients were using preventive medication (rimegepant n=272, placebo n=275). The results showed rimegepant was more effective than placebo in achieving pain freedom at two hours in the subgroup using (20.6% vs. 10.2; p=0.007) and not using (20% vs. 12.6%; p<0.0001) migraine preventive medications, with no significant difference between the two subgroups. Similar trend was observed for the co-primary outcome (freedom from MBS).[100]

Controversies and Uncertainties

Feedback received during this project recommended only comparing the new drugs to placebo, and to each other, for patients in whom triptans have not been effective, are not tolerated or are contraindicated. However, given the availability of triptans for acute treatment of migraine, we also sought to compare these interventions to triptans for patients who do not adequately respond to non-prescription medications and are eligible to use triptans.

We identified 10 RCTs (3 for lasmiditan, 4 for rimegepant and 3 for ubrogepant) comparing the interventions to placebo, but we found only one head-to-head trial of one of the interventions versus a triptan (rimegepant vs sumatriptan). There was no study directly comparing the interventions to each other. Since head-to-head data were generally lacking for the comparisons

between agents, indirect quantitative methods (network meta-analyses) were used. These indirect techniques necessarily have more uncertainty than had the therapies been compared directly.

Patient and patient advocates were concerned that the primary outcomes in the RCTs did not fully reflect the potential benefits of these new therapies. We reported on primary efficacy and side effects of treatment at two hours after initial study medication. As noted, we also evaluated and reported on available data on efficacy of the drugs beyond two hours. However, there were important differences among trial protocols for use of rescue medications and additional study medication dosing (both blinded and open label) after two hours. Though censoring patients who use additional treatments after 2 hours attempts to maintain the placebo-controlled nature of the study, the results may still be confounded by the choice to take or not take additional medication and violate the initial intention to treat design of the trials, raising concerns about whether there is truly an additional, delayed benefit after two hours. Analyses that censored patients who took additional, rescue treatments after two hours suggested delayed benefits with ubrogepant and rimegepant. As discussed in detail above, these results are potentially biased, but an analysis of the ubrogepant trials clearly confirms delayed benefit between at least two and four hours. The design of the trials of ubrogepant and rimegepant differ sufficiently after two hours as to make it difficult to compare the results of the published, censored analyses. Furthermore, in actual use patients are likely to take more or different medication after two hours and so the importance of delayed benefits is difficult to assess. Additionally, we do not have similar analyses for lasmiditan or for the triptans, and so it is possible that there may be delayed benefits with one or more of these agents. In particular, eletriptan has a longer half-life than sumatriptan and might have delayed benefits as well. Thus, the analyses examining a delayed benefit of the gepants should only be used to compare these therapies to placebo and not to lasmiditan or the triptans.

The RCTs present data on efficacy of treatment for a single migraine attack. There is uncertainty about efficacy over time when these medications are used for repeated attacks over the course of a year or longer. Since migraine can impact quality of life for those with frequent, severe and unpredictable attacks, it is uncertain if these new therapies may favorably impact quality of life measures and work and productivity outcomes over time. Data were also limited for subgroups of interest, including patients not responding to triptans, patients intolerant of triptans, and patients taking CGRP monoclonal antagonists for prevention.

Interest in new therapies for acute treatment of migraine are driven in part by data showing low rates of use of triptans among migraine patients, reflecting lack of effectiveness or intolerance. The medications studied had different rates and types of side effects. It is uncertain how differing rates of side effects will affect patient use and satisfaction over time. Single administration RCTs do not provide useful information for understanding this.

Although triptans are considered to have safety concerns related to vasoconstrictive effects and, when used with certain other medications such as SSRIs, carry a risk of serotonin syndrome,

decades of use have suggested that these complications may be extremely infrequent in clinical practice. In contrast, the newer agents are touted as potentially safer, but we have much less clinical information to demonstrate long-term safety at this time.

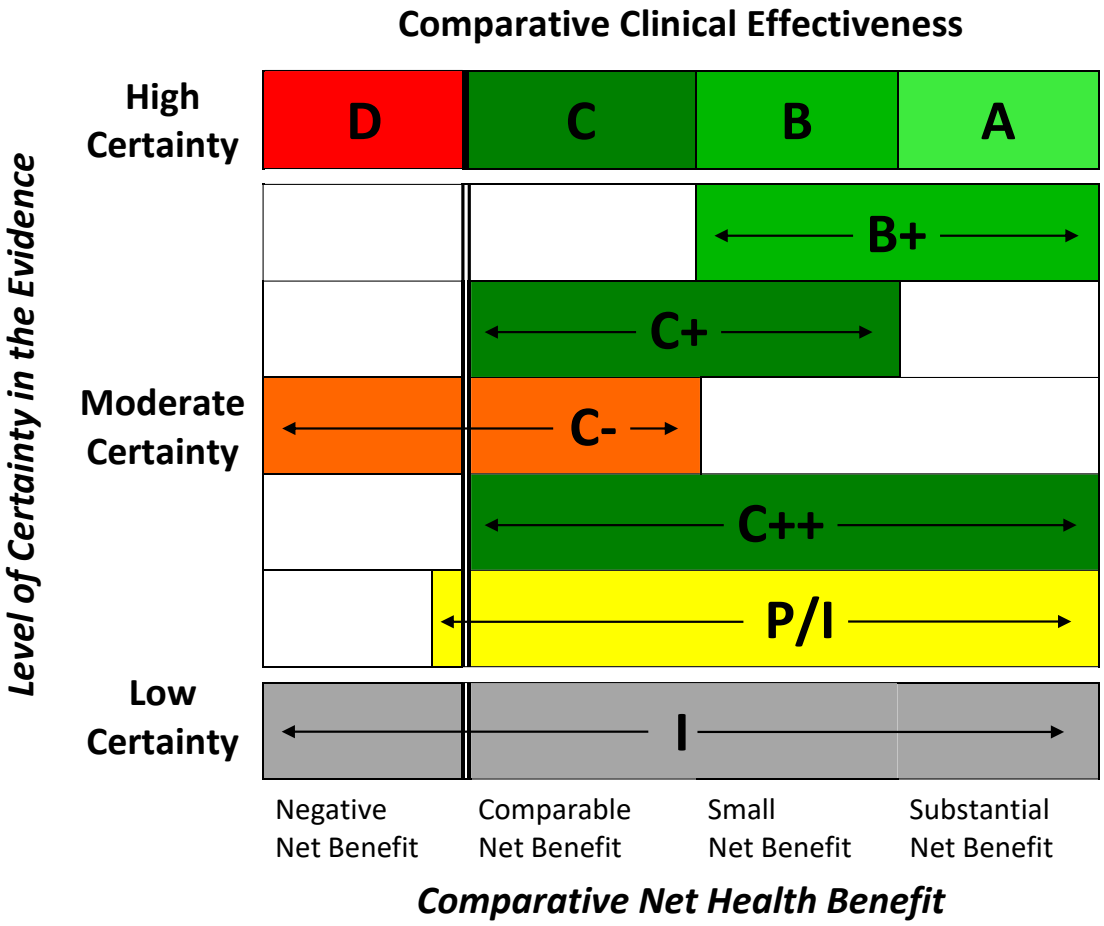
The effect of the newer therapies on migraine frequency over time is uncertain. We heard from multiple stakeholders that decreasing migraine frequency may be an important benefit of these therapies. However, as discussed above, we do not consider it proven that the observed decrease in migraine frequency is due to the treatments. Additionally, it is unknown whether medication overuse headache can occur with these treatments and, if so, whether this occurs more or less frequently than with triptans.

Though migraine is associated with other comorbid conditions and death, it is not known if more effective medications to treat acute migraine episodes may decrease these -longer-term risks.

Because of limitations of existing therapies, there are many individuals in whom no effective, reliable treatment is available. It is hoped that having more treatments for migraine can reduce use of opioids and thus the risk for opioid misuse. Data on this are not yet available.

3.4 Summary and Comment

Figure 3.4. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Lasmiditan, Rimegepant, and Ubrogepant Versus No Additional Migraine-Specific Acute Treatment (Placebo) or Triptans (Sumatriptan and Eletriptan)

Results from clinical trials and from our NMAs suggest that lasmiditan, rimegepant and ubrogepant decrease symptoms of migraine attacks and improve function compared to placebo. Few harms were seen in the single-dose trials of lasmiditan, rimegepant and ubrogepant. However, lasmiditan showed a higher incidence of CNS related AEs (e.g., dizziness, somnolence, paresthesia) in the clinical trials. Below, we provide summary of the evidence for each drug.

Lasmiditan

- Efficacy (RCTs): Results from single-dose clinical trials suggest a greater proportion of patients achieved freedom from pain (OR 1.5-2.6), relief from pain (OR 1.7-2.5), freedom from MBS (OR 1.4-1.9), and ability to function normally (OR 1.7) at two hours post dose, as well as sustained freedom from pain at 24-and 48-hours (OR 1.3 -2.8) with lasmiditan compared with placebo.
- Efficacy (NMA): Results suggest a higher proportion of patients on lasmiditan achieved pain freedom (OR 1.43) and pain relief (OR 1.15-1.16) at two hours compared to rimegepant and ubrogepant, however, these were not statistically significant. Compared to triptans, a lesser proportion of patients on lasmiditan achieved freedom from pain (OR 0.54) and relief from pain (OR 0.61) at two hours post dose versus eletriptan; the results versus sumatriptan followed the same trend but were not statistically significant.
- Safety: Lasmiditan showed a higher incidence of TEAE compared to placebo in single-dose trials, although the majority were mild or moderate in intensity. Specifically, there was a higher incidence of CNS related AEs, with dizziness the most common. NMA results suggest a higher incidence of TEAE compared to rimegepant, ubrogepant and triptans. In the ongoing 12-month extension study, 12.8% of patients discontinued the trial due to adverse events.

Rimegepant

- Efficacy (RCTs): Results from single-dose clinical trials suggest a greater proportion of patients achieved freedom from pain (OR 1.4-2.2), relief from pain (OR 1.5-1.9), freedom from MBS (OR 1.5-1.8), and ability to function normally (OR 1.7) at two hours post dose, as well as sustained freedom from pain at 24- and 48-hours (OR 1.7-3.2) with rimegepant compared with placebo.
- Efficacy (NMA): Results suggest no significant differences between rimegepant compared to ubrogepant (OR 1.00) and lasmiditan (see above) on pain freedom and pain relief at two hours. However, compared to triptans, lesser proportion of patients achieved freedom from pain (OR 0.38-0.51) and relief from pain (OR 0.52-0.73) at two hours post dose with rimegepant compared with triptans.

- Safety: Rimegepant was generally well tolerated in the single-dose trials, showing a similar rate of TEAE compared to placebo. NMA results also suggest comparable incidence of TEAE relative to ubrogepant and triptans, and a lower incidence compared to lasmiditan. In the ongoing 12-month extension study, 2.7% of patients discontinued the trial due to adverse events.

Ubrogepant

- Efficacy (RCTs): Results from single-dose clinical trials suggest a greater proportion of patients achieved freedom from pain (OR 1.5-2.0), relief from pain (OR 1.7-1.8), freedom from MBS (OR 1.4-1.7), and ability to function normally (OR 1.5) at two hours post dose, as well as sustained freedom from pain at 24-hours (OR 1.6 – 2.0) with ubrogepant compared with placebo. In addition, supplemental post-hoc analyses show a delayed benefit with ubrogepant compared with placebo between two and four hours.
- Efficacy (NMA): Results suggest no significant differences between ubrogepant compared to rimegepant (OR 1.00) and lasmiditan (see above) on pain freedom and pain relief at two hours. However, compared to triptans, lesser proportion of patients achieved freedom from pain (OR 0.38-0.52) and relief from pain (OR 0.52-0.73) at two hours post dose, with ubrogepant compared with triptans.
- Safety: Ubrogepant was generally well tolerated in the single-dose trials, showing a similar rate of TEAE compared to placebo. NMA results also suggest comparable incidence of TEAE relative to rimegepant and triptans, and a lower incidence compared to lasmiditan. In the ongoing 12-month extension study, 2.2% of patients discontinued the trial due to adverse events.

Hence, we rated the evidence as follows:

Population 1: For adults (18 years and older) with moderate-severe migraine attacks that have not responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated:

- We consider the evidence on lasmiditan, rimegepant and ubrogepant compared to placebo to be "incremental or better" (B+), demonstrating a moderate certainty of a small or substantial health benefit, with a high certainty of at least a small net health benefit.

Population 2: For adults (18 years and older) with migraine attacks that have not responded to non-prescription medicines (and are eligible to use triptans):

- Based on the results of the NMAs, rimegepant and ubrogepant appear to be less efficacious than triptans (sumatriptan and eletriptan) but have comparable short-term adverse events. Thus, we consider the evidence on rimegepant and ubrogepant compared to triptans to be

"comparable or inferior" (C-), demonstrating moderate certainty that the comparative net health benefit is either comparable or inferior. For lasmiditan, the results of the NMAs suggest it is less efficacious than triptans. However, compared to sumatriptan, the NMAs do not exclude comparable efficacy. In terms of adverse events, the NMA results suggest a higher incidence with lasmiditan compared to triptans. Thus, we consider the evidence on lasmiditan compared to triptans to be "comparable or inferior" (C-).

For all adults with migraine attacks:

- We consider the evidence on rimegepant and ubrogepant to be "comparable" (C), demonstrating a high certainty of a comparable net health benefit. For lasmiditan, the results of the NMAs suggest it may be slightly more efficacious than rimegepant and ubrogepant. However, the NMAs do not exclude comparable efficacy. Patients treated with lasmiditan had more adverse events and more of them discontinued treatment than patients treated with rimegepant or ubrogepant. In addition, while supplemental post-hoc analyses show a delayed benefit for all three agents compared with placebo, the delayed benefits of the gepants relative to their early benefits appeared larger than the delayed benefits of lasmiditan compared to its early benefits. We believe any possible greater efficacy of lasmiditan is at best balanced by these adverse events and may be outweighed by them, and thus we consider the evidence on lasmiditan compared to rimegepant and ubrogepant to be "comparable or inferior" (C-).

Table 3.20. ICER Ratings on the Comparative Net Health Benefit of Interventions versus Comparators

Population	Population 1	Population 2
Interventions	Versus No Treatment	Versus Triptans (sumatriptan and eletriptan)
Lasmiditan	B+	C-
Rimegepant	B+	C-
Ubrogepant	B+	C-

Population 1: Patients with migraine-attacks that have not responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated
Population 2: Patients with migraine-attacks that have not responded to non-prescription medicines (and are eligible to use triptans)

Table 3.21. ICER Ratings on the Comparative Net Health Benefit of Interventions versus Each Other

Population	For All Patients		
Interventions	**Versus Lasmiditan**	**Versus Rimegepant**	**Versus Ubrogepant**
Lasmiditan		C-	C-
Rimegepant	C+		C
Ubrogepant	C+	C	

Note: The table should be read row-to-column. For example, there is moderate certainty that the point estimate for comparative net health benefit of lasmiditan is either comparable or inferior to rimegepant (C-). Conversely, there is moderate certainty of comparable, small or substantial health benefit, with at least a high certainty of at least a comparable health benefit of Rimegepant compared to lasmiditan (C+).

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this economic evaluation was to estimate the cost effectiveness of lasmiditan, rimegepant, and ubrogepant for the acute treatment of migraine using a *de novo* decision analytic model. The outcomes of interest included the incremental cost per quality-adjusted life year (QALY) gained, life-years gained, equal value of life years gained (evLYG), and cost per hour of migraine pain avoided. An analysis of the incremental cost per evLYG is included in this report to complement the cost per QALY calculations and provide policymakers with a broader view of cost effectiveness. A description of the methodology used to derive the evLYG can be found in Appendix E. Lasmiditan, rimegepant, and ubrogepant were compared with each other and to three comparators in separate analyses representing two distinct populations. For the first comparison, we evaluated lasmiditan, rimegepant, and ubrogepant to each other and to no additional migraine-specific acute treatment. For the purpose of this review, no additional migraine-specific acute treatment was estimated by the placebo arms of the clinical trials, although we recognized that in the real-world, patients may use previously failed or untried over-the-counter and prescription treatments for acute migraine including analgesics. For the second comparison, we evaluated lasmiditan, rimegepant, and ubrogepant to each other and to two triptans: sumatriptan and eletriptan. Sumatriptan was chosen because it is one of the most widely used triptans in clinical practice; and eletriptan, a newer triptan, was shown in a recent network meta-analysis to be one of the most efficacious and well tolerated. Since these new agents under review are all orally available, we focused our comparison of triptans on the oral formulations. All costs and outcomes were discounted at a rate of 3%. For this aim, the base-case analysis was conducted using a health care sector perspective (i.e., focus on direct medical care costs only) and a two-year time horizon. Longer time horizons and productivity gains with treatment were considered in scenario analyses. The model was developed in Microsoft Excel 2016 (Redmond, WA).

4.2 Methods

Model Structure

For the cost-effectiveness analysis, we developed a *de novo* semi-Markov model with time-varying proportions of patients with response to treatment. The model was informed by a network meta-analysis of key clinical trials and prior relevant economic models, systematic literature reviews, and input from diverse stakeholders (patients, advocacy groups, clinicians, payers, researchers, and manufacturers of these agents). The base case used a US health sector perspective. Costs and outcomes were discounted at 3% annually. The model cycle was 48 hours based on the typical duration of clinical trials evaluating acute migraine treatments.

The model evaluated two hypothetical cohorts of patients requiring acute treatment for migraine, all being treated with lasmiditan, rimegepant, ubrogepant, or usual care in the first population and all being treated with lasmiditan, rimegepant, ubrogepant, sumatriptan, or eletriptan in the second population.

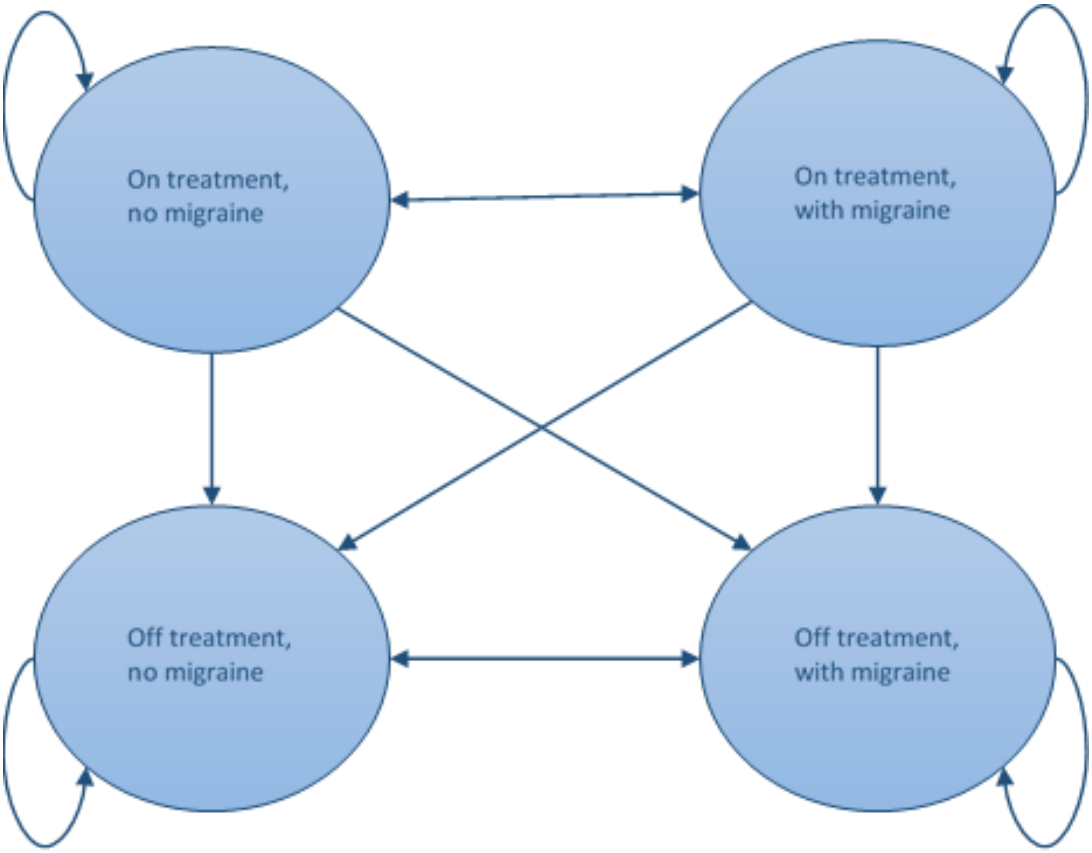
As shown in the model schematic (Figure 4.1), simulated patients entered the model through one of two Markov states, "On treatment, no migraine" or "On treatment, with migraine," according to the average daily probability of having a migraine in the target population (i.e., 4.8 migraines per month, corresponding to a probability of 0.316 migraines in each 48-hour period).

Those patients entering the "On treatment, with migraine" Markov state received the assigned acute initial treatment for migraine (i.e., lasmiditan, rimegepant, ubrogepant, sumatriptan, eletriptan, or usual care). Initial treatment resulted in some proportion of patients achieving complete resolution of migraine pain (pain freedom), an improvement in migraine pain without complete resolution (pain relief), or no improvement in migraine pain at each of four time points: 2, 8, 24, and 48 hours.

Over time, patients were allowed to discontinue treatment due to side effects or insufficient effectiveness. For patients who discontinued treatment due to side effects, 12-month treatment-specific discontinuation rates were used. For patients who discontinued treatment due to insufficient effectiveness, the proportion of patients remaining in the "On treatment, with migraine" Markov state who received benefit from therapy increased, to maintain the *total* proportion of patients who received benefit from treatment constant over time. Since the absolute effectiveness gains of patients remaining in the "On treatment, with migraine" Markov state is not known, this estimate was subjected to a modifier that was set at 50% of full benefit for the base case.

Patients who discontinued treatment transitioned to the "Off treatment, no migraine" or "Off treatment, with migraine" Markov states according to the observed probability of discontinuation derived from Brandes et al.[57] The model was designed with the assumption that patients who discontinued treatment would not return to either of the "On treatment, no migraine" or "On treatment, with migraine" Markov states. Patients transitioned between the "Off treatment, no migraine" and "Off treatment, with migraine" states according to the average probability of having a migraine every 48 hours, similar to those on the initial treatment.

Figure 4.1. Model Framework



Target Population

The population of focus for the economic evaluation was the prevalent cohort of individuals in the United States (US) aged 18 years and over experiencing migraines requiring acute treatment, with or without aura as specified by the International Classification of Headache Disorders (ICHD) 3 diagnostic criteria.[101] Two separate cohorts of patients were evaluated using different comparators. The first cohort was comprised of 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. The second cohort was comprised of patients who had migraine attacks that did not respond adequately to non-prescription medicines, such as non-steroidal anti-inflammatory agents. In this cohort, comparisons were made among lasmiditan, rimegepant, and ubrogepant, and two commonly used oral triptans with different effectiveness and cost, sumatriptan and eletriptan, representing a range of triptan medications. The baseline patient characteristics are presented in Table 4.1.

Table 4.1. Base-Case Model Cohort Characteristics

Baseline Characteristics	Value	Source
Mean Age, years (SD)	40.8	Croop 2019[29]
Female, %	86.0	Lipton 2019[27]
Migraine Days per Month at Baseline	4.8	Doty 2019[102]

Treatment Strategies

Interventions included in the models were lasmiditan 100-200 mg, rimegepant 75 mg, and ubrogepant 50-100 mg. The comparators depended on the population being evaluated. In Population 1 (i.e., patients in whom prior treatment with non-prescription medicines failed and for whom triptans were not effective, were not tolerated, or were contraindicated), the interventions were compared with each other and with usual care, represented by the placebo arm from clinical trials. In Population 2, the interventions were compared with each other and with sumatriptan 50-100 mg and eletriptan 40 mg.

Key Model Characteristics and Assumptions

The model required several assumptions. Key model assumptions and rationale for the assumptions are presented in table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Mortality is not associated with acute treatment for migraine.	There have been no demonstrated mortality benefits with treatment of migraine pain and other symptoms.
Acute treatment of migraine with lasmiditan, rimegepant, ubrogepant, and triptans does not affect migraine frequency.	Studies evaluating new migraine therapies were either short-term single episode studies or non-controlled open label studies and were not designed to demonstrate changes in migraine frequency with treatment. Longer-term, uncontrolled, open-label studies suffer from a possible placebo effect and a high likelihood that regression to the mean may affect the study's results. Should stronger evidence suggest that migraine frequency and/or characteristics are modified with acute treatments for migraine, this assumption will be reevaluated.
A two-year time horizon is sufficient to estimate the cost effectiveness of acute treatments for migraine.	Compared with many other chronic conditions modeled using Markov models, migraine onset is rapid, and resolution occurs quickly. Since costs are incurred with each treatment and benefits are observed immediately, we believe that a two-year time horizon will be sufficient to estimate a stable incremental cost-effectiveness ratio for the acute

Assumption	Rationale
	treatment of migraine. We will test this assumption by extending the time horizon to 5 years and determining whether the cost effectiveness of therapies appreciably change.
Patients who have discontinued treatment received some other medication with a response similar to those in the placebo arm from clinical trials.	This analysis was intended to evaluate the cost effectiveness of new acute treatments for migraine. Since there are a variety of medications available for acute migraine, with varying effectiveness and cost, that could be used in the event that patients discontinued one of the new acute treatments, there was no single alternative available for the model. The discontinuation rates of the new treatments appear to be relatively similar from single arm continuation safety studies, so the impact of this assumption is expected to be minimal. In addition, the cost and effectiveness of the acute treatment used for those who discontinue lasmiditan, rimegepant, and ubrogepant will be subjected to a two-way sensitivity analysis to determine the potential impact of this assumption on the cost-effectiveness results.
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.	Data describing treatment discontinuation due to lack of effect was obtained from a study in which follow up lasted for 12 months.[57] It is unlikely that the majority of patients receiving no or suboptimal benefit would continue taking a medication beyond 12 months.
Patients who did not respond to acute treatments for migraine were assumed to have moderate or severe pain, in proportion to what was observed at baseline.	Sufficiently detailed data evaluating those who did not respond was not uniformly available from clinical trials. This assumption was necessary to assign utility values to those who did not respond to therapy.
Adverse drug events last for 8 hours.	Symptoms of drowsiness, dizziness, fatigue, and paresthesia were more frequent than placebo with certain acute treatments of migraine. The mean time that patients suffered from these treatment-emergent adverse events was not described in studies. In order to determine QALYs lost due to treatment-emergent adverse events, a duration of the event had to be assumed.

Assumption	Rationale
Discontinuations due to "patient request" in the GLADIATOR study represent discontinuations due to lack of treatment effect.[57] Given the similarity in treatment response among lasmiditan, rimegepant, and ubrogepant, we assumed that treatment discontinuation due to lack of effectiveness would be similar.	Discontinuation probability and reasons for discontinuation are not reported for acute treatments for acute migraine. This study described discontinuation reasons but did not include a category stating whether discontinuation was for lack of effectiveness. Given the other categories for discontinuation, this category of "patient request" was likely to represent patients who did not derive benefit from treatment. Assuming patients would continue treatment, even when it wasn't effective, would bias the analysis against lasmiditan, rimegepant, and ubrogepant, when compared to usual care.
If a migraine treatment resulted in migraine pain of "no pain" or "mild pain" at 2 hours, a person would be able to work.	The impact of migraine on productivity is important to patients. However, clinical trials did not evaluate work productivity. Studies that have evaluated work productivity have assessed the impact of migraine on productivity (primarily absenteeism) but have not assessed the impact of treatment and time to pain and/or symptom relief on productivity. This assumption was necessary to apply results of productivity studies in migraine patients to this model for the scenario analysis evaluating a modified societal perspective.

Model Inputs

Clinical Inputs

Short-term clinical inputs for the effectiveness of acute treatments for migraine and the comparators were derived from a network meta-analysis of clinical trials evaluating lasmiditan, rimegepant, ubrogepant, sumatriptan, and eletriptan compared with placebo and with each other, where such studies existed. For the Final Report, there were no changes to how the effectiveness of lasmiditan was assessed at 2, 8, 24, and 48 hours. After evaluation of new data provided on ubrogepant (via personal communication with Allergan) assessing its impact on treatment outcomes after two hours in patients who had not had relief prior to that point, direct comparative data were used in the Final Report to estimate an increased benefit to patients taking rimegepant and ubrogepant at the 8, 24, and 48 hour time points for the base-case comparisons with usual care. The network meta-analysis results were still used for the two-hour time point. As direct comparative data on the effect of rimegepant and ubrogepant versus triptans at 8, 24, and 48 was not available, data from the network meta-analysis were used to estimate the effects of rimegepant and ubrogepant on pain at these time points, as was done in prior versions of the Report.

Clinical Probabilities/Response to Treatment

The decision model was evaluated over a two-year time horizon with 48-hour cycles. The probability of having a migraine in each cycle was estimated using the number of migraine days per month from patients enrolled in clinical trials. Within each cycle, the proportions of patients with severe, moderate, mild, or no pain were evaluated at baseline, 2, 8, 24, and 48 hours using data from clinical trials. Patients **without** migraine had no pain for the entire 48-hour cycle. Patients **with** migraine started in severe or moderate pain, derived from the average proportions of patients with moderate or severe pain at baseline from clinical trials. Tables 4.3 (Population 1) and 4.4 (Population 2) show the calculated proportions of patients with no, mild, moderate, and severe pain at baseline, 2, 8, 24, and 48 hours that were used in the model.

Two-hour response in both populations, all treatments

Two-hour response to acute treatments for migraine was estimated using data directly from clinical trials included in a network meta-analysis described earlier in this report. The proportion of patients who were pain free in clinical trials were considered to have "no pain" at the two-hour time point. Since the proportion of patients who had pain relief in clinical trials included those who were pain free, the proportion who were pain free was subtracted from those with pain relief to estimate the proportion of patients with "mild pain" at two hours and for all subsequent time points. Those who did not have a response in clinical trials were assumed to have moderate or severe pain, in proportion to what was observed at baseline.

Response at 8, 24, and 48 hours in both populations for all treatments other than rimegepant and ubrogepant

In clinical trials evaluating lasmiditan, rimegepant, and ubrogepant, some patients who responded at two hours subsequently lost response to treatment between two and 24 hours. The proportion of patients who did not lose response at 24 hours were considered to have maintained response over that time. For the proportion of patients who did lose response as estimated in the network meta-analysis, we assumed the maximal proportion lost response at eight hours with a linear loss from two to eight hours. After eight hours, we assumed that patients regained response such that at 24 hours the patients who had lost response had the same response rate as in the placebo response from Dodick.[103] This return of response was assumed to be linear from eight to 24 hours. All patients responding at two hours were also assumed to have response at 48 hours.

Patients who did not respond at two hours were similarly assumed to achieve response at eight and 24 hours as per the placebo response from Dodick,[103] with linear achievement of response between two and eight hours, and then a separate linear response between eight and 24 hours. Response at 48 hours was similarly calculated by adding all two-hour responders to the placebo response for non-responders at two hours. The proportion of patients with moderate or severe migraine pain

was calculated by multiplying the proportion of non-responders (i.e., 1 - responders) at 2, 8, 24, and 48 hours by the proportion of patients with “moderate pain” and/or “severe pain” at baseline.

Response at 8, 24, and 48 hours in population 1 (compared with usual care) in patients taking rimegepant, ubrogepant, or lasmiditan

As discussed in the clinical section above, analyses provided by the manufacturer of ubrogepant (Table 3.6) showed a delayed benefit of the initial study drug at four hours for patients who had not had benefit at two hours. Further analyses were used to estimate the relative risk for this increased effectiveness at 8, 24, and 48 hours (data on file). A risk ratio of [redacted] was applied to the 8-hour timepoint, [redacted] for the 24-hour timepoint, and [redacted] for the 48-hour timepoint (date on file). For those who did not respond at two hours, these risk ratios were applied to the placebo response rates used for other treatments from Dodick,[103] as described above, to adjust for this observed increased response over time. Note that for those who responded to treatment at two hours, eight-hour response was calculated as described above. Similar analyses were provided for lasmiditan as described above in the Update to this report.

Table 4.3. Treatment Response Used in Base-Case Model for Population 1

Level of Migraine Pain at Timepoints, %	Lasmiditan	Rimegepant	Ubrogepant	Usual Care
Baseline (0h), %				
None	0.0	0.0	0.0	0.0
Mild	0.0	0.0	0.0	0.0
Moderate	66.6	66.6	66.6	66.6
Severe	33.4	33.4	33.4	33.4
2h, %				
None	28.0	21.0	21.0	11.0
Mild	30.0	33.0	33.0	24.0
Moderate	28.0	30.6	30.6	43.3
Severe	14.0	15.4	15.4	21.7
8h, %				
None	59.5	71.8	71.4	53.5
Mild	29.9	23.6	23.7	32.8
Moderate	7.1	3.1	3.2	9.1
Severe	3.5	1.6	1.6	4.6
24h, %				
None	74.3	76.4	76.4	68.3
Mild	19.0	19.5	19.5	21.5
Moderate	4.4	2.7	2.7	6.8
Severe	2.2	1.4	1.4	3.4
48h				
None	81.8	82.4	82.4	77.4
Mild	12.4	12.9	12.9	13.6
Moderate	3.8	3.1	3.1	5.9
Severe	1.9	1.6	1.6	3.0

Table 4.4. Treatment Response Used in Base-Case Model for Population 2

Level of Migraine Pain at Timepoints, %	Lasmiditan	Rimegepant	Ubrogepant	Sumatriptan	Eletriptan
Baseline (0h), % None Mild Moderate Severe	0.0 0.0 66.6 33.4	0.0 0.0 66.6 33.4	0.0 0.0 66.6 33.4	0.0 0.0 66.6 33.4	0.0 0.0 66.6 33.4
2h, % None Mild Moderate Severe	28.0 30.0 27.9 14.0	21.0 33.0 30.6 15.4	21.0 33.0 30.6 15.4	35.0 27.0 25.3 12.7	42.0 27.0 20.6 10.3
8h, % None Mild Moderate Severe	59.5 29.9 7.1 3.5	58.5 31.2 6.8 3.4	58.0 31.4 7.1 3.5	61.0 29.1 6.6 3.3	62.0 29.9 5.4 2.7
24h, % None Mild Moderate Severe	74.3 19.0 4.4 2.2	71.9 20.9 4.8 2.4	71.9 20.9 4.8 2.4	76.8 17.2 4.0 2.0	79.3 15.8 3.2 1.6
48h None Mild Moderate Severe	81.8 12.4 3.8 1.9	80.0 13.6 4.2 2.1	80.0 13.7 4.2 2.1	83.6 11.2 3.5 1.7	85.3 10.4 2.8 1.4

Probability of migraine-related provider office, emergency room, and hospital visits

The probability of having migraine-related provider office visits or of being admitted to the emergency department or hospital were determined for patients with persistent pain, derived from Silberstein et al[104] and shown in Table 4.5. To estimate the probability of having a migraine-related provider office, emergency, or hospital visit during a migraine, these rates were divided by the baseline number of migraines with severe headache pain per year. In the model, provider office, emergency department, and hospital visits were assumed to occur only in patients who had migraine pain lasting 12 hours. A ratio of having moderate or severe pain at 12 hours with a specific

treatment compared with placebo was used to adjust the likelihood of requiring a provider office, emergency department, or hospital visit due to migraine. Therefore, more effective therapies reducing headache pain at 12 hours resulted in fewer health care visits than did less effective therapies.

Table 4.5. Non-Treatment Dependent Values Used to Calculate Model Event Probabilities

Model Input	12-Month Value	Per Migraine Probability	Source
Mean Number of Migraine-Related Health Care Provider Visits	2.2	3.8%	Silberstein 2018[104]
Mean Number of Migraine-Related Emergency Department Visits	1.2	2.1%	
Mean Number of Migraine-Related Hospitalizations	0.4	0.7%	

Discontinuation

Treatment discontinuation probabilities due to lack of response were derived from the GLADIATOR long-term safety study of lasmiditan.[57] We assumed that "patient request" referred to those patients who discontinued the medication for lack of effect. Discontinuation was primarily due to "patient request" (21.8%) and adverse events (12.8%). Long-term data on treatment discontinuation due to lack of effectiveness were not available for other treatments. Since lasmiditan, rimegepant, and ubrogepant all show similar effectiveness, we assumed that discontinuation for lack of effectiveness would also be similar among all treatments. We also assumed that discontinuation of triptans due to lack of effectiveness was the same as that of the newer acute treatments for migraine. Discontinuation due to lack of effectiveness was set to 0% after one year.

Treatment-specific discontinuation rates due to adverse drug events were obtained from longer term observational studies.[57,90,91] We assumed that adverse events were not related to patient response. Therefore, patients discontinuing treatment due to an adverse event were proportionally removed from all response categories (i.e. pain free, pain relief, and non-responders). Discontinuation due to adverse drug events was set to 0% after two years in the sensitivity analysis evaluating longer time horizons.

Mortality

Therapies for migraine have not demonstrated differences in mortality, nor has a mechanism for differential survival with the current treatments been proposed. In addition, the model used a short time horizon of two years to generate the incremental cost-effectiveness estimates for the

new therapies. Given the relatively young age of the population being evaluated and associated low mortality rate, mortality was not included in the model.

Adverse Events

All adverse events occurring in at least 5% of patients, and their disutilities, were included in the analysis. In addition, fatigue was included even when it did not reach an incidence of 3%, as it had a larger impact on patient utility. Adverse events were assumed to last for eight hours. Discontinuation due to adverse events was also included in the analysis. Table 4.6 shows the adverse events, frequencies, and disutilities used in the model.

Table 4.6. Adverse Drug Event Frequencies and Associated Disutility

Adverse Event	Drug	Frequency, %	Disutility	References
Drowsiness	Lasmiditan	5.5	-0.028	Krege 2019[105] Matza 2019[106]
Dizziness	Lasmiditan	14.7	-0.021	Krege 2019[105] Matza, 2019[106]
Fatigue	Lasmiditan	3.8	-0.069	Krege 2019[105] Matza 2019[106]
	Sumatriptan	3.0	-0.069	Imitrex FDA label[107] Matza, 2019[106]
	Eletriptan	10.0	-0.069	Relpax FDA label[108] Matza 2019[106]
Paresthesia	Lasmiditan	5.7	-0.013	Krege 2019[105] Matza 2019[106]
	Sumatriptan	5.0	-0.013	Imitrex FDA label[107] Matza, 2019[106]
	Eletriptan	4.0	-0.013	Relpax FDA label[108] Matza 2019[106]

Health State Utilities

Table 4.7 shows health state utility values used in the model. Utilities were derived from published literature that estimated migraine-specific utility values using the EQ-5D and stratified by the severity of the migraine. For patients without migraine, a utility associated with "no pain" derived from Xu et al. was used.[109] For patients with migraine, we first estimated the proportion of patients with no, mild, moderate, or severe pain at 0 (baseline), 2, 8, 24, and 48 hours. The trapezoidal method for estimating area under the curve was then used to derive the proportion of patients with no, mild, moderate, or severe pain between 0-2 hours, 2-8 hours, 8-24 hours, and 24-48 hours. Utility estimates from Xu et al., shown in Table 4.5, were applied to these proportions for the appropriate amount of time (e.g., 16 hours for the 8-24-hour time period).[109]

Disutilities of -0.5 were assumed for those patients who were hospitalized or required an ED visit. Hospitalizations were assumed to last for two days, ED visits for one day. We did not include a disutility score for patients suffering from nausea and/or vomiting, photophobia, or phonophobia due to lack of data.

Disutility of adverse events were estimated from the rate of the events, the associated disutility for the event, and an assumed duration of eight hours. The disutility values are noted in the table included in the above section on adverse events.

Table 4.7. Utility Values for Health States

Migraine Symptom	Migraine-Specific Utility Value			Source
	Mean Value	95% CI	Method	
Severe Pain	0.440	(0.374, 0.502)	EQ-5D	Xu 2011[109]
Moderate Pain	0.773	(0.755, 0.789)	EQ-5D	Xu 2011[109]
Mild Pain	0.835	(0.790, 0.883)	EQ-5D	Xu 2011[109]
Pain free	0.959	(0.896, 0.967)	EQ-5D	Xu 2011[109]
Nausea/vomiting	Estimate not found in literature search	Estimate not found in literature search	Estimate not found in literature search	
Photophobia	Estimate not found in literature search	Estimate not found in literature search	Estimate not found in literature search	
Phonophobia	Estimate not found in literature search	Estimate not found in literature search	Estimate not found in literature search	
Hospitalization	-0.5 (for 2 days)			Assumed
Emergency Department Visit	-0.5 (for 1 day)			Assumed
Adverse Events	-0.013—0.069		Time Trade Off	Matza 2019[106]

Economic Inputs

Drug Utilization

Drug utilization for acute treatments for migraine evaluated in this model, used to determine costs, are shown in Table 4.8. When available, the approved indication dosage will be used to model drug costs.

Table 4.8. Treatment Regimen Recommended Dosage

Generic Name	Lasmiditan	Rimegepant	Ubrogepant	Sumatriptan	Eletriptan	Sources
Brand name	Reyvow	Investigational	Ubrelvy	Imitrex, others	Relpax	
Manufacturer	Eli Lilly	Biohaven	Allergan			
Route of Administration	Oral	Oral	Oral	Oral	Oral	
Dosing	50 mg, 100 mg, or 200 mg orally; No more than one dose in 24 hours.	Approved dosing information not available	50-100 mg orally; may repeat after 2 hours; maximum dose is 200 mg/24 hours	50-100 mg orally; may repeat after 2 hours; maximum dose: 200 mg/24 hours	40 mg; may repeat after 2 hours; maximum dose: 80 mg/24 hours	Reyvow prescribing information Ubrelvy prescribing information Micromedex online

Drug Costs

We used the wholesale acquisition cost (WAC) from Redbook to estimate prices for all drugs with prices available.[58] At the time of publishing this report, the price for rimegepant was not available. We therefore estimated the price of rimegepant assuming the same price as was announced for ubrogepant. A 27% industry average discount was applied to all WAC prices.

Costs for treatments for the usual care arm were estimated using a prevalent mix of treatments, estimated from Ford et al., and applying WAC prices from Redbook.[58,59] Since triptans were not indicated for Population 1 and were the comparators for Population 2, we removed triptans from the prevalent mix reported and adjusted the remaining treatments accordingly. After the removal of triptans, the resulting mix of treatments and proportion of patients in which they were used were as follows: butalbital/caffeine/acetaminophen (11.3%), ibuprofen (38.2%), naproxen (32.1%), opioids (28.3%). Aligning with the ICER Reference Case (http://icer-review.org/wp-content/uploads/2018/07/ICER_Reference_Case_July-2018.pdf), we used the WAC without an applied discount as the price for triptans, as they are currently available as generic medications. Table 4.9 shows the WAC prices and sources.

Table 4.9. Drug Cost per Dose

Drug	WAC	Source
Lasmiditan	$80.00	Redbook Online from Micromedex[58]
Rimegepant	WAC not available (used $85.00)	Assumed same price as for ubrogepant.
Ubrogepant	$85.00	Redbook Online from Micromedex[58]
Sumatriptan, Oral tablets 50 mg 100 mg	$1.04	Redbook Online from Micromedex[58]
Eletriptan 40 mg	$11.95	Redbook Online from Micromedex[58]
Usual Care (mix)	$4.81	Ford 2017[59] Micromedex[58]

Non-Drug Health Care Costs

In the model, the non-drug health care costs for the acute treatment of migraine included only those costs demonstrated to be associated with treatment. Costs associated with provider office visits, emergency department visits, and hospitalizations were included, as a rapid decrease in pain and other migraine symptoms were likely to be impacted by improved migraine pain. To estimate the cost of hospitalization, the most recently available year (2016) mean cost of hospitalizations for ICD-10 codes G43.xxx were obtained from the online Health Care Utilization Project (HCUP.net).[110] The cost of emergency department visits was estimated by obtaining the total ED facility and doctor's fees from the Medicare Expenditure Panel Survey online tool (MEPS.AHRQ.gov).[111] The 2019 Center for Medicare & Medicaid Services physician fee schedule was used to estimate the cost of a provider office visit. We assumed a level 2 physician office visit (HCPCS code 99212) for a migraine-related visit. All costs were inflated to 2019 US dollars using the Health Care component of the Bureau of Economic Analysis Personal Consumption Expenditures Price Index (PCE) as per ICER's Reference Case. These costs are shown in Table 4.4.

We included the potential impact of therapies for migraine on productivity losses in a scenario analysis. We used estimates for productivity losses resulting from migraine derived from Mesalli et al. 2016, which captures presenteeism productivity loss, days missed, and losses in housework conducted for full-time employees, part-time employees, and those with other employment status.[8] The total productivity loss costs for acute migraines were estimated to be $245 per month. We used an assumption that if a migraine responded to treatment quickly (i.e. within two hours), people would be able to begin, continue, or return to work. Productivity gains due to effective treatment were estimated by applying a calculated benefit per migraine at two hours to all patients with no pain or mild pain.

Threshold Analyses

Threshold analyses were conducted for Population 1 to determine the price required to result in willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY gained.

Sensitivity Analyses

One-way sensitivity analyses were conducted on all model inputs to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were performed by jointly varying sensitive model parameters over 5,000 simulations and calculating 95% credible range estimates for each model outcome based on the results.

Scenario Analyses

We employed four scenario analyses. In the first scenario analysis, we evaluated the impact of productivity gains added to the base-case analysis, using a modified societal perspective. In this analysis, patients with mild or no pain at two hours were assumed able to continue working.

The second scenario analysis evaluated the impact of decreased migraine frequency in the population over time. Evidence from long-term safety trials suggests that migraine frequency may have decreased over time.[57] One non-controlled, observational study showed that in patients who were observed for one year, migraine frequency decreased from a mean of approximately 6 migraines per quarter to 3.7 migraines per quarter. Since a reduction in migraine frequency would have an impact on medication costs, we conducted a scenario analysis to evaluate the impact of decreasing migraine frequency on cost effectiveness and to generate inputs for the budget impact analysis.

The third scenario analysis extended the time horizon to five years to assess whether a longer timeline impacted the cost effectiveness of treatments.

Model Validation

We have and will use several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined model structure and data inputs used in the model. We performed model verification for model calculations using internal reviewers and varied model input parameters to evaluate face validity of changes in results. Finally, we provided the manufacturers of rimegepant, ubrogepant and lasmiditan an opportunity to review and comment on the most recent draft of the model base case during the comment period for the draft report.

4.3 Results

Base-Case Results

As stated above, pricing was available for lasmiditan and ubrogepant, but not for rimegepant, at the time of this report. All analyses assumed that the price for rimegepant was the same as that for ubrogepant. The total discounted lifetime costs, QALYs, LY, evLYG, and mean hours of migraine pain per attack are shown for lasmiditan, rimegepant, ubrogepant, sumatriptan, eletriptan, and usual care in Table 4.10. Tables 4.10, 4.11, and 4.12 have been updated based on the results described above in the Update to this report.

Cost per QALY gained for the primary comparisons are shown in Table 4.12 for Population 1. The incremental cost-effectiveness ratios for lasmiditan, rimegepant, and ubrogepant compared with usual care were $151,800, $39,800, and $40,000 per QALY gained, respectively. When compared with each other, rimegepant and ubrogepant dominated lasmiditan, being more effective and less costly. Note that these findings change what was reported in the last version of the Report, where lasmiditan dominated rimegepant and ubrogepant. The change in this result is entirely due to the potential for a delayed incremental benefit of rimegepant and ubrogepant compared with placebo beyond two hours and reflects the uncertainty in the true benefits of these drugs due to limitations in the clinical trials. As noted in the Update to this report, all three agents demonstrated a potential delayed benefit compared with placebo, but the delayed benefits of the gepants relative to their early benefits appeared larger than the delayed benefits of lasmiditan compared to its early benefits. Rimegepant and ubrogepant had nearly identical total costs, QALYs, and cost effectiveness.

Table 4.10. Base-Case Results for Lasmiditan, Rimegepant, Ubrogepant, and Usual Care in Population 1

Treatment	Drug Cost (per year)**	Total Cost**	QALYs	Life Years	evLYG	Hours of Pain
Lasmiditan	$3,360	$12,000	1.8271	1.95	1.8271	1,650
Rimegepant*	$3,570	$10,660	1.8295	1.95	1.8295	1,570
Ubrogepant	$3,570	$10,660	1.8295	1.95	1.8295	1,580
Usual Care	$280	$10,050	1.8142	1.95	1.8142	2,100

QALY: quality-adjust life year; LY: life year; evLYG: equal value of life years gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

**Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

In Population 2, both sumatriptan and eletriptan produced higher QALYs at a lower total cost, and therefore dominated lasmiditan, rimegepant, and ubrogepant. As there was no mortality effect in the model, cost per LY gained is not relevant, and the cost per evLYG is essentially the same as the cost per QALY gained. The full results are shown in Tables 4.11 and 4.12.

Table 4.11. Base-Case Results for Lasmiditan, Rimegepant, Ubrogepant, Sumatriptan, and Eletriptan in Population 2

Treatment	Drug Cost (per year)**	Total Cost**	QALYs	Life Years	evLYG	Hours of Pain
Lasmiditan	$3,360	$12,000	1.8271	1.95	1.8271	1,650
Rimegepant*	$3,570	$13,010	1.8222	1.95	1.8222	1,870
Ubrogepant	$3,570	$13,020	1.8221	1.95	1.8221	1,876
Sumatriptan	$60	$6,630	1.8264	1.95	1.8264	1,610
Eletriptan	$690	$6,790	1.8293	1.95	1.8293	1,480

QALY: quality-adjust life year; LY: life year; evLYG: equal value of life years gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

**Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

Table 4.12. Incremental Cost-Effectiveness Ratios for the Base Case in Population 1 and 2

Treatment	Comparator	Cost per QALY Gained	Cost per Hour of Pain Avoided
Population 1			
Lasmiditan	Usual Care	$151,800	$4.32
Rimegepant*	Usual Care	$39,800	$1.15
Ubrogepant	Usual Care	$40,000	$1.15
Population 2			
Lasmiditan	Sumatriptan	Dominated	Dominated
Rimegepant*	Sumatriptan	Dominated	Dominated
Ubrogepant	Sumatriptan	Dominated	Dominated
Lasmiditan	Eletriptan	Dominated	Dominated
Rimegepant	Eletriptan	Dominated	Dominated
Ubrogepant	Eletriptan	Dominated	Dominated

QALY: quality-adjusted life years*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

Differences from Evidence Report

Several changes and corrections were responsible for revisions between the results presented in the Evidence Report and this report:

- Pricing has become available for lasmiditan and ubrogepant. Based on stakeholder input, we used the same price for rimegepant, and ubrogepant. The actual price for rimegepant is still not known.
- Based on the submission of additional analyses by stakeholders, the effectiveness of rimegepant, ubrogepant, and lasmiditan at 8, 24, and 48 hours was revised to reflect emerging evidence that a greater proportion of patients responded at these timepoints than would otherwise be expected when using only the two-hour response. As a result, the base case was modified to incorporate this increased effect of the three agents beyond two hours and the scenario analysis evaluating this effect was removed from the report.

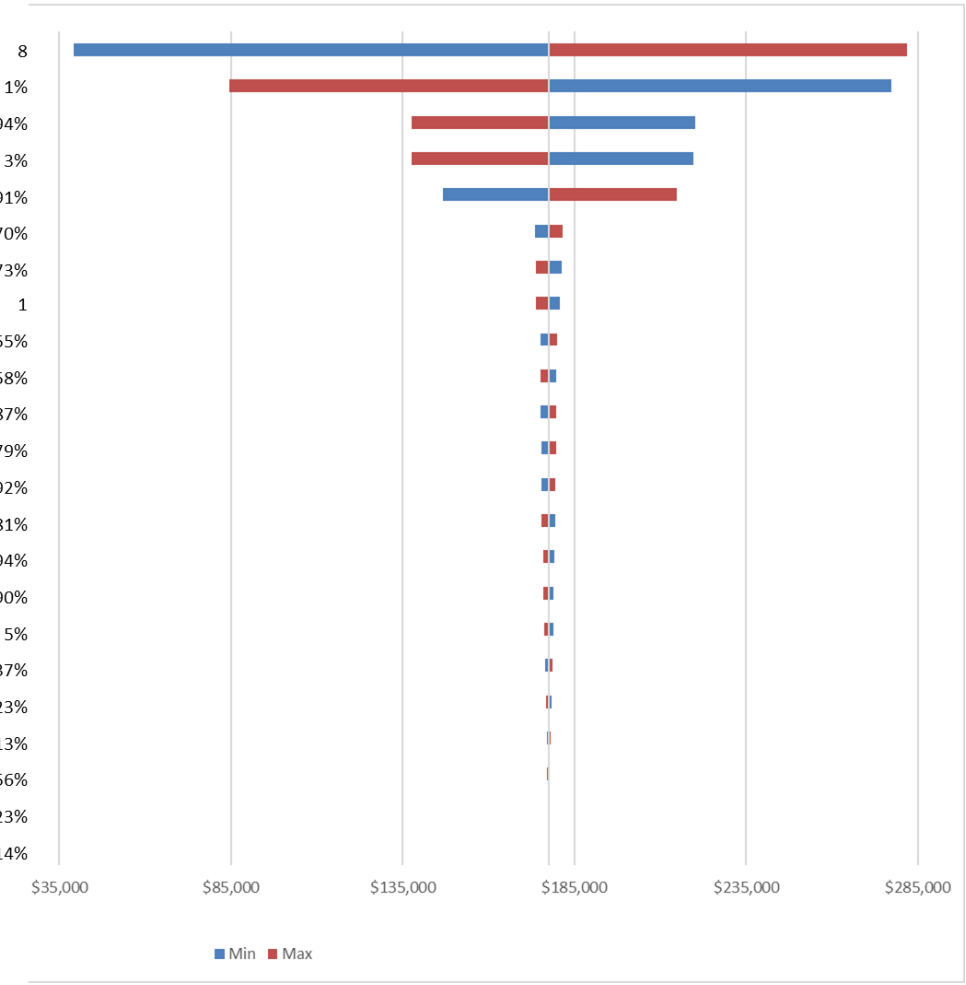
Sensitivity Analysis Results

Since sumatriptan and eletriptan dominated in Population 2, sensitivity analyses were conducted for Population 1 only. The model was sensitive to many of the model inputs. For lasmiditan, the monthly migraine frequency, probability of being hospitalized, probability of having emergency department visits, and proportion with pain relief at 24 hours (in the lasmiditan and/or placebo treatment branches) were considered important variables with the potential to result in incremental cost-effectiveness ratios below $150,000 per QALY gained depending on the input value. For rimegepant and ubrogepant, migraine frequency and probability of hospitalizations had the potential to result in incremental cost-effectiveness ratios above $150,000 per QALY. Tornado diagrams illustrating the impact of input variables on the incremental cost-effectiveness ratios of lasmiditan, rimegepant, and ubrogepant compared with usual care are shown in Figures 4.2.

Figures 4.2. Tornado Diagrams for One-Way Sensitivity Analyses of Lasmiditan, Rimegepant, and Ubrogepant Compared with Usual Care (Placebo)

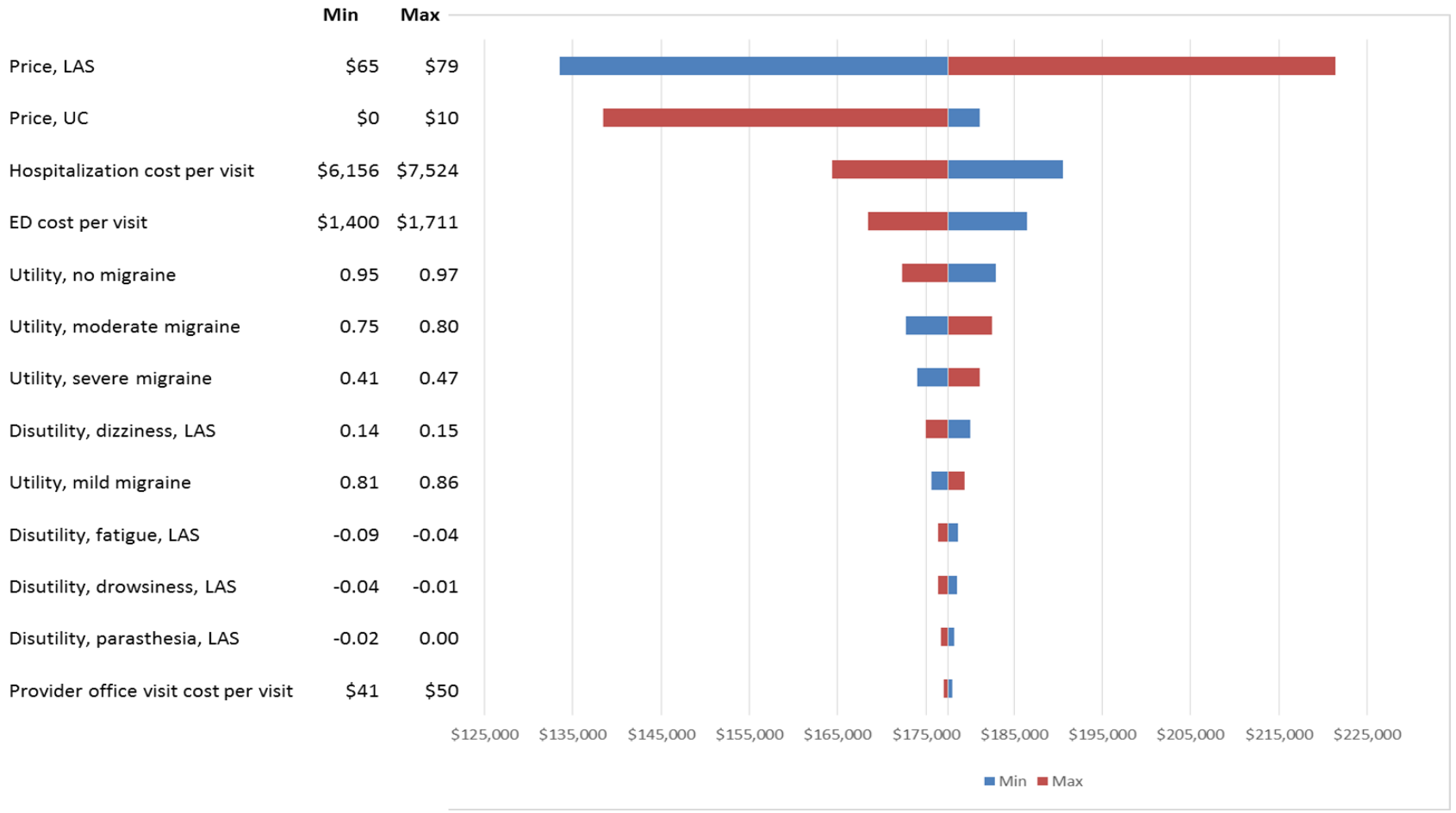
Figure 4.2a. Model Probabilities, Lasmiditan versus Usual Care (Placebo)

	Min	Max
Migraine frequency (new migraines per month)	3	8
Probability of hospitalizations	0%	1%
Probability of 24h pain relief, LAS	92%	94%
Probability of ED visits	1%	3%
Probability of 24h pain relief, UC	89%	91%
Probability of 24h pain free, UC	68%	70%
Probability of 24h pain free, LAS	71%	73%
Probability of improved effectiveness in pts who don't discontinue	0	1
Probability of 8h pain free, UC	53%	55%
Probability of 8h pain free, LAS	56%	58%
Probability of 8h pain relief, UC	86%	87%
Probability of 48h pain free, UC	77%	79%
Probability of 48h pain relief, UC	91%	92%
Probability of 48h pain free, LAS	79%	81%
Probability of 48h pain relief, LAS	93%	94%
Probability of 8h pain relief, LAS	89%	90%
Probability of provider visits due to nausea/vomiting	3%	5%
Probability of 2h pain relief, UC	35%	37%
Probability of 2h pain free, LAS	21%	23%
Probability of 2h pain free, UC	11%	13%
Probability of 2h pain relief, LAS	54%	56%
Probability of discontinuing due to lack of effect, LAS	21%	23%
Discontinuation rate due to adverse events, LAS	12%	14%



LAS: Lasmiditan; UC: Usual Care; ED: emergency department

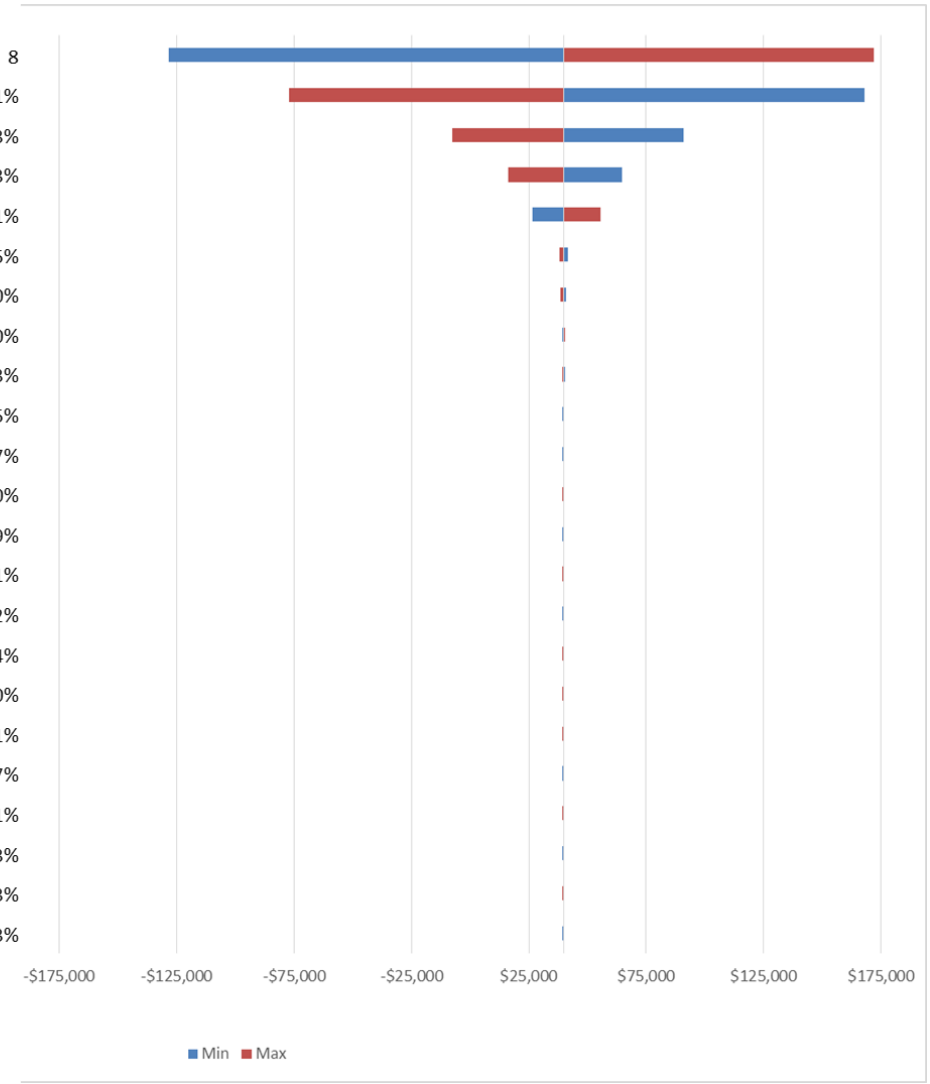
Figure 4.2b. Model Costs and Utilities, Lasmiditan versus Usual Care (Placebo)



LAS: lasmiditan; UC: Usual Care; ED: emergency department

Figure 4.2c. Model Probabilities, Rimegepant versus Usual Care (Placebo)

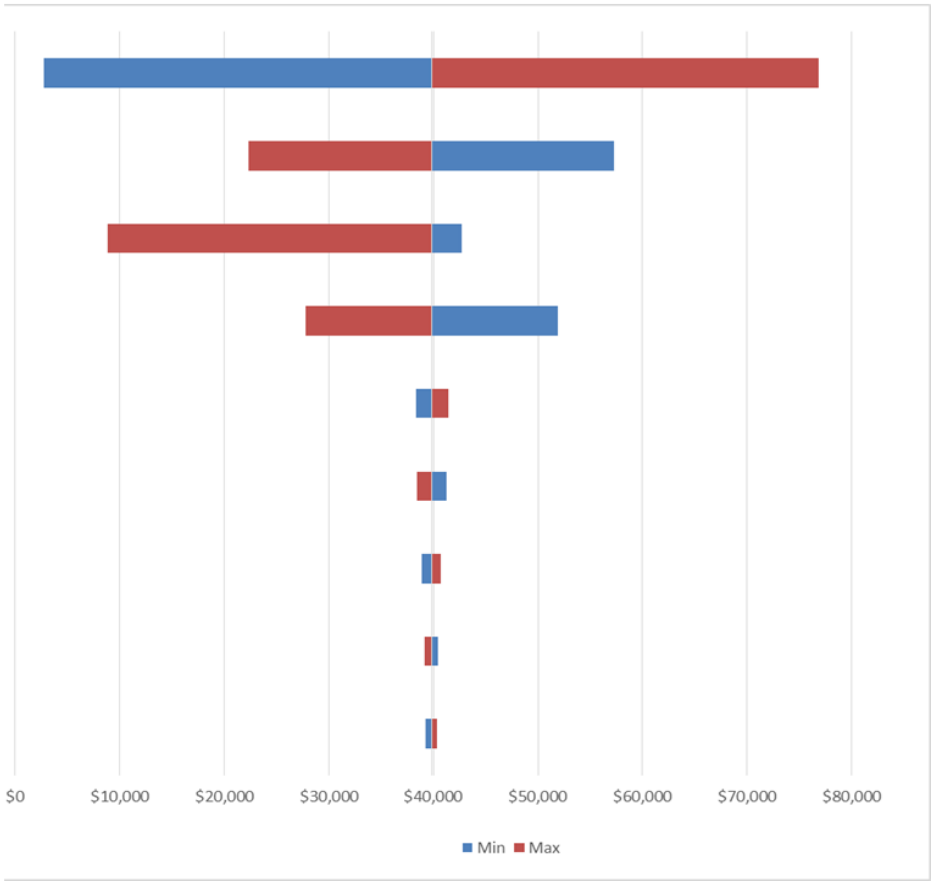
	Min	Max
Migraine frequency (new migraines per month)	3	8
Probability of hospitalizations	0%	1%
Probability of ED visits	1%	3%
Probability of 24h pain relief, RIM	92%	93%
Probability of 24h pain relief, UC	89%	91%
Probability of provider visits due to nausea/vomiting	3%	5%
Probability of improved effectiveness in pts who don't discontinue	0%	100%
Probability of 24h pain free, UC	68%	70%
Probability of 24h pain free, RIM	70%	73%
Probability of 8h pain free, UC	53%	55%
Probability of 8h pain relief, UC	86%	87%
Probability of 8h pain free, RIM	58%	60%
Probability of 48h pain free, UC	77%	79%
Probability of 48h pain free, RIM	79%	81%
Probability of 48h pain relief, UC	91%	92%
Probability of 48h pain relief, RIM	93%	94%
Probability of 8h pain relief, RIM	89%	90%
Probability of 2h pain relief, RIM	49%	51%
Probability of 2h pain relief, UC	35%	37%
Probability of 2h pain free, RIM	19%	21%
Probability of 2h pain free, UC	11%	13%
Discontinuation rate due to lack of effect	21%	23%
Discontinuation rate due to adverse events	2%	3%



RIM: rimegepant; UC: usual care; ED: emergency department

Figure 4.2d. Model Costs and Utilities, Rimegepant versus Usual Care (Placebo)

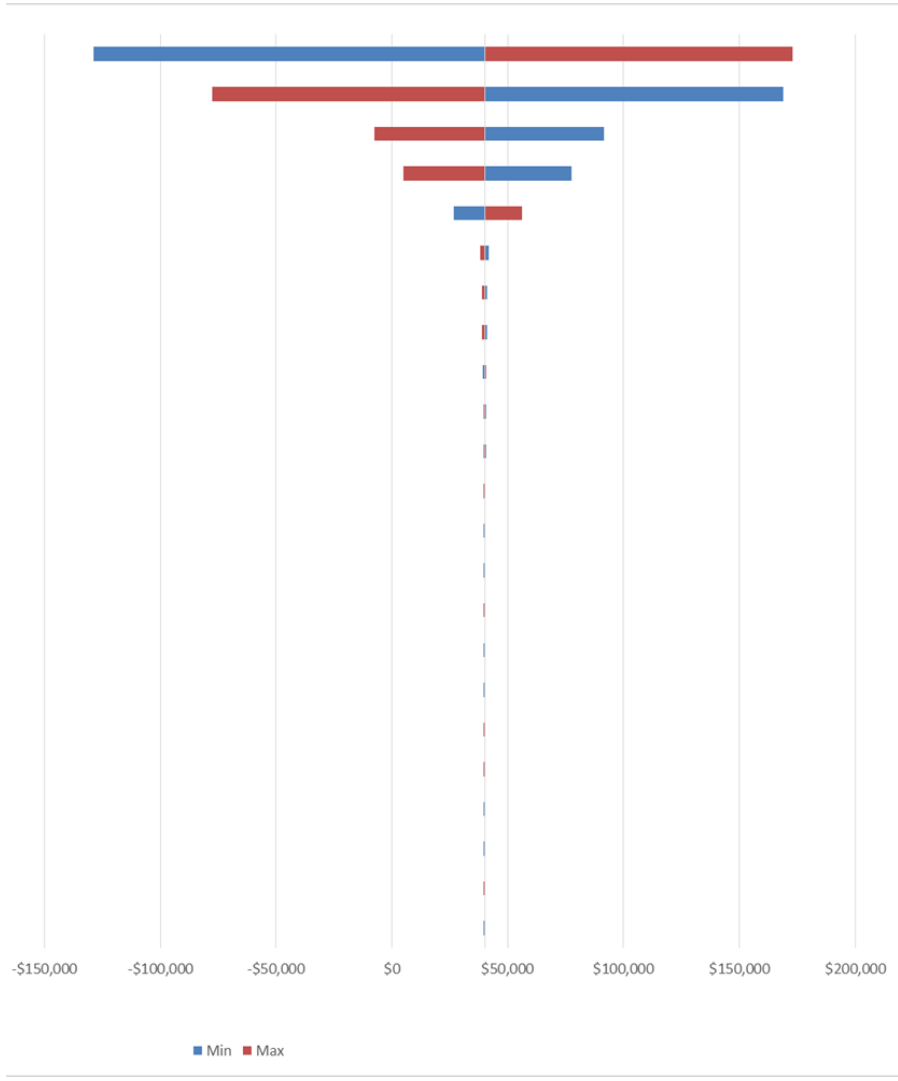
	Min	Max
Price, RIM	$71	$86
Hospitalization Costs per visit	$6,156	$7,524
Price, UC	$0	$10
ED Costs per visit	$1,400	$1,711
Utility, moderate migraine	0.75	0.80
Utility, no migraine	0.95	0.97
Utility, severe migraine	0.41	0.47
Provider office visit cost per visit	$41	$50
Utility, mild migraine	0.81	0.86



RIM: rimegepant; UC: usual care; ED: emergency department

Figure 4.2e. Model Probabilities, Ubrogepant versus Usual Care (Placebo)

	Min	Max
Migraine frequency (new migraines per month)	3	8
Probability of hospitalizations	0%	1%
Probability of ED visits	1%	3%
Probability of 24h pain relief, UBR	91%	93%
Probability of 24h pain relief, UC	89%	91%
Probability of provider visits due to nausea/vomiting	3%	5%
Probability of improved effectiveness in pts who don't discontinue	0	1
Probability of 24h pain free, UBR	70%	73%
Probability of 24h pain free, UC	68%	70%
Probability of 8h pain free, UBR	56%	59%
Probability of 48h pain free, UBR	79%	81%
Probability of 48h pain relief, UBR	92%	94%
Probability of 8h pain free, UC	53%	55%
Probability of 8h pain relief, UC	86%	87%
Probability of 8h pain relief, UBR	88%	90%
Probability of 48h pain free, UC	77%	79%
Probability of 48h pain relief, UC	91%	92%
Probability of 2h pain relief, UBR	47%	51%
Probability of 2h pain free, UBR	20%	22%
Probability of 2h pain relief, UC	35%	37%
Probability of 2h pain free, UC	11%	13%
Discontinuation rate due to lack of effect	21%	23%
Discontinuation rate due to adverse events	2%	3%



UBR: ubrogepant; UC: usual care; ED: emergency department

Figure 4.2f. Model Costs and Utilities, Ubrogepant versus Usual Care (Placebo)

UBR: ubrogepant; UC: usual care; ED: emergency department

Table 4.13 shows the proportion of simulations for which each treatment had the highest net mean benefit at different cost-effectiveness thresholds for lasmiditan, rimegepant, ubrogepant, and usual care. When conducting probabilistic sensitivity analyses on the base case in Population 1, rimegepant and ubrogepant were the most cost-effective options at the $50,000 per QALY gained threshold 36.8% and 47.6% of the time, respectively. Lasmiditan was not considered the most cost-effective option in four-way comparisons at any of the threshold prices. However, when compared with usual care alone, rather than in a four-way comparison, lasmiditan was cost effective at the $100,000 per QALY gained threshold in 5.7% of trials and at the $150,000 per QALY gained threshold in 33.0% of trials.

Table 4.13. Probabilistic Sensitivity Analysis Results: Lasmiditan, Rimegepant, Ubrogepant Compared with Usual Care (Placebo) and each other in Population 1

Treatment Compared with Usual Care	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Lasmiditan	0.0%	0.0%	0.0%
Rimegepant*	36.8%	45.7%	46.5%
Ubrogepant	47.6%	53.5%	53.5%

QALY: quality-adjusted life year

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

Scenario Analyses Results

Modified Societal Perspective

The modified societal perspective included potential labor benefits for reduced migraine pain in the analysis for Population 1. In this scenario, the ICERs for lasmiditan compared to usual care was $57,500, while rimegepant and ubrogepant dominated (i.e. lower cost and higher QALYs gained) usual care.

Other Scenarios

Data from a long-term open-label study suggested that the frequency of migraines decreased over time.[57] In the scenario analysis evaluating the effect of a decreasing migraine frequency over time, total costs were lower, QALYs were higher, and hours of pain were lower for all treatments, including usual care. The cost-effectiveness ratios were similar to the base case.

Extending the timeline to 5 years had almost no effect on the cost-effectiveness estimates for the treatments. The ICERs at 5 years for lasmiditan, rimegepant, and ubrogepant compared with usual care were $176,700, $39,500, and $39,700 per QALY gained, respectively.

The full results of all scenario analyses are presented in the Appendix as tables.

Threshold Analyses Results

Average annual prices that would result in willingness-to-pay thresholds of $50,000 to $150,000 per QALY gained for Population 1 are shown in table 4.14 below.

Table 4.14. Threshold Analysis Results for Population 1 (Patients Who Cannot Take Triptans)

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Lasmiditan	$2,450	$2,900	$3,350
Rimegepant	$3,670	$4,160	$4,640
Ubrogepant	$3,670	$4,150	$4,630

QALY: quality-adjusted life year

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). Model calculations were verified, and model input parameters were varied to evaluate face validity of changes in results. We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

Our systematic review identified 28 potential pharmacoeconomic analyses of migraine therapies. We reviewed all 28 identified studies and found very few economic models for chronic treatment that involved a Markov model or long-term analysis. Also, extremely few included utilities or QALYs as an outcome. When developing the current model, we combined aspects of models for chronic migraine with other aspects from decision trees of acute migraine.[112-123]

Some of the prior cost-effectiveness analyses that were most useful in developing our model examined preventive treatments for episodic and chronic migraine, including topiramate[113] and more recently erenumab.[122,123] We identified three economic analyses of triptans for acute treatment of migraines. Perfetto et al. used a composite outcome measure to compare six triptans on cost per successfully treated patient, with successfully treated defined as requiring only one dose per attack during a 24-hour period.[114] They estimated that eletriptan 40 mg would have the lowest cost per successfully treated patient compared to other triptans. Mullins et al. conducted a similar analysis from a Medicaid perspective, and again found that eletriptan had the lowest cost

per successfully treated patient.[118] Ramsberg and Henriksson analyzed the cost effectiveness of triptan treatment for a single attack from a Swedish societal perspective. They compared the cost per sustained pain-free response without adverse event and found that rizatriptan 10 mg and eletriptan 40 mg had the highest probability of cost effectiveness. However, none of these studies extended beyond the 24-hour time horizon nor estimated cost per LY or QALY ratios, and so could not be directly compared with the current analysis.

4.4 Summary and Comment

In our analysis of the cost effectiveness of lasmiditan, rimegepant, and ubrogepant, we found that for patients for whom triptans are not effective, not tolerated, or are contraindicated, rimegepant (assuming similar pricing to ubrogepant) and ubrogepant are cost effective at commonly used thresholds. These results differed from the prior ICER report because additional post-hoc analyses of data from the trials of ubrogepant suggested a delayed benefit for this drug (and presumably rimegepant) beyond the two-hour primary outcome assessment. As noted in the Update to this report, similar analyses were provided for lasmiditan after the original publication of this report. Lasmiditan continued to slightly exceed commonly accepted thresholds for cost effectiveness. For patients able to take triptans, all of these new agents will be dominated by sumatriptan and eletriptan in that they are both more effective and less expensive. Due to clinical trial designs, there is considerable uncertainty in some estimates used in the base case, such as the impact of the treatments on emergency visits and hospitalizations, pain response at time points beyond two hours, and repeated medication use on migraine frequency. More evidence is required to obtain better precision in cost-effectiveness estimates for lasmiditan, rimegepant, and ubrogepant when compared with usual care.

Limitations

This analysis has several limitations and assumptions that must be considered when evaluating the results. We acknowledge that there is considerable heterogeneity among and even within individuals with migraine in terms of the frequency, severity, and unpredictability of attacks over time. Levels of pain severity (i.e., no, mild, moderate, or severe pain) were not reported in clinical trials. Instead, clinical trials used “freedom from pain” and “pain relief” at 2 hours as their primary outcomes. In addition, response to treatment was not reported for patients who did not have freedom from pain or pain relief at two hours. We therefore had to reconstruct pain levels to be able to apply utilities to the data. In doing so, we took a conservative approach to mapping “pain relief” to levels of pain, with patients potentially deriving more benefit from treatment than was likely observed in clinical trials. The result is that the model relies heavily on the outcomes of “pain freedom” or “pain relief” at two hours. The model was updated from the revised report to address a noted limitation that there may be a delayed onset of action beyond two hours with rimegepant and ubrogepant. Data from clinical trials of ubrogepant and supporting information from

rimegepant trials was used to estimate this delayed effect. However, due to trial designs and the potential for an attrition bias, the magnitude of the delayed effect may be poorly estimated. In addition, such an effect could not be assessed for lasmiditan. This limitation could have a large impact on the estimated cost-effectiveness of these drugs compared with usual care (as estimated by placebo in clinical trials). The effectiveness of sumatriptan and eletriptan compared with usual care (placebo) beyond two hours could also not be estimated. As a result, the model evaluating the new acute treatments compared with triptans (Population 2) did not include delayed benefits after two hours.

Other limitations include that the probability of discontinuing a medication due to ineffective treatment was unknown for rimegepant, ubrogepant, sumatriptan, and eletriptan. As a result, we had to use an estimate derived from lasmiditan. Also, the probabilities for discontinuation due to adverse events were not available for sumatriptan alone or eletriptan. A rate from a trial evaluating sumatriptan plus naproxen was used for both treatments.

Conclusions

In our analysis of the cost effectiveness of lasmiditan, rimegepant, and ubrogepant, we found that for patients for whom triptans are not effective, not tolerated, or are contraindicated (Population 1), rimegepant (assuming similar pricing to ubrogepant) and ubrogepant are cost effective at commonly used thresholds. Lasmiditan slightly exceeds the $150,000 per QALY gained threshold in this population. For patients able to take triptans (Population 2), sumatriptan and eletriptan are both more effective and less expensive than these newer agents. Due to clinical trial designs, there is considerable uncertainty in some estimates used in the base case, such as the impact of the treatments on emergency visits and hospitalizations, pain relief at time points beyond 2 hours, and chronic medication use on migraine frequency. More evidence is required to obtain better precision in cost-effectiveness estimates for lasmiditan, rimegepant, and ubrogepant when compared with usual care.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of lasmiditan, rimegepant and ubrogepant to placebo and triptans (eletriptan and sumatriptan). We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
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.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
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.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
There is significant uncertainty about the long-term risk of serious side effects of this intervention.
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

For patients with migraine attacks, lasmiditan, rimegepant and ubrogepant represent the first new drugs for acute treatment with novel mechanisms of action to be submitted for FDA approval in over 20 years. Lasmiditan was approved on October 11, 2019 by the FDA for acute treatment of migraine and rimegepant and ubrogepant remain under review. These new therapies reflect translational research in which improved understanding of the mechanisms of disease has led to new therapeutics. Lasmiditan, the first ditan approved for use in the US, targets the 5HT1F (5-hydroxytryptamine 1F) receptor, and unlike the triptans does not induce vasoconstriction. The gepants, target CGRP, a peptide neural transmitter found in the pathways that play an important role in migraine. Monoclonal drugs that block CGRP have already been approved by the FDA for migraine prevention. Rimegepant and ubrogepant are the first small molecule gepants under review for relieving migraine attacks.

Similar to most triptans, lasmiditan, rimegepant and ubrogepant are orally available medications and would not be expected to increase the complexity of care. The favorable side effects seen to date with rimegepant and ubrogepant, similar to those seen with placebo, may make these medications attractive to patients and clinicians. The restriction on driving after taking lasmiditan is a potential other disadvantage of that therapy.

Patients and advocates expressed the hope that these new therapies for patients with migraine may provide an effective and safe alternative for individuals who may turn to opioids and barbiturates because existing therapies are not effective, have intolerable side effects, or are not recommended because of the risk of misuse.

5.2 Contextual Considerations

For new medications that have mainly been evaluated in single dose comparative trials or non-comparative open-label studies of up to a year, there is uncertainty about their effects in actual clinical practice over time. Available data suggests that patients can use lasmiditan, rimegepant and ubrogepant for up to a year. However, the long-term benefits and harms of lasmiditan, rimegepant and ubrogepant are uncertain relative to other therapies that have years of experience.

For patients who improve with lasmiditan, rimegepant or ubrogepant and have tolerable side effects, it is expected that prolonged use for migraine attacks will be recommended. Questions remain about the duration of effectiveness, development of new side effects, and the risk of medication overuse headaches with frequent use. Lasmiditan, rimegepant and ubrogepant have not been shown to cause vasoconstriction, but whether they are free of cardiovascular adverse effects, particularly in those with cardiovascular disease or at high risk, remains to be proven.

The availability of new treatments for migraine is likely to allow some patients to remain at work in situations where they would otherwise have needed to miss or leave work.

6. Value-Based Price Benchmarks

Annual value-based price benchmarks (VBPBs) of these drugs (vs. usual care) are presented in Table 6.1. The VBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. The results in this section have been updated based on the above Update to this report.

For lasmiditan, price discounts of 27% from the list price would be required to reach the $150,000 per QALY threshold price (Table 6.1). Price discounts of approximately 37% from list prices would be required to reach the $100,000 per QALY threshold price range. For ubrogepant, price discounts of 5% and 15% would be required to reach the $150,000 and $100,000 threshold prices, respectively. The WAC is not currently available for rimegepant. We have estimated required price discounts in Table 6.1, given the assumption that rimegepant will be priced the same as ubrogepant when a WAC becomes available. Note that for ubrogepant (and rimegepant at that assumed list price), the discount from WAC required to reach these thresholds is less than the 27% discount assumed in our base case analysis.

As there is no mortality effect in the model, cost per LY gained is not relevant, and the cost per evLYG is essentially the same as the cost per QALY gained. We therefore do not report VBPBs for these in the table below.

Table 6.1. Value-Based Price Benchmark Ranges for Lasmiditan, Rimegepant, and Ubrogepant versus Usual Care in Population 1 (Patients Who Cannot Take Triptans)

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC Required to Achieve Threshold Prices
Lasmiditan	$4,610	$2,900	$3,350	27%-37%
Rimegepant*	Not available (Estimated at $4,896)	$4,160	$4,640	WAC not available
Ubrogepant	$4,896	$4,150	$4,630	5%-15%

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Rimegepant price estimated using ubrogepant WAC. The WAC has not been released for rimegepant.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of each drug (lasmiditan, rimegepant, and ubrogepant) for prevalent individuals in the United States (US) aged 18 years and over experiencing migraines requiring acute treatment, with or without aura. We also included a scenario analysis where the frequency of migraines is assumed to decrease over time.

We used the WAC, assumed net price, and three threshold prices for lasmiditan and ubrogepant in our estimates of budget impact. As the price for rimegepant was not available, we assumed the same WAC and net price as for ubrogepant.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis does not include the population cohort of patients with migraines who are eligible for treatment with triptans, as sumatriptan and eletriptan dominated these drugs in our cost-effectiveness analysis. This potential budget impact analysis includes the cohort of 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. To estimate the size of the potential candidate population for treatment, we first used an estimate derived from the 2012 National Health Interview Survey of 14.2% for the prevalence of US adults 18 or older reporting having migraine or severe headache.[4] The American Migraine Prevalence and Prevention Study found in a survey of migraine patients that 48.9% reported using prescription medicines (only or sometimes) for acute treatment.[124] Based on an estimate that triptans work in approximately 60% to 70% of migraine patients,[125] we assumed that 35% of migraine patients attempting prescription treatments would fall into this non-triptan cohort. We applied these estimated proportions to the average 2020-2024 estimated US adult population to arrive at an eligible population size of approximately 6.4 million patients, or approximately 1.3 million patients each year over five years. We assumed in our analysis of potential budget impact in this population

that each drug would be added to usual care, rather than displacing other migraine-specific treatments.

ICER's methods for estimating potential budget impact are described in detail elsewhere[126] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

7.3 Base-Case Results

Results have not been updated based on the above Update to this report.

Table 7.1 illustrates the five-year annualized per-patient potential budget impact of lasmiditan compared to usual care in this population. These results are based on the WAC ($4,610 per year), assumed net price ($3,360 per year), and the annual threshold prices $150,000, $100,000, and $50,000 per QALY versus usual care ($3,150, $2,770, and $2,390, respectively).

Table 7.1. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Lasmiditan versus Usual Care

	Average Annual Per Patient Budget Impact				
	At WAC	At Net Price*	At $150,000/QALY Price	At $100,000/QALY Price	At $50,000/QALY Price
Lasmiditan	$7,020	$6,130	$5,980	$5,710	$5,430
Usual Care	$5,160				
Net Impact	$1,860	$970	$820	$550	$270

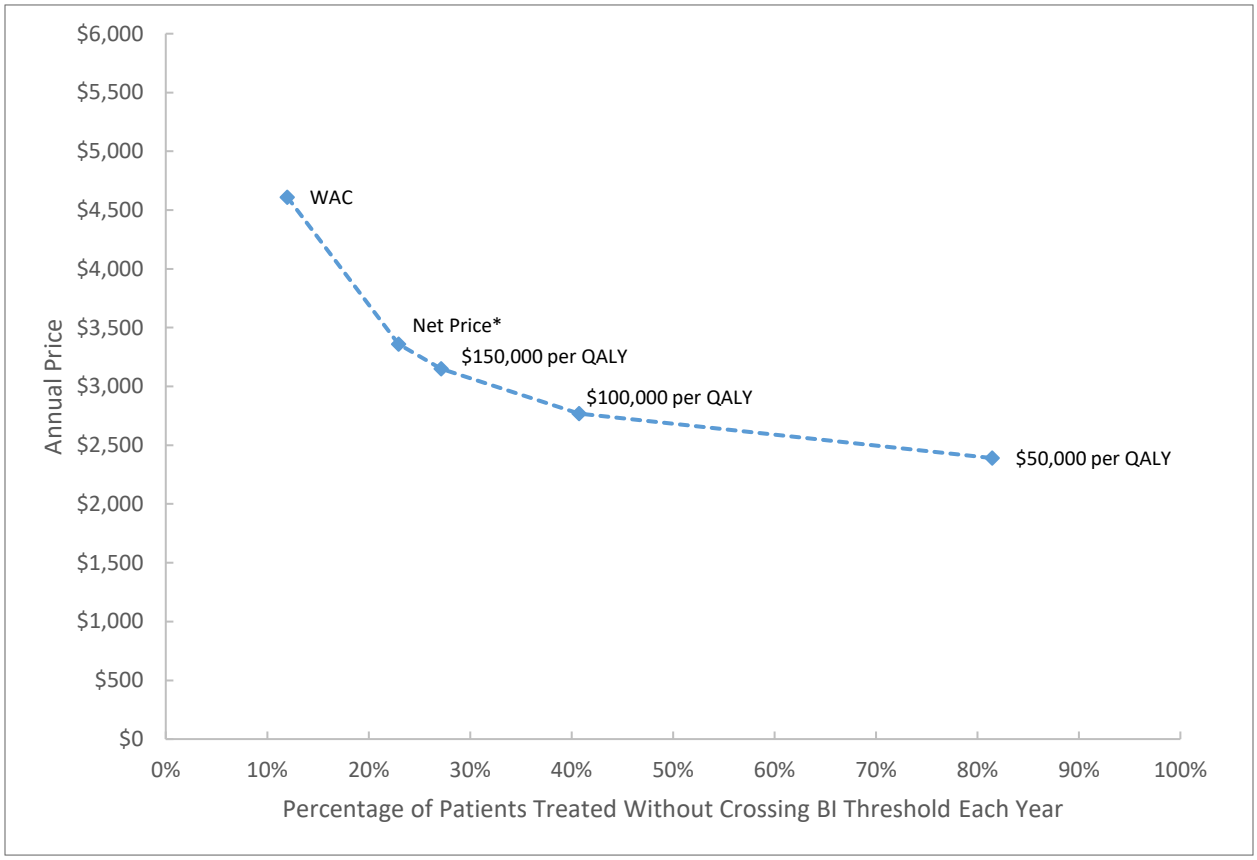
*Assumed 27% discount.
All annualized costs include drug and non-drug health care costs.
QALY: quality-adjusted life year

For lasmiditan, the average annualized potential budgetary impact when using its assumed net price was an additional per-patient cost of approximately $970 versus usual care, while it would be approximately $1,860 at WAC. Its average annualized potential budget impact versus usual care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $270 per patient to approximately $820 per patient.

In this population, as shown in Figure 7.1, approximately 12% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at lasmiditan's WAC.

Approximately 23% of eligible patients could be treated without crossing the budget impact threshold at its assumed net price. Approximately 27% of eligible patients could be treated at the price to reach the cost-effectiveness threshold of $150,000 per QALY, increasing to approximately 82% at the $50,000 threshold price.

Figure 7.1. Potential Budget Impact Scenarios of Lasmiditan versus Usual Care at Different Acquisition Prices



*Assumed 27% discount
BI: budget impact, QALY: quality-adjusted life year

Table 7.2 illustrates the five-year annualized per-patient potential budget impact of rimegepant compared to usual care in the same population. These results are based on the assumed placeholder WAC and net prices ($4,896 and $4,640 per year, respectively), and the annual threshold prices for $150,000, $100,000, and $50,000 per QALY versus usual care ($4,160, $3,670, and $3,570, respectively).

Table 7.2. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Rimegepant versus Usual Care

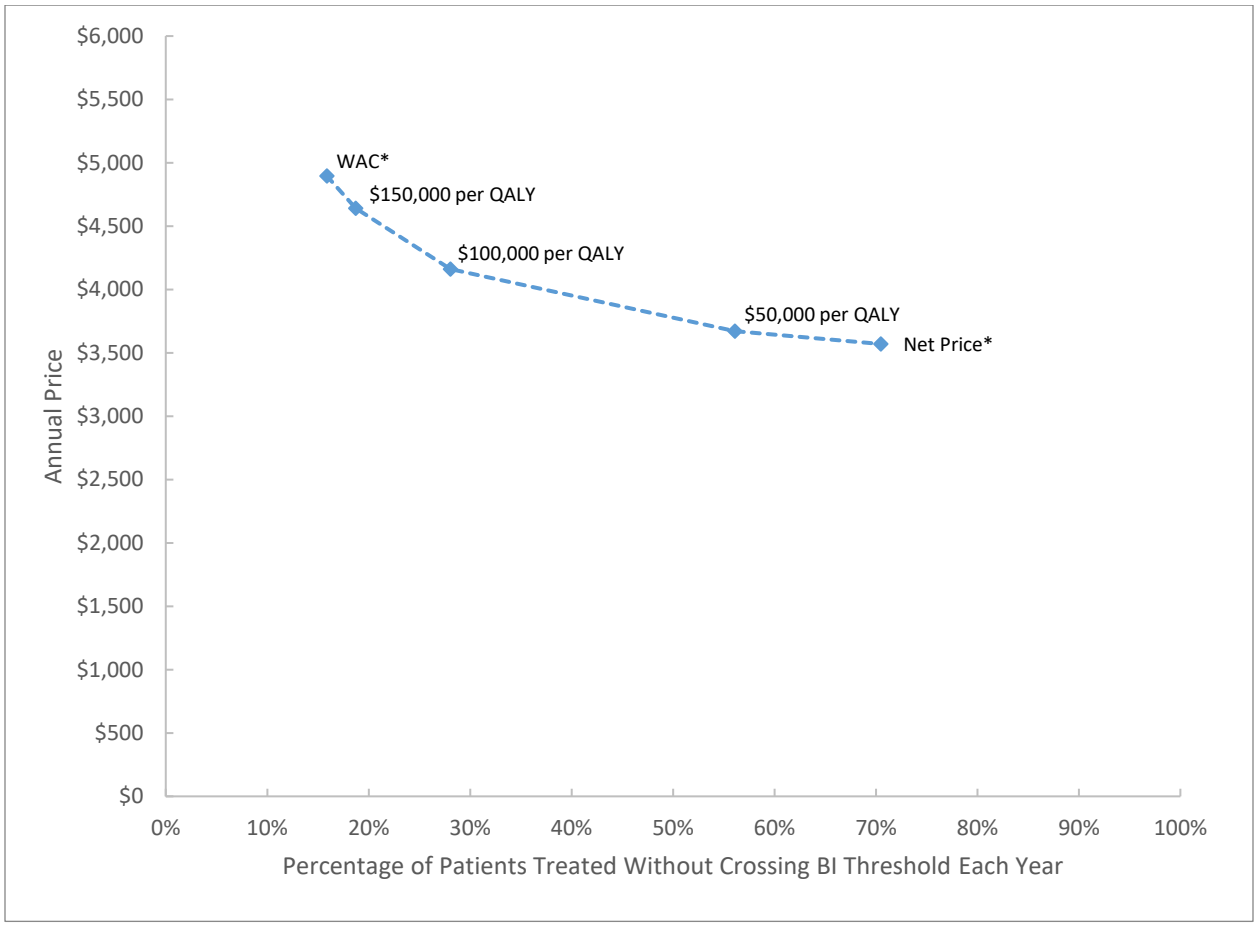
	Average Annual Per Patient Budget Impact				
	At Placeholder WAC*	At Placeholder Net Price*	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Rimegepant	$6,530	$5,470	$6,330	$5,940	$5,550
Usual Care	$5,160				
Net Impact	$1,370	$310	$1,170	$780	$390

All annualized costs include drug and non-drug health care costs.
QALY: quality-adjusted life year
*Assumed placeholder WAC and net price equal to ubrogepant's WAC and assumed net price (27% discount from WAC).

For rimegepant, the average annualized potential budgetary impact when using its assumed WAC was an additional per-patient cost of approximately $1,370 versus usual care. The average annualized potential budgetary impact when using the assumed net price was an additional cost of only $310 per patient versus usual care. Its average annualized potential budget impact versus usual care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $390 per patient to approximately $1,170 per patient.

As shown in Figure 7.2, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at rimegepant's assumed WAC. Approximately 19% of eligible patients could be treated without crossing the budget impact threshold at the $150,000 threshold price, increasing to approximately 56% at the price to reach $50,000 per QALY. Approximately 71% of eligible patients could be treated at the assumed net price.

Figure 7.2. Potential Budget Impact Scenarios of Rimegepant vs. Usual Care at Different Acquisition Prices



*Assumed placeholder WAC and net price equal to ubrogepant's WAC and assumed net price (27% discount from WAC).

BI: budget impact, QALY: quality-adjusted life year

Table 7.3 illustrates the five-year annualized per-patient potential budget impact of ubrogepant compared to usual care in this population. These results are based on the WAC ($4,896 per year), assumed net price ($3,570 per year), and the annual threshold prices for $150,000, $100,000, and $50,000 per QALY versus usual care ($4,630, $4,150, and $3,670, respectively).

Table 7.3. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Ubrogepant versus Usual Care

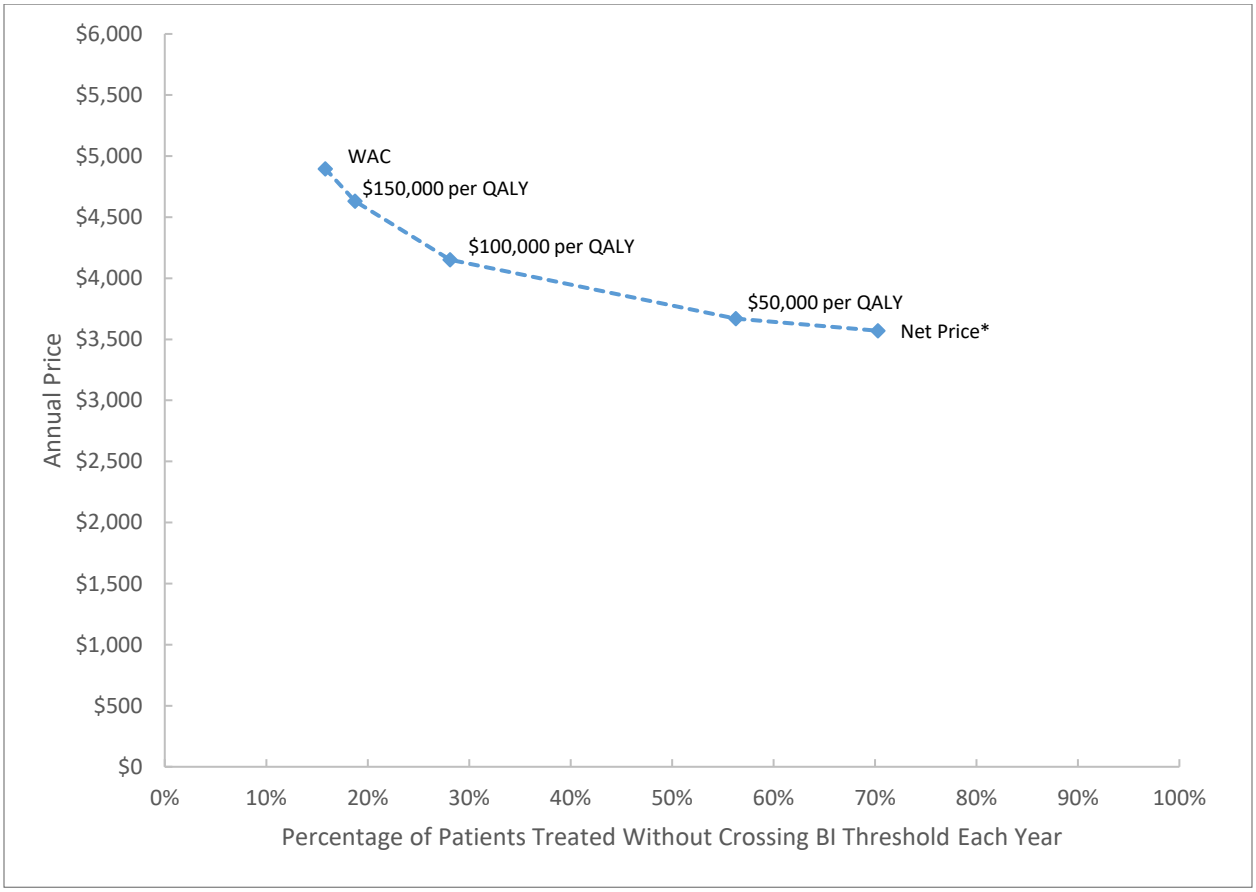
	Average Annual Per Patient Budget Impact				
	At WAC	At Net Price*	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Ubrogepant	$6,540	$5,470	$6,320	$5,930	$5,550
Usual Care	$5,160				
Net Impact	$1,380	$310	$1,160	$780	$390

All annualized costs include drug and non-drug health care costs.
QALY: quality-adjusted life year
*Assumed 27% discount

For ubrogepant, the average annualized potential budgetary impact at WAC was an additional per-patient cost of approximately $1,380 versus usual care. Its average annualized potential budget impact versus usual care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $390 per patient to approximately $1,160 per patient. The average annualized potential budgetary impact when using its assumed net price was an additional per-patient cost of only approximately $310 versus usual care.

As shown in Figure 7.3, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at ubrogepant's WAC. Approximately 19% of eligible patients could be treated without crossing the budget impact threshold at the $150,000 threshold price, increasing to approximately 56% at the price to reach $50,000 per QALY. Approximately 70% of eligible patients could be treated at the assumed net price.

Figure 7.3. Potential Budget Impact Scenarios of Ubrogepant versus Usual Care at Different Acquisition Prices



*Assumed 27% discount BI: budget impact, QALY: quality-adjusted life year

7.4 Scenario Results

Data from a long-term open label safety study suggests that the frequency of migraines decreased over time.[57] While this single-arm trial was not designed to evaluate whether the same effect was observed in a control population, decreasing migraine frequency over time could have a significant impact on budget impact analyses. We therefore created a scenario analysis where we modeled the potential budget impact of these treatments if migraine frequency decreases over time.

Table 7.4 illustrates the five-year annualized per-patient potential budget impact of lasmiditan compared to usual care under this scenario. These results are based on the WAC ($4,610 per year), assumed net price ($3,360 per year), and the same annual prices for thresholds of $150,000, $100,000, and $50,000 per QALY versus usual care ($3,150, $2,770, and $2,390, respectively).

Table 7.4. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Lasmiditan versus Usual Care: Decreased Frequency Scenario

	Average Annual Per Patient Budget Impact				
	At WAC	At Net Price*	At $150,000/QALY Price	At $100,000/QALY Price	At $50,000/QALY Price
Lasmiditan	$4,930	$4,290	$4,180	$3,990	$3,790
Usual Care	$3,590				
Net Impact	$1,330	$700	$590	$390	$200

*Assumed 27% discount.

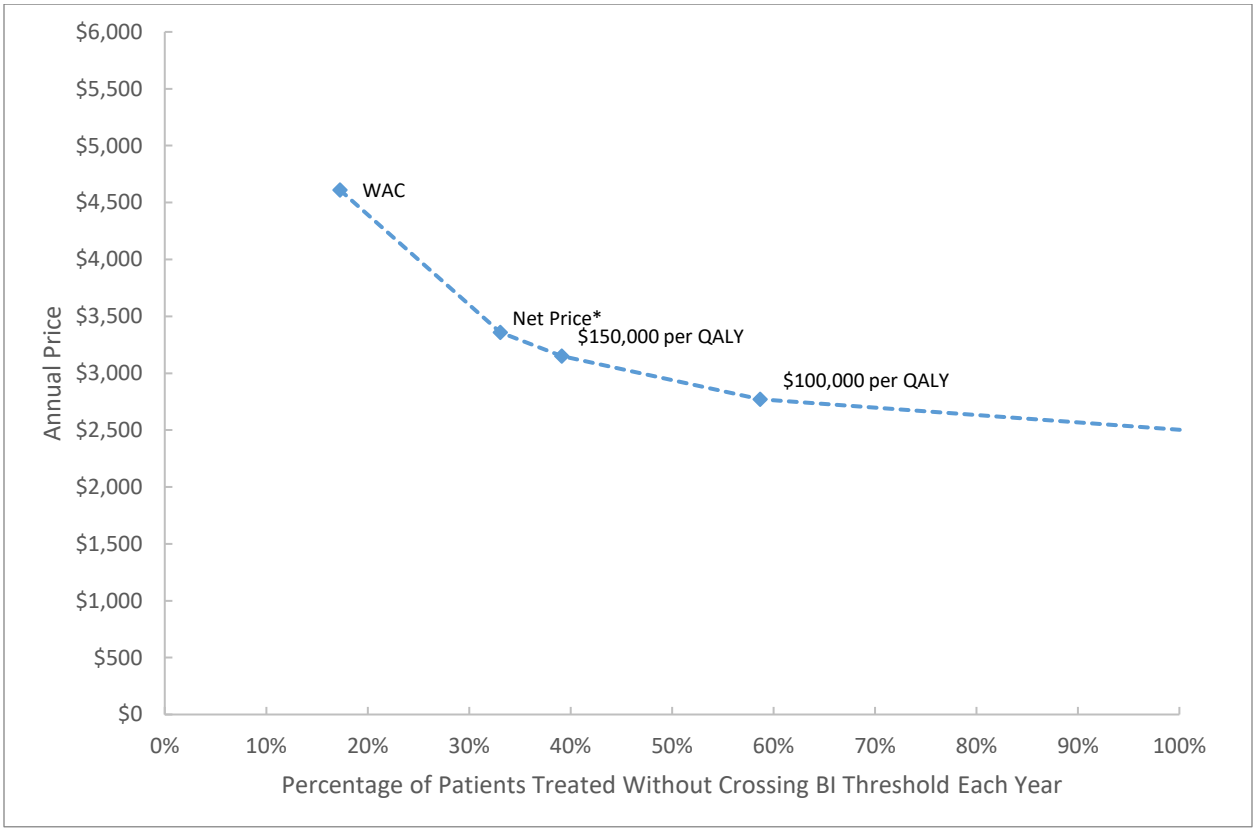
All annualized costs include drug and non-drug health care costs.

QALY: quality-adjusted life year

For lasmiditan, the average annualized potential budgetary impact when using its assumed net price was an additional per-patient cost of approximately $700 versus usual care, while it would be approximately $1,330 at WAC. Its average annualized potential budget impact versus usual care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $200 to approximately $590 per patient.

In this scenario, as shown in Figure 7.4, approximately 17% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at lasmiditan's WAC. Approximately 33% of eligible patients could be treated without crossing the budget impact threshold at its assumed net price. Approximately 39% of eligible patients could be treated at the price to reach the cost-effectiveness threshold of $150,000 per QALY, increasing to approximately 59% at the $100,000 threshold price. All eligible patients could be treated at the $50,000 per QALY threshold price, with estimated potential budget impact of approximately 85% of the threshold.

Figure 7.4. Potential Budget Impact Scenarios of Lasmiditan versus Usual Care at Different Acquisition Prices: Decreased Frequency Scenario



*Assumed 27% discount.
BI: budget impact, QALY: quality-adjusted life year

Table 7.5 illustrates the five-year annualized per-patient potential budget impact of rimegepant compared to usual care in the decreased frequency scenario. These results are based on the assumed placeholder WAC and net prices ($4,896 and $4,640 per year, respectively), and the same annual prices for thresholds of $150,000, $100,000, and $50,000 per QALY versus usual care ($4,160, $3,670, and $3,570, respectively).

Table 7.5. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Rimegepant versus Usual Care: Decreased Frequency Scenario

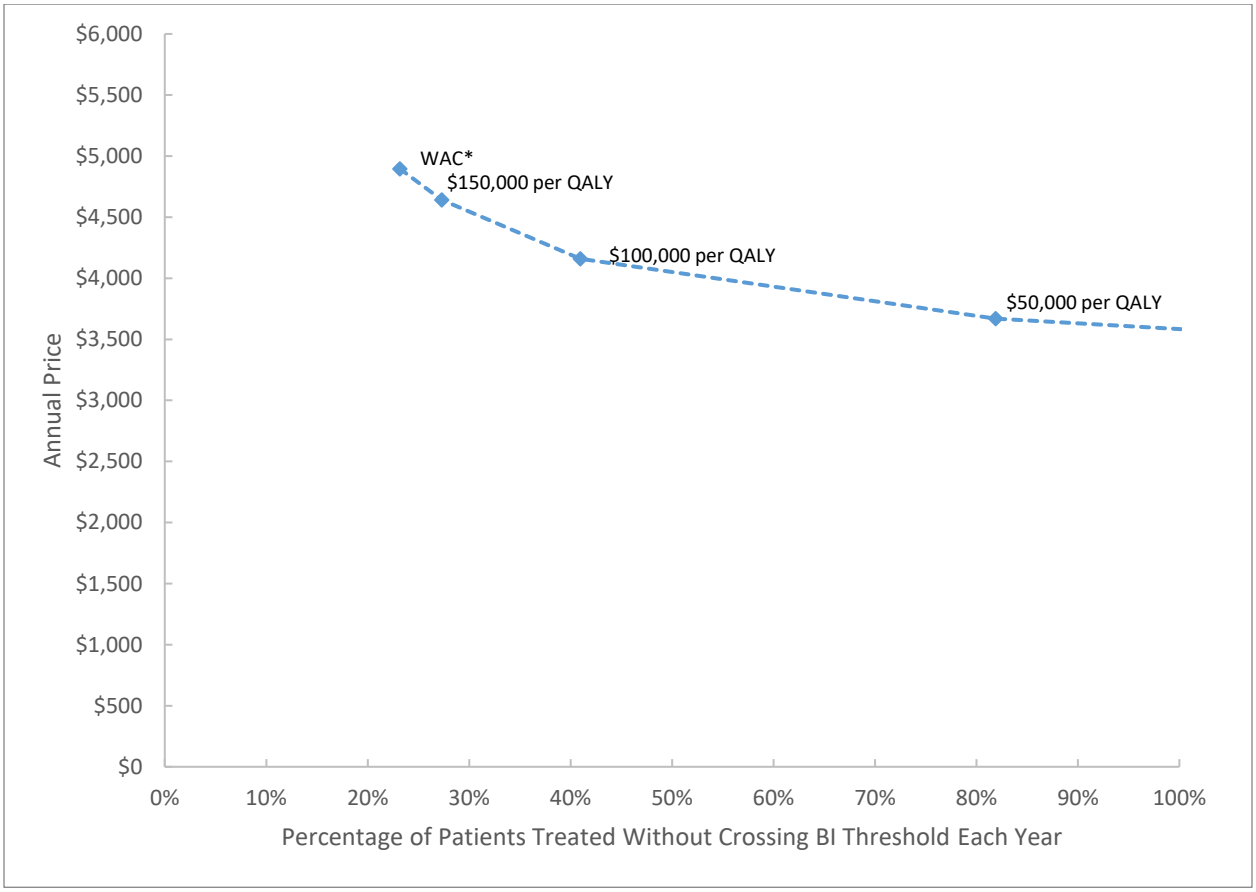
	Average Annual Per Patient Budget Impact				
	At Placeholder WAC*	At Placeholder Net Price*	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Rimegepant	$4,570	$3,810	$4,420	$4,150	$3,870
Usual Care	$3,590				
Net Impact	$970	$220	$830	$550	$280

All annualized costs include drug and non-drug health care costs.
QALY: quality-adjusted life year
*Assumed placeholder WAC and net price equal to ubrogepant's WAC and assumed net price (27% discount from WAC).

For rimegepant in this decreased frequency scenario, the average annualized potential budgetary impact when using its assumed WAC was an additional per-patient cost of approximately $970 versus usual care. The average annualized potential budgetary impact when using the assumed net price was an additional cost of only $220 per patient versus usual care. Its average annualized potential budget impact versus usual care at the threshold prices to reach cost-effectiveness thresholds of $50,000 to $150,000 per QALY ranged from approximately $280 per patient to approximately $830 per patient.

As shown in Figure 7.5, approximately 23% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at rimegepant's assumed WAC. Approximately 27% of eligible patients could be treated without crossing the budget impact threshold at the $150,000 threshold price, increasing to approximately 82% at the price to reach $50,000 per QALY. All eligible patients could be treated at the assumed net price, with estimated potential budget impact of approximately 97% of the threshold.

Figure 7.5. Potential Budget Impact Scenarios of Rimegepant versus Usual Care at Different Acquisition Prices: Decreased Frequency Scenario



*Assumed placeholder WAC and net price equal to ubrogepant's WAC and assumed net price (27% discount from WAC).

BI: budget impact, QALY: quality-adjusted life year

Table 7.6 illustrates the five-year annualized per-patient potential budget impact of ubrogepant compared to usual care under the decreased frequency scenario. These results are based on the WAC ($4,896 per year), assumed net price ($3,570 per year), and the same annual prices for thresholds of $150,000, $100,000, and $50,000 per QALY versus usual care ($4,630, $4,150, and $3,670, respectively).

Table 7.6. Annualized Per-Patient Potential Budget Impact over a Five-year Time Horizon for Ubrogepant versus Usual Care: Decreased Frequency Scenario

	Average Annual Per Patient Budget Impact				
	At WAC	At Net Price*	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Ubrogepant	$4,570	$3,810	$4,420	$4,140	$3,870
Usual Care	$3,590				
Net Impact	$980	$220	$820	$550	$270

QALY: quality-adjusted life year

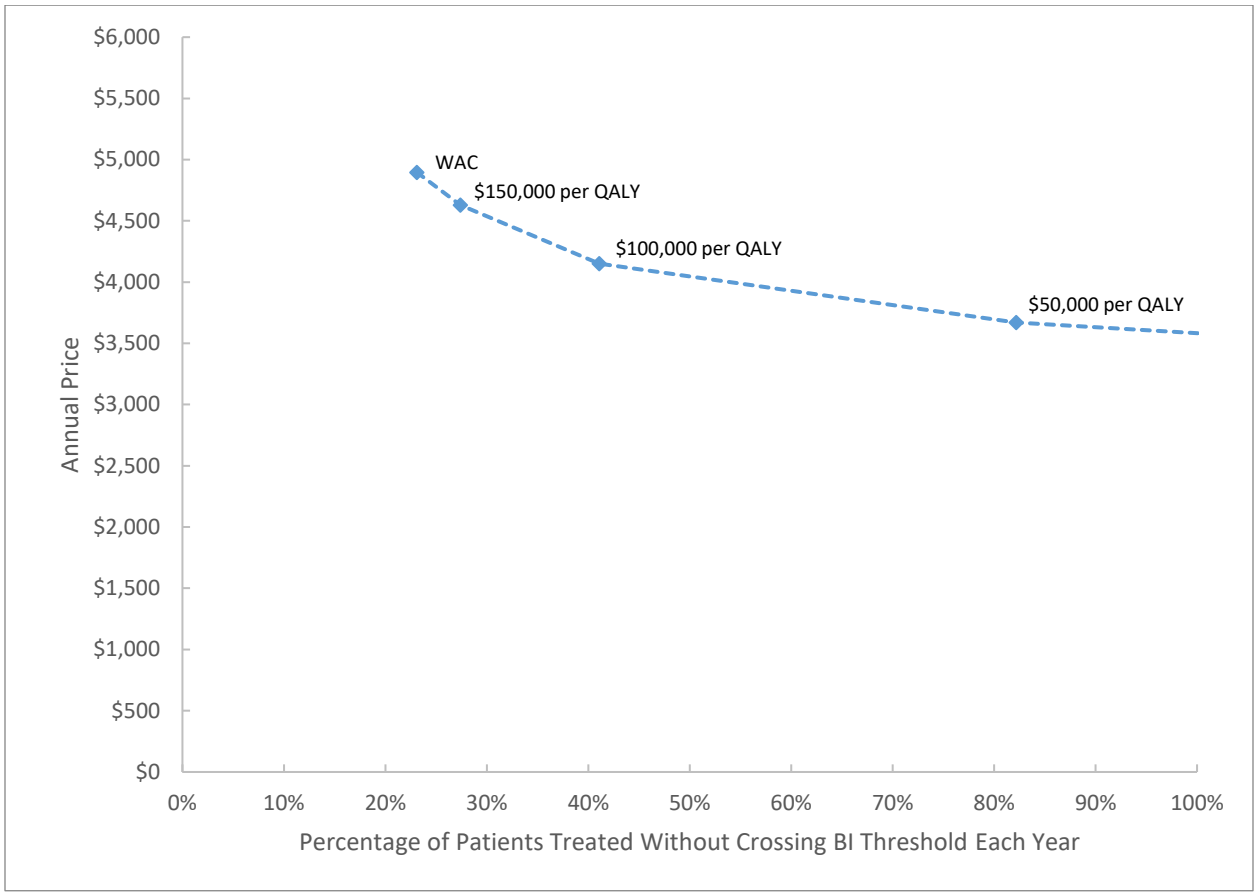
*Assumed 27% discount

All annualized costs include drug and non-drug health care costs.

For ubrogepant in this scenario, the average annualized potential budgetary impact at WAC was an additional per-patient cost of approximately $980 versus usual care. Its average annualized potential budget impact versus usual care at threshold prices to reach cost-effectiveness thresholds of $50,000 to $150,000 per QALY ranged from approximately $270 per patient to approximately $820 per patient. The average annualized potential budgetary impact when using its assumed net price was an additional per-patient cost of only approximately $220 versus usual care.

As shown in Figure 7.6, approximately 23% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at ubrogepant's WAC. Approximately 27% of eligible patients could be treated without crossing the budget impact threshold at its price to reach the cost-effectiveness threshold of $150,000, increasing to approximately 82% at the price to reach $50,000 per QALY. All eligible patients could be treated at the assumed net price, with estimated potential budget impact of approximately 97% of the threshold.

Figure 7.6. Potential Budget Impact Scenarios of Ubrogepant vs. Usual Care at Different Acquisition Prices: Decreased Frequency Scenario



*Assumed 27% discount.

BI: budget impact, QALY: quality-adjusted life year

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the January 23, 2020 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of lasmiditan, rimegepant, and ubrogepant among adults for the acute treatment of migraine. Following the evidence presentation and public comments (public comments from the meeting can be accessed here), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to the use of lasmiditan, ubrogepant, and rimegepant for acute treatment of migraine. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

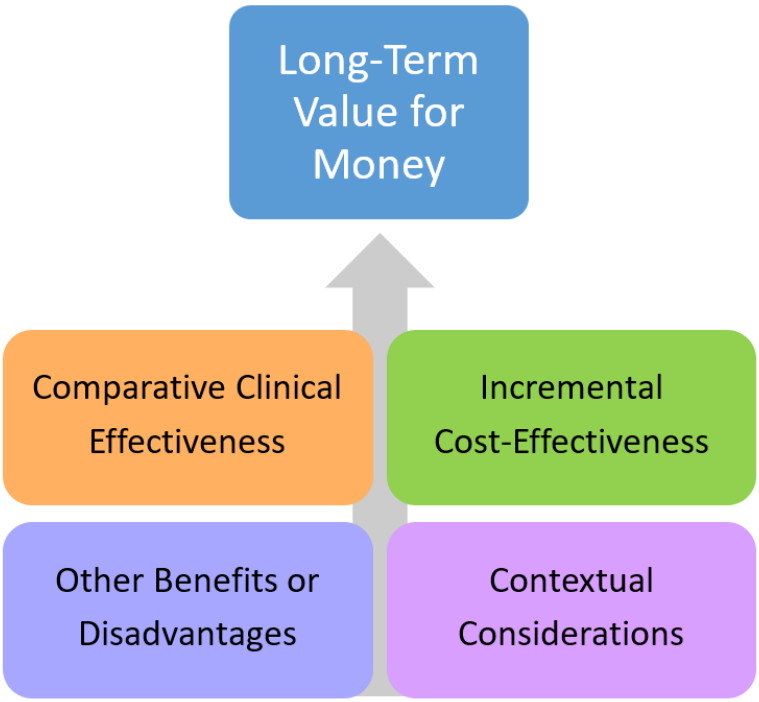
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base-case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

Clinical Evidence

Population for Questions 1-7: *All adults patients with a diagnosis of migraine.*

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

Yes: 12 votes	No: 0 votes

The Council unanimously judged that the evidence was adequate to demonstrate a net health benefit for treatment with lasmiditan compared with no treatment in adult patients with a diagnosis of migraine. Council members noted that the evidence from the clinical trials showed a statistically- and clinically-significant benefit in pain freedom and pain relief at 2 hours compared to placebo net benefit.

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

Yes: 12 votes	No: 0 votes

The Council unanimously judged that the evidence was adequate to demonstrate a net health benefit for treatment with rimegepant compared with no treatment in adult patients with a diagnosis of migraine. The rationale for this yes vote was similar to question one.

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

Yes: 12 votes	No: 0 votes

The Council unanimously judged that the evidence was adequate to demonstrate a net health benefit for treatment with ubrogepant compared with no treatment in adult patients with a diagnosis of migraine. The rationale for this yes vote was similar to question one.

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

Yes: 0 votes	***No: 12 votes***

The Council unanimously voted that the evidence was inadequate to distinguish the net health benefits between the gepants, rimegepant and ubrogepant due to the lack of direct evidence comparing the therapies, and because results from the indirect analyses (NMA) were not statistically significant. One panelist remarked that they would prefer to see future head-to-head trials to determine if there is a difference between the gepants.

If yes:

4a. Which therapy, rimegepant or ubrogepant, has the greater net health benefit?

No vote taken

No vote was taken on Question 4a because the Council voted no on question four.

5. Is the evidence adequate to demonstrate that the **gepants** have a superior net health benefit compared to **triptans**?

Yes: 0 votes	***No: 12 votes***

The Council unanimously judged that the evidence was not adequate to demonstrate that gepants have a positive net health benefit compared to triptans in adult patients with a diagnosis of migraine. One Council member noted that, if anything, the evidence from the NMA results shows that the converse may be true — that triptans demonstrate a superior net health benefit compared to gepants — as the gepants had significantly lower odds of achieving pain relief at 2 hours than the triptans.

The Council highlighted heterogeneity within the patient population, noting that there may be some patients who respond to triptans but not gepants and vice versa, and highlighted that it is important that prescribers and patients work together to determine the drug class that is most effective and least hazardous for the individual patient A clinical expert raised the notion that efficacy may not always be the biggest driver of which treatment clinicians elect to prescribe, and it's possible that clinicians may be more willing to prescribe gepants due to their fewer known side effects compared to the triptans.

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

Yes: 0 votes	***No: 12 votes***

The Council unanimously judged that the evidence was not adequate to demonstrate that lasmiditan has a superior net health benefit compared to triptans in adult patients with a diagnosis of migraine. Several panelists found the results of an NMA demonstrating a significantly lower proportion of patients achieving pain relief/freedom at 2-hours compared to triptans to be persuasive.

7. Is the evidence adequate to distinguish the net health benefits between the **gepants** and **lasmiditan**?

Yes: 1 vote	***No: 11 votes***

The majority of the Council judged that the evidence was not adequate to distinguish the net health benefits between the gepants and lasmiditan in adult patients with a diagnosis of migraine. Several panelists cited that lasmiditan's slightly higher odds of achieving pain freedom/relief was not statistically significant in the indirect comparisons. Most panelists also acknowledged higher discontinuation rates seen with lasmiditan may indicate worse adverse events compared to gepants. One panelist noted that the possibility that lasmiditan and the gepants are equivalent still exists; thus, the evidence is inadequate to distinguish between them.

The panelist who voted in the positive noted that lasmiditan's slightly increased efficacy does not outweigh its higher rate of adverse events compared to the gepants.

If yes:

7a. Which therapy, **gepants** or **lasmiditan**, has the greater net health benefit?

No vote taken

No vote was taken on question 7a because a majority of the council voted no on question seven.

Potential Other Benefits or Disadvantages and Contextual Considerations

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)

This intervention will significantly reduce caregiver or broader family burden.	**11/12**
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.	**12/12**
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity	**11/12**
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention	**See below**

A majority of the council members voted that treating patients with gepants will significantly reduce caregiver or broader family burden and will also have a significant impact on improving patients' ability to return to work and/or their overall productivity in patients who show response to gepants. The council voted unanimously that treating patients with gepants offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. A majority of Council members also noted that treating patients with gepants may have a significant impact on improving patients' ability to return to work and their overall productivity.

Discussion during the vote underscored the challenges women with migraine face when caring for their children or caring for their elderly parents. The Council agreed that while some of these elements are captured in their vote regarding caregiver or broader family

burden, an additional important factor should be captured as women are predisposed to this disease and are an underserved population. The Council unanimously agreed that treatment with gepants may provide an alternative option for women with migraine and may help to address this gender disparity, allowing a greater proportion of women to live independently and return to work. In addition to these other important benefits, the council noted a potential for reduction of opioid (mis)use as patients will now have alternative options.

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

This intervention will significantly reduce caregiver or broader family burden.	**10/12**
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.	**11/12**
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity	**9/12**
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention	**See below**

A majority of the council members voted that treating patients with lasmiditan will significantly reduce caregiver or broader family burden and will offer a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. A majority of the panel also voted that it may have a significant impact on improving patients' ability to return to work and/or their overall productivity. The council noted the caveat of the driving restriction due to the associated adverse effect of dizziness may consequently limit patients' ability to be able to return to work or live independently. For this reason, it may not reduce caregiver burden or improve patient's overall productivity as significantly as it would have without this side effect.

The Council also judged that there are other important benefits or disadvantages that should have an important role in judgements of the value of, similar to those indicated in Question 8.

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

This intervention offers reduced complexity that will significantly improve patient outcomes.	**9/12**
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention	6/12

Three quarters of the Council judged that gepants offer reduced complexity that will significantly improve patient outcomes compared to lasmiditan because of the dizziness side effects associated with lasmiditan and the FDA warning of restricted driving. One half of the Council judged that another important benefit or disadvantage is that clinicians may perceive lasmiditan to be less safe than the gepants due to its mechanism of action being similar to that of triptans. Given the issue of clinicians under-prescribing triptans because of its vasoconstrictive effects, clinicians may subsequently treat lasmiditan similarly to triptans and prefer the gepants, which are not believed to cause the vasoconstriction and may have a better safety profile.

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

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.	**9/12**
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	**11/12**
This intervention is the first to offer any improvement for patients with this condition.	**12/12**
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	4/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention	**8/12**

A majority of Council members judged that gepants are 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, and that gepants are intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. Many Council members cited patient testimony during the public meeting on the severity of their migraines as having factored into their decision to vote "yes" vote on this question. A majority of the panel also voted that there is significant uncertainty about the magnitude or durability of the long-term benefits of treatment with gepants due to lack of longer-term trials.

The Council voted unanimously that gepants are the first to offer any improvement for patients with acute migraine for whom triptans have not been effective, are not tolerated, or are contraindicated. The Council agreed that the gepants are the first new treatment for many patients who have been unable to take triptans for many decades. A third of the members voted that there is significant uncertainty about the long-term risk of serious side effects of gepants. Panelists indicated a lack of long-term trials or real-world data assessing side effects of this new mechanism of action targeting the CGPR pathway. Another Council member judged that, although there is some uncertainty about the long-term risk of side effects associated with gepant use, those concerns were not unusually significant or serious enough to warrant a "yes" vote given their relatively benign safety profile.

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

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.	**10/12**
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	**11/12**
This intervention is the first to offer any improvement for patients with this condition.	**12/12**
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	6/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	6/12

A majority of Council members judged that lasmiditan 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, representing a particularly high lifetime burden of illness. Once more, Council members cited patient testimony as informing this decision. Similar to Question 11, the Council also unanimously agreed that lasmiditan (along with the gepants) is the first to offer any improvement for patients with this condition and for whom triptans have not been effective, well tolerated, or contraindicated.

Half of Council members judged that there is significant uncertainty about the long-term risk of serious side effects of lasmiditan; in particular, side effects associated with the central nervous system. Half of the panelists also determined there was significant uncertainty about the magnitude or durability of the long-term benefits of treatment with lasmiditan. The Council cited a need for long-term studies.

Long-Term Value for Money

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?

No vote taken

No vote was taken on question 13 because there was no price available for rimegepant at the time of the public meeting.

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?

**Note: This vote was based on information presented at the public meeting. Supplemental post-hoc analyses suggest that there is a delayed benefit for the gepants, and the base case cost-effectiveness model was modified to reflect this. As a result, the revised models suggest that the gepants are cost effective based on the WAC cost for ubrogepant.*

Low: 4 votes	***Intermediate: 8 votes***	High: 0 votes

A majority of the Council voted that there is intermediate long-term value for money of treatment with ubrogepant versus no treatment at the current estimated net price of ubrogepant. The base-case analyses indicated an incremental cost-effectiveness ratio of $379,000/QALY based on the outcome at 2 hours. However, additional post-hoc analyses comparing patients who received ubrogepant and a second dose of placebo with patients who received placebo and a second dose of placebo were conducted. These data demonstrated that ubrogepant may have increased effectiveness between 2 and 8 hours. The effect sizes from these analyses were incorporated into a scenario analysis, which led to an incremental cost-effectiveness ratio of $40,000/QALY. Panelists wrestled with the limitations of the base case relying heavily on the 2-hour data and the uncertainty in the post-hoc analyses due to issues of potential confounding. It was agreed that the true ICER is somewhere in between these two ratios.

Panelists who voted intermediate judged that the evidence indicating increased benefit of the gepants beyond 2 hours, while not a perfectly clean analysis, demonstrated a true

benefit of ubrogepant's efficacy past 2 hours. These panelists also indicated that potential other benefits and contextual considerations factored into their decision to vote intermediate value. One panelist noted that voting high value would send a signal that the current price is appropriate, and could even be raised; however, they did not feel that a higher price was merited given the base-case results.

Four members of the Council voted that the long-term value for money of ubrogepant is low. Some panelists judged that the uncertainty in the data used in the scenario analyses signified that the true ICER was likely to be closer to the base-case result of $379,000/QALY, warranting a low value vote.

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?

No vote taken

No vote was taken on question 15 because no price was available for lasmiditan at the time of the public meeting.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of lasmiditan, ubrogepant, and rimegepant for acute treatment of migraine. The policy roundtable members included two patient advocates, two clinical experts, two payers, and three representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 8.1 Policy Roundtable Members

Name	Title and Affiliation
Harold Carter, PharmD	Senior Director, Clinical Solutions, Express Scripts
Erin G. Doty, MD	Senior Medical Advisor, Migraine and Headache Disorders, Eli Lilly
Katie Golden, BA	Director of Patient Relations, Immediate Past Steering Committee Member, Coalition for Headache and Migraine Patients
Christopher Gottschalk, MD, FAHS	Director, Headache Medicine; Chief, General Neurology; Yale School of Medicine
Gil L'Italien, PhD	Senior Vice President of GHEOR and Epidemiology, Biohaven Pharmaceuticals
Mitchell Mathis, MD	Vice President, Chief Medical Officer, CNS, Allergan
Travis Tacheny, PharmD	Clinical Pharmacy Program Consultant, HealthPartners
Sarah Wells Kocsis, MBA	Vice President of Public Policy, Society for Women's Health Research

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

(1) Given that the evidence does not demonstrate superiority of the newer agents to existing less-expensive treatment options, it is reasonable for insurers and other payers to develop prior authorization criteria for lasmiditan, rimegepant and ubrogepant to ensure prudent use of these new therapies.

(2) For ubrogepant and rimegepant, given their similar mechanisms of action and available evidence suggesting no major differences in safety or effectiveness, it is not unreasonable for payers to negotiate lower prices by offering preferential formulary status to one or the other drug, including the possibility of exclusion of one of the drugs. If only one drug is covered, however, clinicians and patients should have the ability to appeal for coverage for the other gepant drug should a trial of the favored drug not produce adequate success.

(3) Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policies are discussed below.

Ubrogepant and Rimegepant

Patient Eligibility Criteria

a. **Patient population:** The Food and Drug Administration (FDA) indication for ubrogepant includes acute treatment of all adults with migraine, with or without aura. We anticipate the same broad language will be used should rimegepant be approved. Clinical trials for both agents included a narrower spectrum of adults: patients generally had a long history of migraine with a high frequency and intensity of symptoms. On average, over 80% were female, with an average age of 40 years, having had migraines for approximately 20 years, with 3-5 migraine attacks per month of a moderate (70%) or severe (30%) intensity. About 20-25% of trial participants were receiving medications to prevent migraine attacks. Clinical experts and patient advocates suggest that although the clinical trial populations were more severely affected, on average, than all patients with migraine, there is no evidence-based reason to try to limit coverage based on some metric of severity such as number of migraines per month. Prior use of triptans as a coverage consideration is discussed below.

b. **Diagnosis**: Clinician attestation of migraine diagnosis is reasonable since there are no specific diagnostic tests.

c. **Ineligible for triptans, intolerance of triptans, or inadequate response to triptans:** Given that the evidence of response to these newer agents does not suggest they are superior to triptans, clinical experts, patient advocates, and manufacturers agreed that requiring patients to try triptans first before receiving coverage for the newer agents is reasonable if patients are clinically eligible. Clinical experts highlighted that triptans are under-prescribed, and some patients have not tried triptans due to concerns about side effects or concerns about vasoconstriction in those not at high risk for cardiovascular disease. Some patients will have tried triptans in the past and had intolerable side effects. Attestation of clinical ineligibility or intolerance was favored by clinical experts and patient advocates over formal medical record documentation given the long-term nature of migraine and the difficulty of finding past medical records to document CV events or prior side effects.

   For patients who are eligible to try triptans, there is no evidence-based basis for a threshold number of different triptans that should be tried to determine whether adequate treatment is achieved. Clinical experts and patient advocates acknowledge that many patients find adequate relief with one triptan even after finding other triptans inadequate. The likelihood of finding a triptan that works does diminish after each trial, however, so a requirement of trying 1-2 triptans was viewed as reasonable whereas requiring more was viewed as less

reasonable. Trying to devise a metric for "inadequate" response by looking at rescue medication use or other factors was not viewed as clinically reasonable.

Provider Criteria

Specialist prescribing requirement: Triptans were originally a specialty-only prescription in many health systems but soon after launch prescribing was broadened to all primary care clinicians. Given that ubrogepant and rimegepant seem to have a benign safety profile it seems reasonable to allow primary care prescribing at launch, although some payers may wish to require consultation with a specialist to ensure that the diagnosis of migraine is being adequately made and that trials of triptans are maximized before consideration of these newer agents.

Renewal criteria

Because patients will have the best sense of whether the treatment is proving successful, it does not seem that requiring attestation from clinicians of clinical benefit before renewing prescriptions will be helpful in achieving appropriate use.

Concurrent Medications

There is no evidence available with which to judge the safety or effectiveness of use of these new agents in conjunction with concomitant triptan use. Clinical experts suggested that concomitant use would be desired by some/many patients but acknowledged the lack of evidence to support this strategy. Given that payers are likely to reserve coverage of these newer agents to patients who have not had adequate relief from triptans, some may consider setting initial coverage conditions that exclude concomitant use, at least until further data become available, but it may also be reasonable to provide coverage for one or more triptans and one of the newer agents.

Quantity Limits

Payers have used limits on the number of triptan pills dispensed per month as a means of reducing the risk of medication overuse headache (MOH). Similar quantity limits could be considered by payers for these new medications. Given that these medications have a different mechanism of action it is unknown whether they will also have the potential to cause MOH. Clinical experts cited the positive clinical experience to date with preventive CGRP medications and were therefore hopeful that gepant acute treatments would not cause MOH, but experts were also aware that triptans themselves were touted as being free of this concern when they were first launched. In general, clinical experts and patient advocates felt that quantity limits would not promote positive outcomes but acknowledged the likelihood that payers would consider quantity limits until longer-term data on MOH were available. Clinical experts also advised that payers should reconsider their quantity limits on triptans. If triptans are working well for patients but the quantity limits leave gaps in treatment, it will be natural for patients to seek other options, such as the gepants or lasmiditan. Loosening quantity limits for triptans may therefore be better clinically for patients as well as ultimately more cost-effective for payers.

Lasmiditan

Patient Eligibility Criteria

a. **Patient population:** The Food and Drug Administration (FDA) indication for lasmiditan includes acute treatment of all adults with migraine, with or without aura. Clinical trials for lasmiditan included a narrower spectrum of adult: patients generally had a long history of migraine with a high frequency and intensity of symptoms. On average, over 80% were female, with an average age of approximately 40 years, having had migraines for 15-20 years, with 3-5 migraine attacks per month of a moderate (approximately 70%) or severe (approximately 30%) intensity, and about 20-25% were receiving medications to prevent migraine attacks. Clinical experts and patient advocates suggest that although the clinical trial populations were more severely affected, on average, than all patients with migraine, there is no evidence-based reason to try to limit coverage based on some metric of severity such as number of migraines per month.

   Because the mechanism of action of lasmiditan has some similarities to that of triptans, some payers may wonder whether there should be any CV restrictions. Clinical trials excluded patients with known coronary artery disease; clinically significant arrythmia; uncontrolled hypertension; or conditions increasing the risk of seizures. The FDA, however, put no restrictions on the label, and clinical experts advised that except for clear evidence of major CAD they did not believe there were reasons to consider lasmiditan an inappropriate treatment option. Unlike triptans, lasmiditan does not cause vasoconstriction.

b. **Diagnosis**: Clinician attestation of migraine diagnosis is reasonable since there are no specific diagnostic tests.

c. **Ineligible for triptans or inadequate response to triptans:** Given that the evidence of response to lasmiditan does not suggest it is superior to triptans, clinical experts, patient advocates, and manufacturers agreed that requiring patients to try triptans first before receiving coverage is reasonable if patients are clinically eligible. Clinical experts highlighted that triptans are under-prescribed, and some patients have not tried triptans due to concerns about side effects or concerns about vasoconstriction in those who not at high risk for cardiovascular disease. Attestation of clinical ineligibility was still favored over formal medical record documentation given the long-term nature of migraine and the difficulty of finding past medical records to document CV events that would make a patient ineligible.

   For patients who are eligible to try triptans, there is no evidence-based basis for a threshold number of different triptans that should be tried to determine whether adequate treatment is achieved. Clinical experts and patient advocates acknowledge that many patients find adequate relief with one triptan even after finding other triptans inadequate. The likelihood of finding a triptan that works does diminish after each trial, however, so a requirement of trying 1-2 triptans was viewed as reasonable whereas requiring more was viewed as less reasonable. Trying to devise a metric for "inadequate" response by looking at rescue

medication use or other factors was not viewed as clinically reasonable.

Provider Criteria

Specialist prescribing requirement: Triptans were originally a specialty-only prescription in many health systems but very soon prescribing was broadened to all primary care clinicians. Given that lasmiditan seems to have a benign safety profile and may have less risk of vasoconstriction than the triptans, it does seems reasonable to allow primary care prescribing at launch, although some payers may wish to require consultation with a specialist to ensure that the diagnosis of migraine is being adequately made and that trials of triptans are maximized before consideration of these newer agents. This may be more likely for lasmiditan than for the gepants given the FDA warning about driving within 8 hours of taking lasmiditan.

Renewal criteria

Because patients will have the best sense of whether the treatment is proving successful, it does not seem that requiring attestation from clinicians of clinical benefit before renewing prescriptions will be helpful in achieving appropriate use.

Concurrent Medications

There is no evidence available with which to judge the safety or effectiveness of use of lasmiditan in conjunction with concomitant triptan or gepant use. Clinical experts suggested that concomitant use would be desired by some/many patients but acknowledged the lack of evidence to support this strategy. Given that the mechanism of action for lasmiditan affects the same pathway as triptans it would seem to be more reasonable to limit coverage to one or the other. Coverage for simultaneous gepant and lasmiditan use at this time does not seem likely given that all agents are new to practice and there are no data on concomitant use. As the safety profiles of the drugs become more established, payers should consider whether requests for concomitant use appear more reasonable.

Quantity Limits

Payers have used limits on the number of triptan pills dispensed per month as a means of reducing the risk of medication overuse headache (MOH). Similar quantity limits are very likely to be considered by payers for lasmiditan. Given that lasmiditan is thought to have a similar mechanism of action, it is possible that it will also have the potential to cause MOH. In general, clinical experts and patient advocates acknowledged the likelihood that payers would consider quantity limits until longer-term data on MOH were available. Clinical experts also advised that payers should reconsider their quantity limits on triptans. If triptans are working well for patients but the quantity limits leave gaps in treatment, it will be natural for patients to seek other options, such as the gepants or lasmiditan. Loosening quantity limits for triptans may therefore be better clinically for patients as well as ultimately more cost-effective for payers.

Providers

(1) With the advent of these new treatment options, specialists in migraine treatment should seek new avenues to educate primary care clinicians on the appropriate use of triptans and other acute treatment options in order to maximize the appropriate care of the substantial population of patients with migraine while helping to control costs.

During the roundtable discussion, experts in migraine treatment described how triptans are often under-prescribed for acute treatment of migraine because of clinician concerns about potential risks, most prominently vasoconstriction. Triptans have been used for over 20 years and the evidence for clinically important vasoconstriction is very limited. Though this may be due to the cautious use of this class of medications in individuals at high risk for cardiovascular disease, it is more likely that the actual risks of these medications are lower than some clinicians may think. Migraine specialists should therefore work through their specialty societies and through their own care delivery systems to develop educational content for primary care and emergency medicine clinicians to help dispel old ideas about existing therapies and provide guidance on how best to incorporate new medications into clinical practice.

(2) Migraine specialists and specialty societies should update guideline recommendations to address the role of these new medications for acute treatments for migraine.

The availability of new medications for acute treatment of migraine with novel mechanisms of action point to a potentially major change in clinical practice. Patients and experts highlighted that that the large number of individuals with migraine in whom these new medications may be considered mean that it will not be practical to require specialist assessment and care of all eligible patients. In order to ensure clinicians have up to date information about the role of these new medications, it is incumbent on professional societies to develop and update clinical practice guidelines, especially in the setting of potentially major changes in available therapies. Placing these new agents into practice and helping clinicians identify their role in a rapidly changing landscape is critical to ensuring clinicians have the knowledge to wisely use these new therapies. A key aspect of these efforts is to ensure that guidelines are developed using rigorous methods that include input from a range of experts, primary care clinicians and patients with the condition, as well as explicit disclosure and monitoring of potential conflicts of interest.

Manufacturers and Researchers

(1) Manufacturers and researchers should develop long term comparative trials of acute treatments for migraine that assess outcomes over the entire course of a migraine attack.

Comments during the policy roundtable highlighted some of the important research gaps that limit identifying the best treatment for an individual patient. Though the choice of assessing primary outcomes at two hours was recognized to be arbitrary, it limits the rigorous assessment of outcomes over the entire course of a migraine attack, particularly between two and eight hours. Patients and experts described that to be effective, migraine medications need to work quickly and then remain active or be able to be re-dosed. The selection of a two-hour outcome focuses on quick action but may miss the time of maximal benefit if it is delayed. Data presented at the meeting on rimegepant and ubrogepant suggested that benefits continue to increase after two hours and that as a result, cost effectiveness looking at two-hour benefits may underestimate the true cost-effectiveness of these agents. Assessing primary outcomes over longer time periods in placebo controlled and/or active comparator studies would help address this issue.

(2) Manufacturers and researchers should develop comparative trials of acute treatments for migraine that assess whether new medications have a lower risk for medication overuse headache and can reduce the frequency of migraine attacks over time.

The use of single dose trials for FDA approval does not lead to comparative data that relate to how these new medications will be used in clinical practice where dosing with each new migraine attack is to be expected. Patient and experts highlighted the risk of medication overuse headache with frequent, repeat dosing of existing medications. It is uncertain whether this will be seen with the new medications. In addition, the potential for these new medications to decrease the frequency of headaches over time was highlighted. ICER did not consider these potential benefits in its cost-effectiveness models because of the lack of data or uncertainty about the effect or its magnitude.

(3) Manufacturers and researchers should conduct real-world comparative studies of acute treatments for migraine that assess important outcomes including quality of life, work, productivity and disability.

Patients highlighted the impact that frequent, severe migraine attacks over time can have on all aspects of life. As an episodic and chronic condition that affects patients throughout their lives, it can disrupt personal relationships with friends and family, and their ability to function at home and work. If the migraine attack is not aborted quickly and without medication related side effects, ability to work or work productively is profoundly affected. The combination of frequent, severe and unpredictable migraine attacks impacts ability to work, increases the risk of disability, and can

have a long-term negative economic impact on the patient and her/his family. Studies are needed to assess whether new treatments are effective in improving these important outcomes.

Regulators

(1) The patient population which may be considered for treatment with lasmiditan, rimegepant and ubrogepant is very large. Regulators have an important role to play in how new therapeutics enter clinical practice and therefore should require post-approval, long-term comparative outcomes studies for new acute treatments for migraine that are initially evaluated and approved in single-dose randomized trials.

The patient population which may be considered for acute treatment of migraine with these new medications is very large. Though triptans are effective and safe for many, patient advocates and experts highlighted that patients commonly end up looking for other treatments because of lack of effect, loss of efficacy, side effects or contraindications to their use. With lasmiditan and ubrogepant having received FDA approval and rimegepant likely to be approved shortly, clinical experts during the roundtable discussion highlighted the challenge of selecting which drug to use in which patient. Given the broad indications for these new medications, comparisons of the new drugs to each other, and to triptans among those who are triptan naïve are needed.

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This is the third ICER review of interventions for migraine.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Strategies for Acute Treatments for Migraine

Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (via Ovid) - Lasmiditan/Rimegepant/Ubrogepant

#	Search Terms
1	exp migraine disorders/
2	exp migraine with aura/
3	exp migraine without aura/
4	((acute AND migraine*) OR migraine* OR migraine syndrome OR migraine disorder).ti,ab.
5	OR/1-4
6	(lasmiditan OR COL-144 OR LY573144 OR rimegepant OR BHV-3000 OR BMS-927711 OR ubrogepant OR MK-1602).ti,ab.
7	5 AND 6
8	(animals not (humans and animals)).sh.
9	7 NOT 8
10	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
11	9 NOT 10
12	Limit 11 to English language
13	Remove duplicates from 12

Table A3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (via Ovid) – Sumatriptan & Eletriptan (updated)

#	Search Terms
1	exp migraine disorders/
2	exp migraine with aura/
3	exp migraine without aura/
4	((acute AND migraine*) OR migraine* OR migraine syndrome OR migraine disorder).ti,ab.
5	OR/1-4
6	(sumatriptan OR eletriptan).ti,ab.
7	5 AND 6
8	(animals not (humans and animals)).sh.
9	7 NOT 8
10	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
11	9 NOT 10
12	Limit 11 to English language
13	limit 12 to yr="2016- Current"
14	Remove duplicates from 13

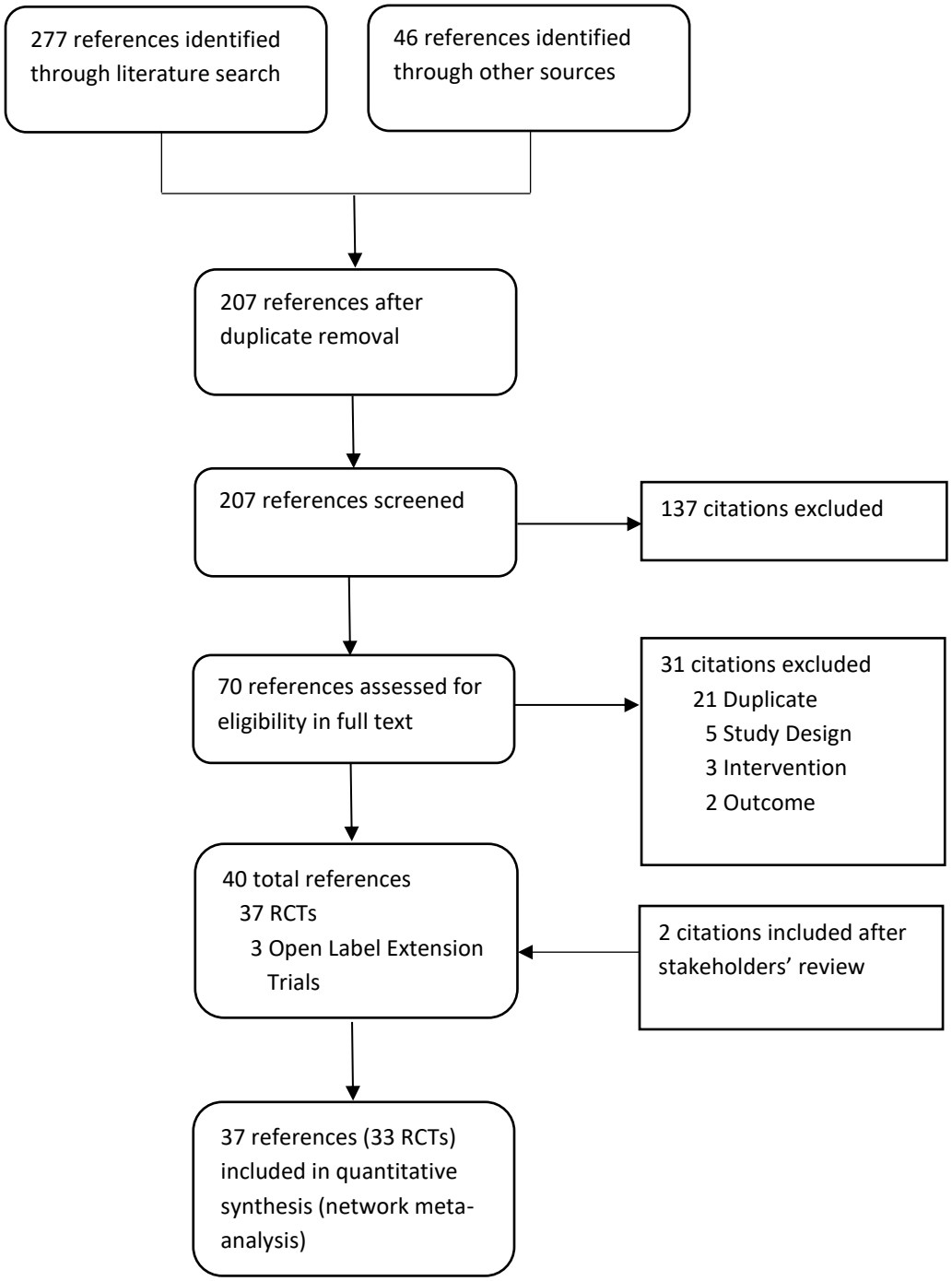
Table A4. Search Strategy of EMBASE Search - Lasmiditan/Rimegepant/Ubrogepant

#	Search Terms
#1	acute AND ('migraine'/exp OR migraine)
#2	'lasmiditan'/exp OR 'lasmiditan' OR 'COL-144' OR 'LY573144'
#3	'rimegepant'/exp OR 'rimegepant' OR 'BHV-3000' OR 'BMS-927711'
#4	'ubrogepant'/exp OR 'ubrogepant' OR 'MK-1602'
#5	#2 OR #3 OR #4
#6	#1 AND #5
#7	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp NOT 'human'/exp
#8	#6 NOT #7
#9	#8 AND [english]/lim
#10	#9 AND [medline]/lim
#11	#9 NOT #10
#12	#11 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)

Table A5. Search Strategy of EMBASE Search – Sumatriptan & Eletriptan (updated)

#	Search Terms
#1	acute AND (‘migraine’/exp OR migraine)
#2	‘Sumatriptan’/exp OR ‘Sumatriptan’
#3	‘eletriptan’/exp OR ‘eletriptan’
#4	#2 OR #3
#5	#1 AND #4
#6	‘animal’/exp or ‘nonhuman’/exp or ‘animal experiment’/exp NOT ‘human’/exp
#7	#5 NOT #6
#8	#7 AND [english]/lim
#9	#8 AND [medline]/lim
#10	#8 NOT #9
#11	#10 AND [01-01-2016]/sd
#12	#11 NOT (‘case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey’/it)
#13	#12 AND 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR placebo:ti,ab OR 'drug therapy':lnk OR trial:ti,ab OR groups:ti,ab

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Acute Treatments for Migraine



RCT: randomized control trial

Appendix B. Previous Systematic Reviews and Technology Assessments

Xu F, Sun W. Network Meta-Analysis of Calcitonin Gene-Related Peptide Receptor Antagonists for the Acute Treatment of Migraine. *Frontiers in pharmacology.* 2019;10:795.

The investigators performed a network meta-analysis (NMA) to indirectly compare and rank six different calcitonin gene-related peptide (CGRP) receptor antagonists (telcagepant, olcegepant, BI 44370, rimegepant, MK3207, and ubrogepant) for the acute treatment of migraine. Ten randomized controlled trials (RCTs) in adult patients with migraine were included in the quantitative analysis. Efficacy was evaluated based on pain-freedom at 2-hours, and safety was assessed based on the occurrence of adverse events (AEs) and drug-related AEs. Olcegepant, ubrogepant, and BI 44370 were statistically significantly better than placebo in achieving pain freedom at 2-hours. In addition, olcegepant was found to show greater efficacy than the other CGRP receptor antagonists and to be marginally more efficacious than triptans, however, statistical significance was not reached. Telcagepant, olcegepant, MK3207, rimegepant, and ubrogepant were found to have a safety profile comparable to placebo, while BI 44370 was associated with an increased risk for AEs. Of note, research regarding olcegepant, telcagepant, BI 44370, and MK3207 has been discontinued, primarily due to concerns of hepatoxicity.

Thorlund K, Toor K, Wu P, et al. Comparative tolerability of treatments for acute migraine: A network meta-analysis. *Cephalalgia: an international journal of headache.* 2017;37(10):965-978.

This systematic literature review and NMA was conducted to evaluate the comparative tolerability of acute treatments for migraine with regards to AEs, treatment-related AEs (TRAEs), and serious AEs (SAEs). The NMA included 141 RCTs, comparing acute oral treatments for migraine in adults, including triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan), NSAIDs (diclofenac, ibuprofen, naproxen, and selective COX-2 inhibitors), acetaminophen, as well as ergotamines. Triptans were generally associated with the highest odds ratios (ORs) for the occurrence of any AEs and TRAEs (i.e. fatigue, dizziness, chest discomfort, somnolence and nausea). Specifically, sumatriptan, eletriptan, rizatriptan, zolmitriptan, and the combination treatment of sumatriptan and naproxen had statistically significant higher odds of TRAE occurring compared with placebo. Among the non-triptans, only acetaminophen had an increased odd for TRAE compared with placebo. In general, triptans and non-triptans were not associated with increased odds of SAEs compared to placebo. The authors concluded however that differences in safety profiles were not large enough to necessitate prioritizing one treatment over another.

Xu H, Han W, Wang J, Li M. Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. *J Headache Pain.* 2016;17(1):113.

The investigators performed an NMA to compare the relative efficacy and tolerability of NSAIDs and triptans in the acute treatment for migraine in adults. Eighty-eight RCTs pertaining to sumatriptan, zolmitriptan, almotriptan, rizatriptan, naratriptan, eletriptan, ibuprofen, sumatriptan-naproxen, diclofenac-potassium, and aspirin were included in the analysis. Efficacy was evaluated based on pain-freedom, pain-relief, absence of nausea, rate of recurrence, and the use of rescue medication. Safety was evaluated based on the occurrence of AEs. With regards to pain-freedom and pain-relief at 2-hours, all treatments included in the NMA were found to be statistically more effective than placebo. Eletriptan exhibited superior efficacy over sumatriptan, zolmitriptan, almotriptan, ibuprofen, and aspirin with regards to 2-hour pain-freedom, while rizatriptan was superior to sumatriptan, zolmitran, almotriptan, ibuprofen, and aspirin. The difference between eletriptan and rizatriptan was not found to be statistically significant. With regards to absence of nausea at 2-hours, rizatriptan was found to have better efficacy outcomes compared to sumatriptan, while no other meaningful differences were found between the other treatments including placebo. The AE incidence of sumatriptan was higher compared to diclofenac-potassium, ibuprofen, and almotriptan. Similarly, the safety profile for naratriptan was found to be inferior to that of ibuprofen and diclofenac-potassium. Results overall suggested that eletriptan exhibited the best efficacy results while also having an acceptable safety profile. Sumatriptan-naproxen and diclofenac-potassium also showed favorable efficacy as well as tolerability, while ibuprofen appeared the best tolerated treatment option. The authors concluded that eletriptan may be the most suitable treatment option for the acute treatment of migraines when taking both efficacy and safety outcomes into account. Additionally, ibuprofen was also considered to be an appropriate treatment option due to its excellent safety profile.

Cameron C, Kelly S, Hsieh SC, et al. Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis. *Headache.* 2015;55 Suppl 4:221-235.

This systematic review and NMA sought to compare triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) to each other, versus placebo, and versus other acute migraine treatments such as NSAIDs, ASA, acetaminophen, ergotamines, opioids, or antiemetics. A total of 133 single-attack RCTs evaluating acute treatments for migraines in adults were included in the quantitative analysis. Efficacy was evaluated based on pain-freedom and headache relief at 2-hours, sustained pain-freedom and headache relief at 24-hours, as well as the use of rescue medication. Results found that rizatriptan (oral), eletriptan (oral), and sumatriptan (subcutaneous injection) have the largest effect on 2-hour pain-freedom among all monotherapies. With respect to 2-hour pain-relief, sumatriptan (subcutaneous injection), rizatriptan (oral), and zolmitriptan (oral) showed the largest effect compared to the other monotherapies. Eletriptan (oral) and rizatriptan (oral) exhibited the largest effect on sustained freedom of pain, while zolmitriptan (oral) and eletriptan (oral) were found to be most efficacious with respect to sustained

pain relief. Participants treated with eletriptan (oral) and zolmitriptan (oral) required the least amount of rescue medications, while those treated with NSAIDs, sumatriptan (oral), and ASA required the most doses. The authors concluded that the majority of triptans, with the exception of frovatriptan and naratriptan, are comparable in terms of efficacy. However, it was suggested that eletriptan and rizatriptan may be slightly superior in providing pain relief.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Key Outcomes	Estimated Completion Date
Lasmiditan					
Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks **NCT03670810** **Sponsor: Eli Lilly**	Phase 3, Randomized, double-blind, parallel assignment Estimated N: 1600 Time Frame: 16 weeks	• Lasmiditan high dose • Lasmiditan low dose • Placebo	Inclusions: ≥18 years; Migraine with or without aura; History of disabling migraine for at least 1 year; Migraine onset before the age of 50 years; 3 to 8 migraine attacks/month (<15 headache days/month) during the past 3 months; MIDAS score ≥11 Exclusion: Known hypersensitivity to lasmiditan; History of hemorrhagic stroke, epilepsy, or any other condition placing the participant at increased risk of seizures; History of recurrent dizziness and/or vertigo; History of diabetes mellitus with complications; History of orthostatic hypotension with syncope; Significant renal or hepatic impairment; Participants who are deemed to be at significant risk for suicide; History of chronic migraine or other forms of primary or secondary chronic headache disorder within past 12 months; Use of more than 3 doses/month of either opioids or barbiturates; Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes within 3 months prior to screening; SUD within 1 year prior to screening; Currently enrolled in any other clinical study involving an investigational product	Primary Outcomes: Pain freedom at 2-hours postdose during the first attack; Pain freedom at 2-hours postdose in at least 2 out of 3 attacks Secondary Outcomes: 2-hour pain freedom; Freedom of MBS; 24-hour sustained pain freedom; Use of rescue medication; Freedom of associated symptoms at 2-hours; Migraine recurrence at 24-hours; Pain freedom, pain relief, freedom from MBS, and no disability at 2-hours; Change in MIDAS score; No disability at 2-hours; PGI-C at 2-hours; MQoLQ score at 24-hours; Patient satisfaction; Change in EQ-5D-5L at 24-hours	March 2020
Randomized, Double-blind, Placebo-controlled Trial Of Lasmiditan in a Single	Phase 2, Randomized, double-blind, parallel assignment	• Lasmiditan high dose • Lasmiditan mid dose	Inclusions: ≥18 years; Migraine with or without aura; History of disabling migraine for at least 1 year; MIDAS score ≥11; Migraine onset before the age of 50 years;	Primary Outcomes: Pain freedom at 2-hours (high dose)	March 2020

Migraine Attack in Japanese Patients Suffering From Migraine With or Without Aura - the MONONOFU Study **NCT03962738** **Sponsor: Eli Lilly**	Estimated N: 36 Time Frame: up to 50 days	• Lasmiditan low dose • Placebo	History of 3 to 8 migraine attacks/month and <15 headache days/month during the past 3 months Exclusions: Known hypersensitivity to lasmiditan; History of hemorrhagic stroke, epilepsy, or any other condition placing the patient at increased risk of seizures; History of recurrent dizziness and/or vertigo; History of diabetes mellitus with complications; History of orthostatic hypotension with syncope	Secondary Outcomes: Pain freedom in each dose group at 2-hours; Pain relief at 2-hours; Freedom of MBS at 2-hours; 24- and 48-hour sustained pain freedom; Freedom of phonophobia, photophobia, nausea, and vomiting; No disability at 2-hours; Change in EQ-5D-5L at 24-hours; PGI-C at 2-hours; MQoLQ score at 24-hours	
Rimegepant					
An Open-label, Intermediate-size, Expanded Access Study of BHV-3000 in the Acute Treatment of Migraine **NCT03934086** **Sponsor: Biohaven Pharmaceuticals, Inc.**	Expanded Access	---	Inclusions: Patients who participated in a previous BHV-3000/Rimegepant Clinical Trial Exclusions: History of basilar migraine or hemiplegic migraine; History with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease; HIV; Uncontrolled hypertension or diabetes; Current diagnosis of major depression, other pain syndromes, psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that might interfere with study assessments; History of gastric, or small intestinal surgery, or disease that causes malabsorption	*The purpose of this protocol is to allow subjects who completed any BHV3000 (rimegepant) clinical study to continue to have access to rimegepant while collecting ongoing safety data*	

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BMI: Body mass index, EQ-5D-5L: EuroQol 5-Dimension 5-Level Scale, HbA1c: Hemoglobulin A1c, HIV: Human Immunodeficiency Virus, MBS: most bothersome symptom, MIDAS: Migraine Disability Assessment Test, MQoLQ: Migraine Quality of Life Questionnaire, N: total number, PGI-C: Patient Global Impression of Change, ULN: Upper Limit

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2).[127] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Note that case series are not considered under this rating system–because of the lack of comparator, these are generally considered to be of poor quality.

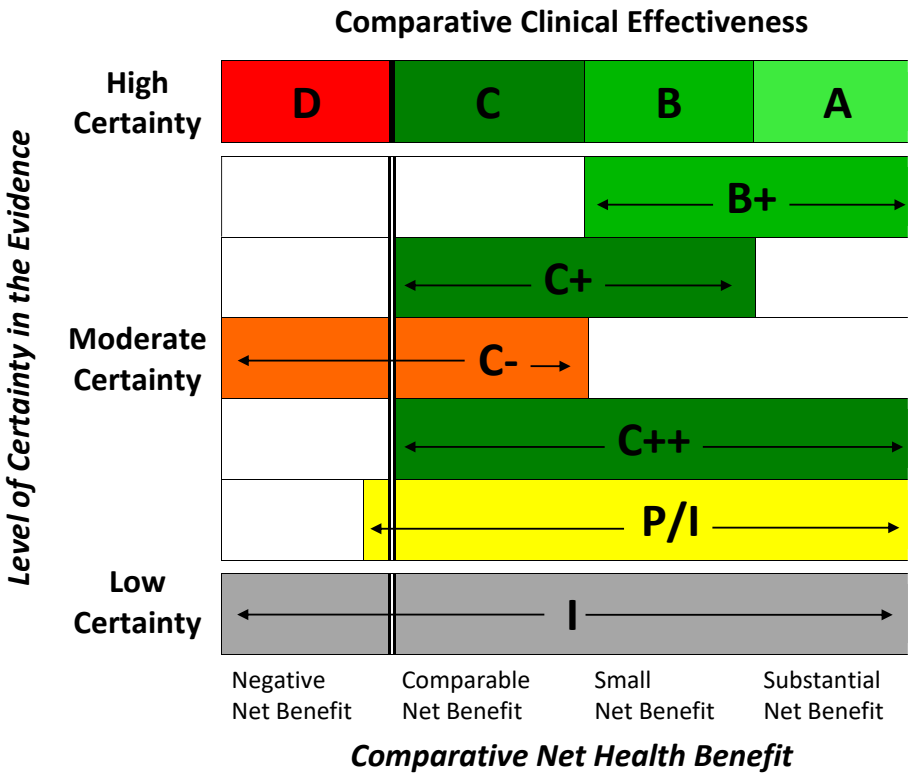
ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND

The level of certainty in the best point estimate of net health benefit.[87]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table D1. Key Baseline Characteristics of Patients in the Trials of Lasmiditan, Rimegepant, Ubrogepant and Triptans

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	History of Migraine, Mean Years (SD)	Migraine Attacks/ Month in Past 3 Months, Mean (SD)
Lasmiditan						
SAMURAI[24]	Lasmiditan 200mg	609	41.4 (12.0)	515 (84.6)	18.9 (13.1)	5.3 (2.3)
	Lasmiditan 100mg	630	42.2 (11.7)	512 (81.3)	19.7 (13.0)	5.1 (1.8)
	Placebo	617	42.4 (12.3)	525 (85.1)	19.3 (12.7)	5.1 (1.8)
SPARTAN[25]	Lasmiditan 200mg	649	41.8 (12.4)	536 (82.6)	17.6 (12.6)	5.3 (1.9)
	Lasmiditan 100mg	635	43.4 (12.6)	539 (84.9)	19.2 (13.6)	5.3 (1.9)
	Lasmiditan 50mg	654	42.8 (13.2)	554 (84.7)	18.6 (12.9)	5.2 (2.0)
	Placebo	645	42.6 (12.9)	545 (84.5)	17.9 (12.8)	5.5 (2.4)
Farkkila 2012[26]	Lasmiditan 200mg	71	39.5 (10.3)	65 (91.5)	NR	3.3 (1.9)
	Lasmiditan 100mg	82	42.0 (10.6)	68 (82.9)		3.3 (1.7)
	Lasmiditan 50mg	82	40.4 (12.5)	69 (84.1)		3.3 (1.6)
	Placebo	86	40.5 (10.3)	75 (87.2)		3.1 (1.7)
Rimegepant						
Study 301[28]	Rimegepant 75mg	543	41.9 (12.3)	464 (85.5)	NR	4.8 (1.7)
	Placebo	541	41.3 (12.1)	463 (85.6)		4.7 (1.8)
Study 302[27]	Rimegepant 75mg	537	40.2 (11.9)	479 (89.2)	NR	4.5 (1.9)
	Placebo	535	40.9 (12.1)	472 (88.2)		4.6 (1.8)
Study 303[29]	Rimegepant 75mg	669	40.3 (12.1)	568 (84.9)	NR	4.6 (1.8)
	Placebo	682	40.0 (11.9)	579 (84.9)		4.5 (1.8)
Marcus 2014[30]	Rimegepant 75mg	91	38.5 (11.9)	81 (89.0)	NR	3.9 (1.7)*
	Sumatriptan 100mg	109	40.6 (10.5)	91 (83.5)		4.1 (1.8)*
	Placebo	229	37.9 (11.4)	196 (85.6)		4.0 (1.8)*
Ubrogepant						
ACHIEVE I[32]	Ubrogepant 100mg	485	40.6 (12.0)	418 (86.2)	18.9 (12.3)	4.6 (1.8)
	Ubrogepant 50mg	466	40.1 (11.7)	418 (89.7)	17.9 (11.9)	4.6 (1.9)
	Placebo	485	40.9 (11.7)	430 (88.7)	19.1 (12.3)	4.4 (1.7)
ACHIEVE II[31]	Ubrogepant 50mg	488	41.2 (12.5)	444 (91.0)	18.1 (12.3)	4.4 (1.8)
	Ubrogepant 25mg	478	41.6 (12.4)	431 (90.2)	18.9 (12.2)	4.8 (1.8)

	Placebo	499	41.7 (12.1)	442 (88.6)	19.2 (12.6)	4.6 (1.8)
Voss 2016[33]	Ubrogepant 100mg	102	41.9 (11.0)	90 (88.2)	NR	NR
	Ubrogepant 50mg	106	40.7 (12.3)	92 (86.8)		
	Ubrogepant 25mg	104	41.4 (11.5)	91 (87.5)		
	Placebo	113	40.5 (11.7)	99 (87.6)		
Triptans						
Diener 2002[35]	Eletriptan 40mg	210	40 (11.0)	181 (86.2)	Range: 10.9 - 23.3	Range: 6.7 - 8.0
	Placebo	106	42 (11.0)	91 (85.8)		
Steiner 2003[49]	Eletriptan 40mg	392	40.3 (10.4)	345 (88.0)	16.6 (12.1)	2.5 (1.3)
	Placebo	144	39.9 (10.6)	124 (86.0)	16.2 (12.1)	2.6 (1.3)
Garcia-Ramos 2003[37]	Eletriptan 40mg	192	36.3 (11.1)	152 (79)	10.3 (9.7)	2.8 (NR)
	Placebo	92	36.4 (11.1)	75 (82)	11.9 (10.4)	2.8 (NR)
The EMSASI Study Group 2004[52]	Sumatriptan 50mg	226	38.2 (12.5)	182 (80.5)	With aura: 19.4 (14.0) Without aura: 16.0 (12.7)	NR
	Placebo	222	38.3 (12.2)	180 (81.1)	With aura: 18.9 (13.0) Without aura: 15.1 (11.6)	
Diener 2004[34]	Sumatriptan 50mg	135	43.7 (12.1)	111 (82.2)	NR	NR
	Placebo	152	41.9 (11.7)	127 (83.6)		
Geraud 2000[38]	Sumatriptan 100mg	504	38.0 (10.6)	424 (84.0)	NR	2.8 (1.4)
	Placebo	56	37.9 (9.7)	49 (86.0)		2.7 (1.3)
Sheftell 2005[47] -Study 1	Sumatriptan 100mg	462	41.5 (11.2)	389 (84.2)	NR	NR
	Sumatriptan 50mg	448	41.6 (10.8)	380 (84.9)		
	Placebo	456	41.2 (10.8)	401 (87.9)		
Sheftell 2005[47] - Study 2	Sumatriptan 100mg	440	40.2 (10.8)	361 (82.0)	NR	NR
	Sumatriptan 50mg	454	39.9 (10.8)	387 (85.2)		
	Placebo	436	39.2 (10.5)	378 (86.7)		
Havanka 2000[40]	Sumatriptan 100mg	98	NR	89 (89.0)	NR	NR
	Placebo	91		81 (89.0)		
Smith 2005[48]	Sumatriptan 50mg	229	41.2 (11.3)	208 (90.8)	21.5 (NR)	NR
	Placebo	242	41.2 (10.2)	214 (88.4)	20.0 (NR)	
Tfelt-Hansen 1995[50]	Sumatriptan 100mg	139	39 (Range: 18 - 58)	108 (77.7)	18 (Range: 1 - 50)	3.3 (Range: 2 - 6)
	Placebo	137	39 (Range: 18 - 63)	106 (77.4)	19 (Range: 1 - 51)	3.4 (Range: 2 - 8)

Myllyla 1998[44]	Sumatriptan 100mg	46	40 (10.0)	39 (84.8)	NR	NR
	Placebo	48	39 (9.5)	45 (93.8)		
Tfelt-Hansen 1998[51]	Sumatriptan 100mg	388	39.2 (10.1)	309 (79.6)	NR	NR
	Placebo	160	38.3 (10.3)	132 (82.5)		
Dowson 2002[36]	Sumatriptan 100mg	194	42.0 (10.5)	162 (83.5)	NR	NR
	Placebo	99	40.2 (10.1)	88 (88.9)		
Kudrow 2005[41]	Sumatriptan 50mg	144	41.1 (9.9)	130 (90.3)	NR	NR
	Placebo	141	39.0 (9.8)	124 (87.9)		
Lines 2001[42]	Sumatriptan 50mg	No baseline characteristics reported				
	Placebo					
Nappi 1994[45]	Sumatriptan 100mg	158	38 (9)	120 (76)	Median: 17.5	NR
	Placebo	86	38 (11)	68 (79)	Median: 18.0	
Pfaffenrath 1998[46]	Sumatriptan 100mg	298	40.0	247 (82.9)	17.2 (NR)	NR
	Sumatriptan 50mg	303	40.4	266 (87.8)	17.2 (NR)	
	Placebo	99	40.4 (10.7)	80 (80.8)	18.0 (NR)	
Oral Sumatriptan International Multiple-Dose Study Group 1991[53]	Sumatriptan 100mg	148	42 (10)	128 (86.5)	Median: 20.0	NR
	Placebo	84	40 (10)	70 (83.3)	Median: 18.0	
Mathew 2003[43]	Eletriptan 40mg	822	41.1 (10.8)	716 (87.0)	13.4 (11.3)	2.7 (1.3)
	Sumatriptan 100mg	831	41.8 (10.4)	715 (86.0)	14.0 (11.2)	2.7 (1.3)
	Placebo	419	41.6 (10.6)	365 (87.0)	13.6 (11.5)	2.8 (1.4)
Goadsby 2000[39]	Eletriptan 40mg	136	41 (11)	115 (84.6)	NR	NR
	Eletriptan 20mg	144	40 (11)	118 (81.9)		
	Sumatriptan 100mg	129	40 (10)	108 (83.7)		
	Placebo	142	41 (10)	113 79.6)		
Kolodny 2004[54]	Sumatriptan 50mg	285	No baseline characteristics reported across group. Average age in study is 40 years, and patients were predominantly female (86%)			
	Placebo	288				
Pini 1995[55]	Sumatriptan 100mg	151	37	186 (78)		4 per month (45%); 1-3 per month (48%); Daily (2.6%)
	Placebo	87				4 per month (42%); 1-3 per month (47%); Daily (9%)

mg: milligram, n: number of participants, N: total number of participants, NR: not reported, SD: standard deviation
*in the past 12 months

Table D2. Baseline Characteristics of Treated Migraine Attacks in the Trials of Lasmiditan, Rimegepant, Ubrogepant, and Triptans

Trial	Arm	Headache Pain Intensity, n (%)				Baseline Symptoms, n (%)					MBS, n (%)			
		N	Severe	Moderate	Mild	N	Phono-phobia	Photo-phobia	Nausea	Vomiting	N	Phono-phobia	Photo-phobia	Nausea
Lasmiditan														
SAMURAI[24]	Lasmiditan 200mg	518	148 (28.6)	355 (68.5)	15 (2.9)	518	322 (62.2)	391 (75.5)	232 (44.8)	NR	481	96 (20.0)	267 (55.5)	118 (24.5)
	Lasmiditan 100mg	503	132 (26.2)	366 (72.8)	5 (1.0)	503	303 (60.2)	386 (76.7)	210 (41.7)		469	117 (24.9)	237 (50.5)	115 (24.5)
	Placebo	524	145 (27.7)	370 (70.6)	9 (1.7)	524	327 (62.4)	416 (79.4)	221 (42.2)		488	104 (21.3)	269 (55.1)	115 (23.6)
SPARTAN[25]	Lasmiditan 200mg	528	147 (27.8)	374 (70.8)	7 (1.3)	528	326 (61.7)	397 (75.2)	219 (41.5)	NR	483	110 (20.8)	269 (50.9)	104 (19.7)
	Lasmiditan 100mg	532	159 (29.9)	364 (68.4)	9 (1.7)	532	345 (64.8)	406 (76.3)	235 (44.2)		500	110 (20.7)	276 (51.9)	114 (21.4)
	Lasmiditan 50mg	556	152 (27.3)	392 (70.5)	12 (2.2)	556	330 (59.4)	427 (76.8)	245 (44.1)		512	108 (19.4)	277 (49.8)	127 (22.8)
	Placebo	540	165 (30.6)	369 (68.3)	5 (0.9)	540	353 (65.4)	419 (77.6)	249 (46.1)		514	119 (22.0)	268 (49.6)	127 (23.5)
Farkkila 2012[26]	Lasmiditan 200mg	71	34 (48.0)†	36 (51.0)†	0 (0)	71	48 (66.4)*	57 (79.8)*	48 (66.6)*	1 (0.1)*	NR			
	Lasmiditan 100mg	82	33 (40.0)	49 (60.0)	0 (0)	82	52 (63.2)*	61 (73.9)*	43 (51.4)*	3 (2.6)*				
	Lasmiditan 50mg	82	32 (39.0)†	49 (60.0)†	0 (0)	82	56 (68.2)*	59 (72.0)*	48 (58.1)*	3 (2.8)*				
	Placebo	86	34 (40.0)†	51 (59.0)†	0 (0)	86	56 (64.2)*	66 (76.3)#	52 (60.4)*	8 (8.7)*				
Rimegepant														
Study 301[28]	Rimegepant 75mg	NR				NR					543	89 (16.4)‡	302 (55.6)‡	152 (28.0)‡
	Placebo										541	101 (18.7)‡	302 (55.8)‡	138 (25.5)‡

Study 302[27]	Rimegepant 75mg	537	537 (100)#		0 (0)	537	362 (67.4)	489 (91.1)	355 (66.1)	NR	537	72 (13.4)	277 (51.6)	169 (31.5)
	Placebo	535	535 (100)#		0 (0)	535	374 (69.9)	477 (89.2)	336 (62.8)		535	92 (17.2)	279 (52.1)	148 (27.7)
Study 303[29]	Rimegepant 75mg	669	669 (100)#		0 (0)	NR					669	108	359	189
	Placebo	682	682 (100)#		0 (0)						682	101	374	195
Marcus 2014[30]	Rimegepant 75mg	91	91 (100)#		0 (0)	NR					NR			
	Sumatriptan 100mg	109	109 (100)#		0 (0)									
	Placebo	229	229 (100)#		0 (0)									
Ubrogepant														
ACHIEVE I[32]	Ubrogepant 100mg	448	160 (35.7)	288 (64.3)	0 (0)	448	360 (80.4)	391 (87.3)	274 (61.2)	18 (4.0)	448	116 (25.9)	246 (54.9)	86 (19.2)
	Ubrogepant 50mg	423	163 (38.5)	260 (61.5)	0 (0)	423	315 (74.5)	390 (92.2)	237 (56.0)	27 (6.4)	423	82 (19.4)	248 (58.6)	90 (21.3)
	Placebo	456	169 (37.1)	287 (62.9)	0 (0)	456	362 (79.4)	416 (91.2)	292 (64.0)	26 (5.7)	456	98 (21.5)	254 (55.7)	102 (22.4)
ACHIEVE II[31]	Ubrogepant 50mg	488	175 (37.7)	289 (62.3)	0 (0)	488	374 (80.6)	420 (90.5)	297 (64.0)	21 (4.5)	488	115 (24.8)	265 (57.1)	83 (17.9)
	Ubrogepant 25mg	478	178 (40.9)	257 (59.1)	0 (0)	478	353 (81.1)	399 (91.7)	284 (65.3)	19 (4.4)	478	102 (23.4)	257 (59.1)	75 (17.2)
	Placebo	499	198 (43.4)	258 (56.6)	0 (0)	499	370 (81.1)	404 (88.6)	279 (61.2)	22 (4.8)	499	136 (29.8)	245 (53.7)	75 (16.4)
Voss 2016[33]	Ubrogepant 100mg	102	27 (26.5)	75 (73.5)	0 (0)	102	79 (77.5)	85 (83.3)	58 (56.9)	4 (3.9)	NR			
	Ubrogepant 50mg	106	31 (29.2)	75 (70.8)	0 (0)	106	78 (72.6)	88 (83.0)	57 (53.8)	5 (4.7)				
	Ubrogepant 25mg	104	38 (36.5)	65 (62.5)	0 (0)	104	82 (78.8)	94 (90.4)	53 (51.0)	2 (1.9)				
	Placebo	113	41 (36.3)	72 (65.7)	0 (0)	113	87 (77.0)	100 (88.5)	65 (57.5)	2 (1.8)				
Triptans														
Diener 2002[35]	Eletriptan 40mg	210	97 (46.2)	113 (53.8)	0 (0)	210	155 (73.8)	153 (72.9)	143 (68.1)	21 (10.0)	NR			
	Placebo	106	51 (48.1)	55 (51.9)	0 (0)	106	75 (70.8)	80 (75.5)	72 (67.9)	12 (11.3)				

Steiner 2003[49]	Eletriptan 40mg	392	185 (47.0)	207 (53.0)	NR	392	290 (74.0)	306 (78.0)	255 (65.0)	NR	NR
	Placebo	144	67 (46.0)	77 (54.0)		144	103 (71.0)	114 (79.0)	87 (60.0)		
Garcia-Ramos 2003[37]	Eletriptan 40mg	192	102 (53)	90 (47)#	NR	192	NR		102 (52)	NR	NR
	Placebo	92	42 (46)	50 (54)#		92			47 (51)		
The EMSASI Study Group 2004[52]	Sumatriptan 50mg	226	113 (50.0)	113 (50.0)	NR	224	129 (57.6)	148 (66.1)	NR	39 (17.4)	NR
	Placebo	222	107 (48.2)	115 (51.2)		222	128 (57.7)	138 (62.2)		33 (14.9)	
Diener 2004[34]	Sumatriptan 50mg	135	135 (100)#		0 (0)	NR					NR
	Placebo	152	152 (100)#		0 (0)						
Geraud 2000[38]	Sumatriptan 100mg	503	192 (38.0)	310 (62.0)	1 (0.2)	503	356 (70.7)	346 (68.8)	273 (54.3)	NR	NR
	Placebo	55	18 (33.0)	37 (67.0)	0 (0)	55	43 (78.2)	42 (76.4)	25 (45.5)		
Sheftell 2005[47] - Study 1	Sumatriptan 100mg	488	488 (100)#		0 (0)	NR					NR
	Sumatriptan 50mg	494	494 (100)#		0 (0)						
	Placebo	495	495 (100)#		0 (0)						
Sheftell 2005[47] - Study 2	Sumatriptan 100mg	485	485 (100)#		0 (0)	NR					NR
	Sumatriptan 50mg	496	496 (100)#		0 (0)						
	Placebo	494	494 (100)#		0 (0)						
Havanka 2000[40]	Sumatriptan 100mg	98	68 (69.0)	31 (31.0)	0 (0)	98	NR		77 (78.0)	NR	NR
	Placebo	91	69 (75.0)	23 (75.0)	0 (0)	91			72 (79.0)		
Smith 2005[48]	Sumatriptan 50mg	229	229 (100)#		0 (0)	NR					NR

	Placebo	242	242 (100)#		0 (0)						
Tfelt-Hansen 1995[50]	Sumatriptan 100mg	122	40 (32.8)	82 (67.2)	0 (0)	122	NR		84 (68.9)	10 (8.2)	NR
	Placebo	126	42 (33.3)	84 (66.7)	0 (0)	126			81 (64.3)	11 (8.7)	
Myllyla 1998[44]	Sumatriptan 100mg	46	46 (100)#		0 (0)	46	30/45 (66.7)	38/45 (84.4)	20 (43.5)	2/45 (4.4)	NR
	Placebo	48	48 (100)#		0 (0)	48	33 (68.8)	42 (87.5)	20 (41.7)	4 (8.3)	
Tfelt-Hansen 1998[51]	Sumatriptan 100mg	388	196 (50.5)	191 (49.2)	0 (0)	NR					NR
	Placebo	160	84 (52.5)	75 (46.9)	0 (0)						
Dowson 2002[36]	Sumatriptan 100mg	194	82 (42.3)	111 (57.2)	0 (0)	NR					NR
	Placebo	99	32 (32.3)	67 (67.7)	0 (0)						
Kudrow 2005[41]	Sumatriptan 50mg	144	47 (32.9)	96 (67.1)	0 (0)	144	104 (72.7)	125 (87.4)	95 (66.4)	3 (2.1)	NR
	Placebo	141	56 (39.7)	85 (60.3)	0 (0)	141	106 (75.2)	134 (95.0)	97 (68.8)	7 (5.0)	
Lines 2001[42]	Sumatriptan 50mg	No baseline characteristics reported									
	Placebo										
Nappi 1994[45]	Sumatriptan 100mg	158	77 (48.7)	71 (44.9)	10 (6.4)	NR					NR
	Placebo	86	40 (46.5)	41 (47.7)	5 (5.8)						
Pfaffenrath 1998[46]	Sumatriptan 100mg	298	277 (93.0)		NR	NR					NR
	Sumatriptan 50mg	303	285 (94.1)		NR						
	Placebo	99	91 (91.9)		NR						
Oral Sumatriptan Internation	Sumatriptan 100mg	148	52 (35.1)	79 (53.4)	17 (11.5)	NR					NR

al Multiple-Dose Study Group 1991[53]	Placebo	84	27 (32.1)	51 (60.8)	6 (7.1)						
Mathew 2003[43]	Eletriptan 40mg	822	321 (39.0)	501 (61.0)	0 (0)	822	526 (64.0)	592 (72.0)	510 (62.0)	NR	NR
	Sumatriptan 100mg	831	341 (41.0)	490 (59.0)	0 (0)	831	557 (67.0)	624 (75.0)	516 (62.0)		
	Placebo	419	172 (41.0)	247 (59.0)	0 (0)	419	269 (64.0)	315 (75.0)	269 (64.0)		
Goadsby 2000[39]	Eletriptan 40mg	136	63 (46.3)	68 (50.0)	NR	136	NR		83 (61.0)	11 (8.1)	NR
	Eletriptan 20mg	144	62 (43.1)	82 (56.9)		144			91 (63.2)	8 (5.6)	
	Sumatriptan 100mg	129	56 (43.4)	71 (55.0)		129			82 (63.6)	14 (10.9)	
	Placebo	142	66 (46.5)	74 (52.1)		142			90 (63.4)	12(8.5)	

MBS: most bothersome symptom, mg: milligram, n: number of participants, N: total number of participants, NR: not reported.

*Data are digitized and should be interpreted with caution,

†due to missing data, percentages do not add up to 100%,

‡historical, # assumption made based on study protocol

Table D3. Study Designs of the Trials on Lasmiditan, Rimegepant, Ubrogepant

Trial (NCT) & Author	Design and duration of follow up	Interventions & dosing procedure	Inclusion Criteria	Exclusion Criteria
Lasmiditan				
SAMURAI (NCT02439320) **Kuca 2018[24]**	Randomized, double-blind, placebo-controlled, multicentre, phase III, single attack study; follow-up visit 7 days after treated migraine attack	Lasmiditan (100 or 200mg) vs placebo - study medication to be taken within 4-hours of migraine onset (moderate to severe pain); second dose for rescue allowed 2-24 hours after first dose	Adults ≥18 years; ≥1-year history of disabling migraines with or without aura; onset before age 50; 3-8 migraine attacks/month (<15 headache days/month)	History of chronic migraine or other forms of primary or secondary headache disorder in past 12 months; ≥15 headache days/month within past 12 months; initiation of or change in migraine preventative medication within 3 months; known coronary artery disease; clinically significant arrythmia; uncontrolled hypertension; condition increasing risk of seizures
SPARTAN (NCT02605174) **Goadsby 2019[25]**	Prospective, randomized, double-blind, placebo controlled, multicentre phase III, single attack study; follow-up visit 7 days after treated migraine attack	Lasmiditan (50, 100, or 200mg) vs placebo - study medication to be taken within 4-hours of migraine onset (moderate to severe pain); second dose for rescue or recurrence allowed 2-24 hours after first dose	Adults ≥18 years; ≥1-year history of disabling migraines with or without aura; MIDAS score ≥11; onset before age 50; 3-8 migraine attacks/month (<15 headache days/month)	History of chronic migraine; other forms of primary or secondary headache disorder; ≥15 headache days/month within past 12 months; condition increasing risk of seizures; recurrent dizziness or vertigo; diabetes mellitus with complications; orthostatic hypotension with syncope; renal or hepatic impairment; current SUD within past 3 years; imminent risk of suicide or suicide attempt within past 6 months

Trial (NCT) & Author	Design and duration of follow up	Interventions & dosing procedure	Inclusion Criteria	Exclusion Criteria
Farkkila 2012[26]	Randomized, double-blind, parallel-group, multicentre, single attack, dose-ranging study (Phase II); follow-up visit within 14 days of treated migraine attack	Lasmiditan (50, 100, 200, or 400mg) vs placebo - study medication to be taken within 4-hours of migraine onset (moderate to severe pain); second dose for rescue allowed (excl. triptans or ergotamines) 2-hours after first dose	Adults ≥18 years; ≥1-year history of acute migraines with or without aura; onset before age 50; 1-8 migraine attacks/month	Use of migraine prophylaxis (unless discontinued at least 15 days prior to screening), vasoactive drugs, serotonin reuptake inhibitors, or known cytochrome P450 inhibitors
Rimegepant				
Study 301 (NCT03235479) - not yet published **Lipton 2018[28]**	Randomized, double-blind, placebo-controlled, multicentre, phase III, single attack study; follow-up visit within 7 days of treated migraine attack	Rimegepant (75mg) vs placebo; rescue medication was allowed within 24-hours	Adults ≥18 years of age; ≥1-year history of migraine; 2-8 migraine attacks/month (moderate to severe intensity); <15 headache days/month within the past 3 months; patients receiving preventative migraine medications had to be receiving stable dose for at least 3 months before trial entry	HIV; uncontrolled, unstable or recently diagnosed CVD; patients with MI, ACS, PCI, cardiac surgery, stroke, or TIA within 6 months of screening; uncontrolled hypertension or diabetes; current diagnosis of major depression, other pain syndromes, psychiatric conditions, dementia, or significant neurologic conditions; history of GI surgery or disease that causes malabsorption; SUD within past 12 months

Trial (NCT) & Author	Design and duration of follow up	Interventions & dosing procedure	Inclusion Criteria	Exclusion Criteria
Study 302 (NCT03237845) **Lipton 2019[27]**	Randomized, double-blind, placebo-controlled, multicentre, phase III, single attack study; follow-up visit within 7 days of treated migraine attack	Rimegepant (75mg) vs placebo - study medication to be taken when migraine of moderate to severe intensity occurred; use of second dose as rescue medication was allowed within 24-hours	Adults ≥18 years of age; ≥1-year history of migraine with or without aura; onset before age 50; 2-8 migraine attacks/month (moderate to severe intensity); <15 days/month with headache within the past 3 months; Patients receiving preventative migraine medications had to be receiving stable dose for at least 3 months before trial entry	History of any clinically significant or unstable medical condition, including alcohol or drug abuse and substance-use disorder; Use of any biologic investigational agents within 90 days of baseline visit; received nonbiologic investigational agents within 30 days before baseline visit
Study 303 (NCT03461757) **Croop 2019[29]**	Randomized, double-blind, placebo-controlled, multicentre, phase III, single attack study; follow-up visit within 7 days of treated migraine attack	Rimegepant (75mg) vs placebo - study medication to be taken when migraine attack of moderate to severe intensity occurred; rescue medications (e.g., aspirin, ibuprofen, acetaminophen [up to 1000 mg/day], naproxen[or any other NSAIDs], antiemetics, or baclofen) after 2-hours postdose	Adults ≥18 years of age; ≥1-year history of migraine with or without aura; onset before age 50; 2-8 migraine attacks/month (moderate to severe intensity); <15 days per month with headache within the past 3 months	SUD within past 12 months; history of drug or other allergy that made them unsuitable for participation; ECG or laboratory test findings that raised safety or tolerability concerns
Marcus 2014[30]	Randomized, double-blind, multicentre, placebo-controlled, phase II, single attack study; follow-up visit within 7 days of treated migraine attack	Rimegepant (10, 25, 75, 150, 300, or 600mg) vs sumatriptan (100mg) and placebo - study medication to be taken at onset of moderate to severe migraine; use of rescue medication (aspirin, ibuprofen, acetaminophen,	Adults aged 18-65 years; ≥1-year history of migraine with or without aura; onset before age 50; duration of migraine attack 4-72 hours if untreated; 2-7 attacks/month (moderate to severe	General: History of stroke/transient ischemic attacks, ischemic heart disease, coronary artery vasospasm, other significant underlying CVD, uncontrolled hypertension or diabetes, HIV; current diagnosis of major depression, other pain syndromes, psychiatric conditions, dementia, or significant neurological disorders, other than migraine; SUD within the past 12

Trial (NCT) & Author	Design and duration of follow up	Interventions & dosing procedure	Inclusion Criteria	Exclusion Criteria
		NSAIDs, anti-emetics, or baclofen) allowed 2-hours post-dose	intensity) in 3 months prior to study; < 15 headache days/month in previous 3 months	months. For sumatriptan: history of basilar-type or hemiplegic migraine; nonresponse to triptans
Ubrogepant				
ACHIEVE I (NCT02828020) **Dodick 2018[32]**	Randomized, double-blind, placebo-controlled, multicentre, phase III, single attack study; follow-up visit within 7 days of treated migraine attack	Ubrogepant (50 or 100mg) vs placebo, second dose or rescue medication allowed in patients with inadequate response or headache recurrence	Adults 18-75 years old; ≥1-year history of migraines with or without aura; onset before age 50; duration of migraine attack 4-72h and separated by ≥48h; 2-8 migraine attacks/month with moderate to severe headache pain in previous 3 months	Taken medication for acute treatment of headache on ≥10 days/month in previous 3 months; history of aura with diplopia or impairment of level of consciousness, hemiplegic or retinal migraine; current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia, or painful cranial neuropathy; required hospital treatment of a migraine attack ≥3 times in previous 6 months; chronic non-headache pain condition requiring daily pain medication; history of malignancy in the prior 5 years; history of any prior GI conditions that may affect the absorption or metabolism; history of hepatitis within previous 6 months
ACHIEVE II (NCT02867709) **Lipton 2019[31]**	Randomized, double-blind, placebo-controlled, multicentre, phase III, single attack study; follow-up visit within 7 days of treated migraine attack	Ubrogepant (25, 50, or 100mg) vs placebo, second dose or rescue medication allowed in patients with inadequate response or headache recurrence	Adults 18-75 years old; ≥1-year history of migraines with or without aura; onset before age 50; duration of migraine attack 4-72 hours and separated by ≥48 hours; 2-8 migraine attacks/month (moderate to severe intensity) in previous 3 months	Taken medication for acute treatment of headache on ≥10 days/month in the previous 3 months; history of migraine aura with diplopia or impairment of level of consciousness, hemiplegic or retinal migraine; current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia, or painful cranial neuropathy; required hospital treatment of a migraine attack ≥3 times in previous 6 months; chronic non-headache pain condition requiring daily pain medication; history of malignancy in the prior 5 years; history of any prior GI conditions that may affect the absorption or metabolism; history of hepatitis within previous 6 months

Trial (NCT) & Author	Design and duration of follow up	Interventions & dosing procedure	Inclusion Criteria	Exclusion Criteria
Voss 2016[33]	Randomized, double-blind, placebo-controlled, Phase IIb, single attack study; follow-up visit five days post-treatment	Ubrogepant (1, 10, 25, 50, or 100mg) vs placebo - study drug to be taken to treat a migraine of moderate to severe intensity; non-study medication allowed as rescue or recurrence treatment	Adults ≥18 years; ≥1-year history of acute migraines with or without aura; onset before age 50; 1-8 migraine attacks/month	Difficulty distinguishing migraine attacks from tension type headaches; uncontrolled hypertension; basilar-type or hemiplegic migraine headache; >15 headache days/month or had taken medication for acute headache on >10 days/month in the three months prior to screening; acute attack within past 2 months that required inpatient or ER treatment; use of an opioid or barbiturate for migraine in the past 2 months; recent change in dose of migraine-prophylactic medication

ACS: acute coronary syndrome, CVD: cardiovascular disease, ECG: echocardiogram, excl: excluding, GI: gastrointestinal, HIV: human immunodeficiency virus, MI: myocardial infarction, PCI: percutaneous coronary intervention, SUD: substance use disorder, TIA: transient ischemic attack

Table D4. Quality Ratings for Trials of Lasmiditan, Rimegepant, Ubrogepant and Triptans

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding (Double-Blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Selective outcome reporting	Measurements Valid	Intention-to-Treat Analysis	Approach to Missing Data	UPSTF Rating
Lasmiditan										
SAMURAI[25]	Yes	No	Yes	Yes	Yes	No	Yes	mITT†	N/A	good
SPARTAN[24]	Yes	No	Yes	Yes	Yes	No	Yes	mITT†	N/A	good
Farkkila 2012[26]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	good
Rimegepant										
Study 301[28]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	*
Study 302[27]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	good
Study 303[29]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	good
Marcus 2014[30]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	good
Ubrogepant										
ACHIEVE I[32]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	good
ACHIEVE II[31]	Yes	No	Yes	Yes	Yes	No	Yes	mITT	N/A	good
Voss 2016[33]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Triptans										
Diener 2002[35]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Steiner 2003[49]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Garcia-Ramos 2003[37]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
The EMSASI Study Group 2004[52]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Diener 2004[34]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Geraud 2000[38]	Yes	No	Yes	Yes	Yes	No	Yes	All-treated	N/A	good
Sheftell 2005[47] – Study 1	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Sheftell 2005[47] – Study 2	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding (Double-Blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Selective outcome reporting	Measurements Valid	Intention-to-Treat Analysis	Approach to Missing Data	UPSTF Rating
Havanka 2000[40]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Smith 2005[48]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Tfelt-Hansen 1995[50]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Myllyla 1998[44]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Tfelt-Hansen 1998[51]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Dowson 2002[36]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Kudrow 2005[41]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Lines 2001[42]	‡	No	Yes	Yes	Yes	No	Yes	mITT	N/A	fair
Nappi 1994[45]	Yes	No	Yes	Yes	Yes	No	Yes	Per-protocol	N/A	fair
Pfaffenrath 1998[46]	Yes	No	Yes	Yes	Yes	No	Yes	Per-protocol	N/A	fair
Oral Sumatriptan International Multiple-Dose Study Group 1991[53]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Mathew 2003[43]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Goadsby 2000[39]	Yes	No	Yes	Yes	Yes	No	Yes	ITT	N/A	good
Kolodny 2004[54]	‡	No	Yes	Yes	Yes	No	Yes	mITT	N/A	fair
Pini 1995[55]	Yes	No	Yes	Yes	Yes	No	Yes	NR	N/A	good

ITT: intention-to-treat, mITT: modified intention-to-treat, N/A: not applicable, USPSTF: US Preventive Services Task Force

*Data was only available in grey literature. Due to this, we did not assign an overall quality rating for the trials and were not able to assess selective outcome reporting. We will assign an overall quality rating and update quality categories where necessary upon publication of peer-reviewed results.

† Primary outcomes were analyzed with a modified intention-to-treat and secondary outcomes with intention-to-treat.

‡Baseline characteristics were stated to be similar between both intervention arms, however specific values were not reported

Data included in the NMA

Table D5. Efficacy Outcomes at 2-hours

Trial	Arms	Headache Pain Freedom			Headache Pain Relief			Free of MBS			Ability to Function Normally		
		n	N	%	n	N	%	n	N	%	n	N	%
Lasmiditan													
SAMURAI[25]	Lasmiditan 200mg	167	518	32.2	330	555	59.5	196	481	40.7	180	555	32.4
	Lasmiditan 100mg	142	503	28.2	334	562	59.4	192	469	40.9	181	562	32.2
	Placebo	80	524	15.3	234	554	42.2	144	488	29.5	119	554	21.5
SPARTAN[24]	Lasmiditan 200mg	205	528	38.8	367	565	65.0	235	483	48.7	209	565	37.0
	Lasmiditan 100mg	167	532	31.4	370	571	64.8	221	500	44.2	193	571	33.8
	Placebo	115	540	21.3	274	576	47.6	172	514	33.5	143	576	24.8
Farkkila 2012[26]	Lasmiditan 200mg	13	69	18.8	35	69	50.7	NR			NR		
	Lasmiditan 100mg	11	81	13.6	52	81	64.2						
	Placebo	6	81	7.4	21	81	25.9						
Rimegepant													
Study 301[28]	Rimegepant 75mg	104	543	19.2	304	543	56.0	199	543	36.6	181	543	33.3
	Placebo	77	541	14.2	247	541	45.7	150	541	27.7	118	541	21.8
Study 302[27]	Rimegepant 75mg	105	537	19.6	312	537	58.1	202	537	37.6	175	537	32.6
	Placebo	64	535	12.0	229	535	42.8	135	535	25.2	125	535	23.4
Study 303[29]	Rimegepant 75mg	142	669	21.2	397	669	59.3	235	669	35.1	225	669	38.1
	Placebo	74	682	10.9	295	682	43.3	183	682	26.8	176	682	25.8
Marcus 2014[30]	Rimegepant 75mg	27†	86†	31.4†	62	86	72.1	NR			NR		
	Sumatriptan 100mg	35†	100†	35.0†	72	100	72.0						
	Placebo	31†	203†	15.3†	104	203	51.2						
Ubrogepant													
ACHIEVE I[32]	Ubrogepant 100mg	95	448	21.2	275	448	61.4	169	448	37.7	193	448	42.9
	Ubrogepant 50mg	81	422	19.2	256	422	60.7	162	420	38.6	171	423	40.6
	Placebo	54	456	11.8	224	456	49.1	126	454	27.8	136	456	29.8
ACHIEVE II[31]	Ubrogepant 50mg	101	464	21.8	291	464	62.7	180	463	38.9	188	464	40.5

Trial	Arms	Headache Pain Freedom			Headache Pain Relief			Free of MBS			Ability to Function Normally		
		n	N	%	n	N	%	n	N	%	n	N	%
	Placebo	65	456	14.3	220	456	48.2	125	456	27.4	156	456	34.2
Voss 2016[33]	Ubrogepant 100mg	26	102	25.5	60	102	58.8	NR			NR		
	Ubrogepant 50mg	22	106	20.8	60	106	56.6						
	Placebo	10	113	8.8	50	113	44.2						
Triptans													
Diener 2002[35]	Eletriptan 40mg	58	206	28.2	111	206	53.9	NR			NR		
	Placebo	5	102	4.9	21	102	20.6						
Steiner 2003[49]	Eletriptan 40mg	115	359	32.0	229	359	63.8	NR			NR		
	Placebo	8	135	5.9	30	135	22.2						
Garcia-Ramos 2003[37]	Eletriptan 40mg	67	192	35.0	108	192	56.0	NR			NR		
	Placebo	17	91	19.0	28†	91†	31.0†						
The EMSASI Study Group 2004[52]	Sumatriptan 50mg	83	224	37.1	125	224	55.8	NR			NR		
	Placebo	28	222	12.6	68	222	30.6						
Diener 2004[34]	Sumatriptan 50mg	33	135	24.4	66	135	48.8	NR			NR		
	Placebo	22	152	14.5	50	152	32.9						
Geraud 2000[38]	Sumatriptan 100mg	150	499	30.1	304	498	61.0	NR			NR		
	Placebo	7	55	12.7	24	55	43.6						
Sheftell 2005[47] - Study 1	Sumatriptan 100mg	219	462	47.4	331	462	71.6	NR			NR		
	Sumatriptan 50mg	180	448	40.2	310	448	69.2						
	Placebo	84	456	18.4	208	456	45.6						
Sheftell 2005[47] - Study 2	Sumatriptan 100mg	207	440	47.0	318	440	72.3	NR			NR		
	Sumatriptan 50mg	178	454	39.2	293	454	64.5						
	Placebo	53	436	12.2	167	436	38.3						
Havanka 2000[40]	Sumatriptan 100mg	NR	NR	NR	59	98	60.0	NR			NR		
	Placebo	NR	NR	NR	29	91	31.0						
Smith 2005[48]	Sumatriptan 50mg	45	226	20.0	111	226	49.0	NR			NR		
	Placebo	14	241	6.0	65	241	27.0						
Tfelt-Hansen 1995[50]	Sumatriptan 100mg	NR	NR	NR	63	119	52.9	NR			NR		
	Placebo	NR	NR	NR	30	124	24.2						

Trial	Arms	Headache Pain Freedom			Headache Pain Relief			Free of MBS			Ability to Function Normally		
		n	N	%	n	N	%	n	N	%	n	N	%
Myllyla 1998[44]	Sumatriptan 100mg	21	42	50.0	33	42	78.6	NR			NR		
	Placebo	3	41	7.3	12	41	29.3						
Tfelt-Hansen 1998[51]	Sumatriptan 100mg	127	387	32.8	239	387	61.8	NR					
	Placebo	15	159	9.4	64	159	40.3						
Dowson 2002[36]	Sumatriptan 100mg	65	193	33.7	123	193	63.7	NR			NR		
	Placebo	15	99	15.2	42	99	42.4						
Kudrow 2005[41]	Sumatriptan 50mg	NR	NR	NR	60	144	42.0	NR			NR		
	Placebo	NR	NR	NR	42	141	30.0						
Lines 2001[42]	Sumatriptan 50mg	NR	NR	NR	239	356	67.0	NR			NR		
	Placebo	NR	NR	NR	18	80	23.0						
Nappi 1994[45]	Sumatriptan 100mg	34	142	24.0	73	142	51.4	NR			NR		
	Placebo	10	81	12.0	25	81	30.9						
Pfaffenrath 1998[46]	Sumatriptan 100mg	NR	NR	NR	177†	298†	59.5†	NR					
	Sumatriptan 50mg	NR	NR	NR	180†	303†	59.5†						
	Placebo	NR	NR	NR	28†	99†	28.1†						
Oral Sumatriptan International Multiple-Dose Study Group 1991[53]	Sumatriptan 100mg	38	148	26.0	74	148	50.0	NR			NR		
	Placebo	4	84	5.0	16	84	19.0						
Mathew 2003[43]	Eletriptan 40mg	281	779	36.0	522	779	67.0	NR			NR		
	Sumatriptan 100mg	216	799	27.0	472	799	59.0						
	Placebo	21	404	5.0	105	404	26.0						
Goadsby 2000[39]	Eletriptan 40mg	34	117	29.0	76	117	65.0	NR			NR		
	Sumatriptan 100mg	26	115	23.0	63	115	55.0						
	Placebo	8	126	6.0	30	126	24.0						

MBS: most bothersome symptom, mg: milligram, n: number of participants, N: total number of participants, NR: not reported

† Data are digitized and should be interpreted with caution

Table D6. Sustained Efficacy Outcomes

Trial	Arms	Sustained Pain Freedom, 24-hours			Sustained Pain Freedom, 48-hours			Sustained Pain Relief, 24-hours		
		n	N	%	n	N	%	n	N	%
Lasmiditan										
SAMURAI[24]	Lasmiditan 200mg	103	555	18.6	111	565	19.6	NR		
	Lasmiditan 100mg	83	562	14.8	86	571	15.1			
	Placebo	42	554	7.6	89	598	14.9			
SPARTAN[25]	Lasmiditan 200mg	128	565	22.7	68	576	11.8	NR		
	Lasmiditan 100mg	102	571	17.9	91	555	16.4			
	Placebo	77	576	13.4	42	554	7.6			
Farkkila 2012[26]	Lasmiditan 200mg	NR			NR			NR		
	Lasmiditan 100mg									
	Placebo									
Rimegepant										
Study 301[28]	Rimegepant 75mg	76	543	14.0	90	669	13.5	211	543	38.9
	Placebo	44	541	8.1	37	682	5.4	151	541	27.9
Study 302[27]	Rimegepant 75mg	66	537	12.3	53	537	9.9	229	537	42.6
	Placebo	38	535	7.1	32	535	6.0	142	535	26.5
Study 303[29]	Rimegepant 75mg	105	669	15.7	63	543	11.6	320	669	47.8
	Placebo	38	682	5.6	39	541	7.2	189	682	27.7
Marcus 2014[30]	Rimegepant 75mg	24	86	27.9	24	86	27.9	60	86	69.8
	Sumatriptan 100mg	26	100	26.0	26	100	26.0	63	100	63.0
	Placebo	15	203	7.4	15	203	7.4	86	203	42.4
Ubrogepant										
ACHIEVE I[32]	Ubrogepant 100mg	68	441	15.4	NR			165	434	38.0
	Ubrogepant 50mg	53	418	12.7				150	413	36.3
	Placebo	39	452	8.6				93	447	20.8
ACHIEVE II[31]	Ubrogepant 50mg	66	457	14.4	NR			165	449	36.7
	Placebo	37	451	8.2				93	443	21.0
Voss 2016[33]	Ubrogepant 100mg	22	102	21.6	21	102	20.6	47	102	46.1

Trial	Arms	Sustained Pain Freedom, 24-hours			Sustained Pain Freedom, 48-hours			Sustained Pain Relief, 24-hours		
		n	N	%	n	N	%	n	N	%
	Ubrogepant 50mg	16	106	15.1	15	106	14.2	48	106	45.3
	Placebo	7	113	6.2	7	113	6.2	32	113	28.3
Triptans										
Diener 2002[35]	Eletriptan 40mg	42*	209*	20.0*	NR			84*	209*	40.1*
	Placebo	2*	104*	1.7*				7*	104*	7.0*
Steiner 2003[49]	Eletriptan 40mg	75	349	21.5	NR			151	345	43.8
	Placebo	6	134	4.5				14	131	10.7
Garcia-Ramos 2003[37]	Eletriptan 40mg	37	168	22.0	NR			64	168	38.0
	Placebo	10	85	12.0				16	85	19.0
The EMSASI Study Group 2004[52]	Sumatriptan 50mg	NR			NR			NR		
	Placebo									
Diener 2004[34]	Sumatriptan 50mg	NR			NR			97	135	71.4
	Placebo							101	152	66.4
Geraud 2000[38]	Sumatriptan 100mg	NR			NR			195	498	39.2
	Placebo							14	55	25.5
Sheftell 2005[47] - Study 1	Sumatriptan 100mg	107	426	25.1	NR			163	420	38.8
	Sumatriptan 50mg	85	419	20.3				154	405	38.0
	Placebo	46	449	10.2				92	446	20.6
Sheftell 2005[47] - Study 2	Sumatriptan 100mg	108	424	25.5	NR			181	421	43.0
	Sumatriptan 50mg	96	442	21.7				173	437	39.6
	Placebo	21	430	4.9				69	429	16.1
Havanka 2000[40]	Sumatriptan 100mg	NR			NR			44	98	44.0
	Placebo							20	91	22.0
Smith 2005[48]	Sumatriptan 50mg	25	226	11.0	NR			66	226	29.0
	Placebo	12	241	5.0				41	241	17.0
Tfelt-Hansen 1995[50]	Sumatriptan 100mg	NR			NR			NR		
	Placebo									

Trial	Arms	Sustained Pain Freedom, 24-hours			Sustained Pain Freedom, 48-hours			Sustained Pain Relief, 24-hours		
		n	N	%	n	N	%	n	N	%
Myllyla 1998[44]	Sumatriptan 100mg	NR			NR			NR		
	Placebo									
Tfelt-Hansen 1998[51]	Sumatriptan 100mg	NR			NR			NR		
	Placebo									
Dowson 2002[36]	Sumatriptan 100mg	NR			NR			NR		
	Placebo									
Kudrow 2005[41]	Sumatriptan 50mg	NR			NR			NR		
	Placebo									
Lines 2001[42]	Sumatriptan 50mg	NR			NR			NR		
	Placebo									
Nappi 1994[45]	Sumatriptan 100mg	NR			NR			NR		
	Placebo									
Pfaffenrath 1998[46]	Sumatriptan 100mg	NR			NR			NR		
	Sumatriptan 50mg				NR			NR		
	Placebo									
Oral Sumatriptan International Multiple-Dose Study Group 1991[53]	Sumatriptan 100mg	NR			NR			NR		
	Placebo									
Mathew 2003[43]	Eletriptan 40mg	NR			NR			342	795	43
	Sumatriptan 100mg							276	812	34
	Placebo							58	414	14
Goadsby 2000[39]	Eletriptan 40mg	NR			NR			NR		
	Sumatriptan 100mg									
	Placebo									

mg: milligram, n: number of participants, N: total number of participants, NR: not reported.
*Data are digitized and should be interpreted with caution

Table D7. Adverse Events

Trial	Arms	Any AE			TEAEs			Nausea			Dizziness			Somnolence		
		n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Lasmiditan																
SAMURAI[24]	Lasmiditan 200mg	260	609	42.7	237	609	38.9	32	609	5.3	99	609	16.3	33	609	5.4
	Lasmiditan 100mg	229	630	36.3	205	630	32.5	19	630	3.0	79	630	12.5	36	630	5.7
	Placebo	101	617	16.4	78	617	12.6	12	617	1.9	21	617	3.4	14	617	2.3
SPARTAN[25]	Lasmiditan 200mg	253	649	39.0	NR			17	649	2.6	117	649	18.0	42	649	6.5
	Lasmiditan 100mg	230	635	36.2				21	635	3.3	115	635	18.1	29	635	4.6
	Lasmiditan 50mg	167	654	25.5				18	654	2.8	56	654	8.6	35	654	5.4
	Placebo	75	645	11.6				8	645	1.2	16	645	2.5	13	645	2
Farkkila 2012[26]	Lasmiditan 200mg	NR			61	71	85.9	2	71	2.8	27	71	38.0	8	71	11.3
	Lasmiditan 100mg				59	82	72.0	8	82	9.8	21	82	25.6	10	82	12.2
	Lasmiditan 50mg				53	82	64.6	4	82	4.9	19	82	23.2	8	82	9.8
	Placebo				19	86	22.1	0	86	0	0	86	0	2	86	2.3
Rimegepant																
Study 301[28]	Rimegepant 75mg	69	546	12.6	3	546	0.5	5	546	0.9	4	546	0.7	NR		
	Placebo	59	549	10.7	1	549	0.2	6	549	1.1	2	549	0.4			
Study 302[27]	Rimegepant 75mg	93	537	17.3	NR			10	537	1.8	NR			NR		
	Placebo	77	535	14.4				6	535	1.1						
Study 303[29]	Rimegepant 75mg	90	682	13.5	47	682	6.9	11	682	1.6	6	682	0.9	NR		
	Placebo	73	693	10.7	36	693	5.2	3	693	0.4	7	693	1.0			
Marcus 2014[30]	Rimegepant 75mg	NR			NR			3	86	3.5	1	86	1.2	NR		
	Sumatriptan 100mg							2	100	2.0	1	100	1.0			
	Placebo							5	209	2.4	2	209	1.0			
Ubrogepant																
ACHIEVE I[32]	Ubrogepant 100mg	79	485	16.3	58	485	12.0	16	485	3.3	7	485	1.4	11	485	2.3

	Ubrogepant 50mg	44	466	9.4	27	466	5.8	7	466	1.5	4	466	0.9	3	466	0.6
	Placebo	62	485	12.8	41	485	8.5	8	485	1.6	3	485	0.6	4	485	0.8
ACHIEVE II[31]	Ubrogepant 50mg	63	488	12.9	42	488	8.6	10	488	2.0	7	488	1.4	4	488	0.8
	Ubrogepant 25mg	44	478	9.2	30	478	6.3	12	478	2.5	10	478	2.1	4	478	0.8
	Placebo	51	499	10.2	30	499	6.0	10	499	2.0	8	499	1.6	2	499	0.4
Voss 2016[33]	Ubrogepant 100mg	30	102	29.4	25	102	24.5	7	102	6.9	6	102	5.9	4	102	3.9
	Ubrogepant 50mg	23	107	21.5	18	107	16.8	8	107	7.5	2	107	1.9	3	107	2.8
	Ubrogepant 25mg	21	103	20.4	14	103	13.6	6	103	5.8	3	103	2.9	5	103	4.9
	Placebo	28	113	24.8	23	113	20.4	4	113	3.5	1	113	0.9	6	113	5.3
Triptans																
Diener 2002[35]	Eletriptan 40mg	NR			NR			10	210	4.8	10	210	4.8	5	210	2.4
	Placebo							7	106	6.6	2	106	3.8	2	106	1.9
Steiner 2003[49]	Eletriptan 40mg	117	392	30	NR			NR			6	392	1.5	9	392	2.3
	Placebo	57	144	40							2	144	1.4	0	0	0
Garcia-Ramos 2003[37]	Eletriptan 40mg	60	192	31	50	192	26	17	192	8.9	12	192	6.3	10	192	5.2
	Placebo	32	92	35	15	92	16	13	92	14.1	3	92	3.3	2	92	2.2
The EMSASI Study Group 2004[52]	Sumatriptan 50mg	44	224	19.8	15	224	6.6	NR			NR			NR		
	Placebo	32	222	14.4	10	222	4.5									
Diener 2004[34]	Sumatriptan 50mg	19	135	14.1	9	135	6.7	NR			NR			NR		
	Placebo	16	153	10.5	6	153	3.9									
Geraud 2000[38]	Sumatriptan 100mg	279	492	56.7	NR			35	492	7.1	46	492	9.3	29	492	5.9
	Placebo	13	56	23.2				1	56	1.8	1	56	1.8	2	56	3.6
Sheftell 2005[47] - Study 1	Sumatriptan 100mg	NR			57	488	11.7	13	488	2.7	NR			NR		
	Sumatriptan 50mg				40	494	8.1	11	494	2.2						
	Placebo				17	495	3.4	5	495	1						
Sheftell 2005[47] - Study 2	Sumatriptan 100mg	NR			94	485	19.4	16	485	3.3	NR			NR		
	Sumatriptan 50mg				58	496	11.7	10	496	2						
	Placebo				25	494	5.1	5	494	1						
Havanka 2000[40]	Sumatriptan 100mg	25	98	26	NR			1	98	1.0	NR			NR		

	Placebo	21	91	23				1	91	1.1						
Smith 2005[48]	Sumatriptan 50mg	55	229	24	NR			3	229	1.3	11	229	4.8	6	229	2.6
	Placebo	36	242	15				4	242	1.7	8	242	3.3	0	0	0
Tfelt-Hansen 1995[50]	Sumatriptan 100mg	35	125	28	NR			14	125	11.2	3	125	2.4	6	125	4.8
	Placebo	16	126	13				11	126	8.7	1	126	0.8	0	0	0
Myllyla 1998[44]	Sumatriptan 100mg	17	46	38	NR			8	46	17.4	NR			NR		
	Placebo	9	48	19				2	48	4.2						
Tfelt-Hansen 1998[51]	Sumatriptan 100mg	202	388	52.1	160	388	41.2	35	388	9	35	388	9	28	388	7.2
	Placebo	51	160	31.9	32	160	20	4	160	2.5	6	160	3.8	9	160	5.6
Dowson 2002[36]	Sumatriptan 100mg	43	194	22.2	NR			NR			4	194	2.1	4	194	2.1
	Placebo	6	99	6.1							2	99	2	0	0	0
Kudrow 2005[41]	Sumatriptan 50mg	45	141	31.9	30	141	21.3	6	141	4.3	3	141	2.1	3	141	2.1
	Placebo	41	140	29.3	24	140	17.1	2	140	1.4	4	140	2.9	3	140	2.1
Lines 2001[42]	Sumatriptan 50mg	NR			NR			NR			NR			NR		
	Placebo															
Nappi 1994[45]	Sumatriptan 100mg	47	162	29	NR			12	162	7.4	NR			NR		
	Placebo	14	88	15.9				6	88	6.8						
Pfaffenrath 1998[46]	Sumatriptan 100mg	111	298	37.2	NR			13	298	4.4	14	298	4.7	NR		
	Sumatriptan 50mg	82	303	27.1				18	303	5.9	4	303	1.3			
	Placebo	20	99	20.2				2	99	2	2	99	2			
Oral Sumatriptan International Multiple-Dose Study Group 1991[53]	Sumatriptan 100mg	57	149	38	NR			12	149	8	7	149	5	NR		
	Placebo	19	84	23				5	84	6	2	84	2			
Mathew 2003[43]	Eletriptan 40mg	259	835	31	NR			99	835	11.9	NR			NR		
	Sumatriptan 100mg	314	849	37				125	849	14.7						
	Placebo	146	429	34				54	429	12.6						
Goadsby 2000[39]	Eletriptan 40mg	47	136	34.6	NR			2	136	1.5	5	136	3.7	NR		
	Eletriptan 20mg	49	144	34				4	144	2.8	3	144	2.1			
	Sumatriptan 100mg	52	129	40.3				4	129	3.1	5	129	3.9			

	Placebo	24	142	16.9				1	142	0.7	1	142	0.7			
Kolodny 2004	Sumatriptan 50mg	142	287	49.5	110	287	38.3	19	287	6.6	30	287	10.5	18	287	6.3
	Placebo	102	288	35.4	61	288	21.2	12	288	4.2	13	288	4.5	13	288	4.5
Pini 1995	Sumatriptan 100mg	NR			18	151	12	NR			NR			NR		
	Placebo				6	87	7									

AE: adverse event, mg: milligrams, n: number of participants, N: total number of participants, NR: not reported, TEAE: treatment-emergent adverse event.

Additional Efficacy Outcomes from the Trials of Lasmiditan, Rimegepant, and Ubrogepant (Not Included in the NMA)

Table D8. Efficacy Outcomes at 2 Hours: Associated Migraine Symptoms

Trial	Arms	N	Phonophobia-Free		Photophobia-Free		Nausea-Free		Vomiting-Free	
			n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value
Lasmiditan										
SAMURAI[25]	Lasmiditan 200mg	555	419 (75.5)	1.5 (1.1, 1.9), 0.005	379 (68.3)	2.0 (1.5, 2.6), <0.001	449 (80.9)	1.2 (0.9, 1.7), 0.153	546 (98.4)	0.9 (0.3, 2.3), 0.773
	Lasmiditan 100mg	562	426 (75.8)	1.6 (1.2, 2.0), 0.002	388 (69.0)	2.1 (1.7, 2.8), <0.001	448 (79.7)	1.2 (0.9, 1.6), 0.276	549 (97.7)	0.6 (0.3, 1.5), 0.286
	Placebo	554	374 (67.5)	---	294 (53.1)	---	427 (77.1)	---	546 (98.6)	---
SPARTAN[24]	Lasmiditan 200mg	565	431 (76.3)	1.8 (1.4, 2.4), <0.001	391 (69.2)	2.0 (1.5, 2.6), <0.001	460 (81.4)	1.0 (0.8, 1.4), 0.834	557 (98.6)	0.6 (0.2, 1.8), 0.373
	Lasmiditan 100mg	571	428 (75.0)	1.7 (1.3, 2.2), <0.001	380 (66.5)	1.8 (1.4, 2.3), <0.001	468 (82.0)	1.1 (0.8, 1.5), 0.629	567 (99.3)	1.2 (0.3, 4.6), 0.749
	Lasmiditan 50mg	598	428 (71.6)	1.4 (1.1, 1.9), 0.004	368 (61.5)	1.4 (1.1, 1.8), 0.005	473 (79.1)	0.9 (0.7, 1.2), 0.443	588 (98.3)	0.5 (0.2, 1.5), 0.229
	Placebo	576	368 (63.9)	---	309 (53.6)	---	465 (80.7)	---	571 (99.1)	---
Farkkila 2012[26]	Lasmiditan 200mg	N not reported	60.5*	NR, n.s.	48.5*	NR, 0.031	64.4*	NR, n.s.	92.5*	NR, n.s.
	Lasmiditan 100mg	N not reported	76.9*	NR, 0.0013	69.3*	NR, <0.0001	75.6*	NR, 0.034	99.9*	NR, 0.0027
	Lasmiditan 50mg	N not reported	58.1*	NR, n.s.	53.4*	NR, 0.018	68.5*	NR, n.s.	94.6*	NR, n.s.
	Placebo	N not reported	52.1*	---	34.9*	---	59.4*	---	88.9*	---
Rimegepant										
Study 301[28]	Rimegepant 75mg	See results column	133/345 (38.6)	1.4 (1.0, 1.9), 0.03†	164/470 (34.9)	1.6 (1.2, 2.1), <0.001†	149/318 (46.9)	1.2 (0.9, 1.7), n.s.†	NR	

Trial	Arms	N	Phonophobia-Free		Photophobia-Free		Nausea-Free		Vomiting-Free	
			n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value
	Placebo	See results column	113/366 (30.9)		120/483 (24.8)		134/322 (41.6)			
Study 302[27]	Rimegepant 75mg	See results column	133/362 (36.7)	1.6 (1.2, 2.2), 0.004†	183/489 (37.4)	2.1 (1.6, 2.8), <0.0001†	171/355 (48.1)	1.2 (0.9, 1.7), n.s.†	NR	
	Placebo	See results column	100/374 (26.8)		106/477 (22.3)		145/336 (43.3)			
Study 303[29]	Rimegepant 75mg	See results column	188/451 (41.7)	1.7 (1.3, 2.2), <0.001†	198/593 (33.4)	1.5 (1.2, 2.0), <0.001†	203/397 (51.0)	1.3 (1.0, 1.7), n.s.†	NR	
	Placebo	See results column	135/447 (30.2)		150/611 (24.5)		194/430 (45.2)			
Marcus 2014[30]	Rimegepant 75mg	86	45 (52.3)	2.8 (1.7, 4.8), <0.0001†	36 (41.9)	2.3 (1.3, 3.9), 0.003†	58 (67.4)	2.0 (1.2, 3.4), 0.01†	NR	
	Sumatriptan 100mg	100	49 (49.0)	2.5 (1.5, 4.1), <0.001†	47 (47.0)	2.8 (1.7, 4.7), <0.0001†	60 (60.0)	1.4 (0.9, 2.4), n.s.†		
	Placebo	204	57 (28.1)	---	49 (24.1)	---	104 (51.2)	---		
Ubrogepant										
ACHIEVE I[32]	Ubrogepant 100mg	448	244 (49.0)	1.5 (1.1, 2.0), n.s.	205 (45.8)	1.8 (1.4, 2.4), 0.004	310 (69.2)	1.4 (1.0, 1.8), n.s.	NR	
	Ubrogepant 50mg	423	245 (57.9)	1.6 (1.2, 2.1), n.s.	172 (40.7)	1.6 (1.2, 2.2), n.s.	297 (70.2)	1.3 (1.0, 1.8), n.s.		
	Placebo	456	215 (47.1)	---	143 (31.4)	---	284 (62.3)	---		
ACHIEVE II[31]	Ubrogepant 50mg	464	251 (54.1)	1.4 (1.1, 1.8), 0.044	203 (43.8)	1.5 (1.1, 2.0), 0.0167	331 (71.3)	1.1 (0.8, 1.5), n.s.	NR	
	Ubrogepant 25mg	435	234 (53.6)	1.4 (1.0, 1.8), n.s.	171 (39.3)	1.3 (1.0, 1.7), n.s.	307 (70.6)	1.1 (0.8, 1.5), n.s.		
	Placebo	456	212 (46.3)	---	162 (35.5)	---	319 (70.0)	---		

Trial	Arms	N	Phonophobia-Free		Photophobia-Free		Nausea-Free		Vomiting-Free	
			n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value	n (%)	OR (95%CI), p-value
Voss 2016[33]	Ubrogepant 100mg	102	62 (60.8)	2.1 (1.2, 3.7), 0.006†	56/102 (54.9)	2.8 (1.6, 4.9), <0.001†	72/102 (70.6)	1.4 (0.8, 2.6), n.s.†	NR	
	Ubrogepant 50mg	105	59 (56.2)	1.8 (1.0, 3.0), 0.04†	50 (47.6)	2.1 (1.2, 3.6), 0.0†	72 (68.6)	1.3 (0.7, 2.3), n.s.†		
	Ubrogepant 25mg	103	57 (55.3)	1.7 (1.0, 2.9), n.s.†	41 (39.8)	1.5 (0.9, 2.7), n.s.†	76 (73.8)	1.7 (0.9, 3.0), n.s.†		
	Placebo	112	47 (42.0)	---	34 (30.4)	---	70 (62.5)	---		

95%CI: 95% Confidence Interval, mg: milligram, n: number of participants, N: total number of participants, NR: not reported, n.s.: not significant, OR: odds ratio

*data are digitized and should be interpreted with caution

†calculated

Table D9. Patient-Reported Outcomes at 2 Hours

Trial	Arms	N	Global Impression of Change at 2 Hours, n (%)							
			Very Much Better	Much Better	A Little Better	No Change	A Little Worse	Much Worse	Very Much Worse	p-Value vs. Placebo
Lasmiditan										
SAMURAI[25]	Lasmiditan 200mg	555	57 (10.3)	153 (27.6)	143 (25.8)	60 (10.8)	31 (5.6)	13 (2.3)	5 (0.9)	<0.001
	Lasmiditan 100mg	562	54 (9.6)	155 (27.6)	153 (27.2)	83 (14.8)	16 (2.8)	8 (1.4)	8 (1.4)	<0.001
	Placebo	554	34 (6.1)	87 (15.7)	159 (28.7)	146 (26.4)	28 (5.1)	14 (2.5)	3 (0.5)	---
SPARTAN[24]	Lasmiditan 200mg	565	82 (14.5)	158 (28.0)	155 (27.4)	70 (12.4)	20 (3.5)	13 (2.3)	5 (0.9)	<0.001
	Lasmiditan 100mg	571	74 (13.0)	161 (28.2)	163 (28.5)	75 (13.1)	27 (4.7)	10 (1.8)	3 (0.5)	<0.001
	Lasmiditan 50mg	598	66 (11.0)	153 (25.6)	175 (29.3)	98 (16.4)	29 (4.8)	11 (1.8)	4 (0.7)	<0.001
	Placebo	576	46 (8.0)	115 (20.0)	162 (28.1)	152 (26.4)	25 (4.3)	15 (2.6)	1 (0.2)	---
Farkkila 2012[26]	Lasmiditan 200mg	69	19 (28.0)	NR						n.s.
	Lasmiditan 100mg	81	29 (36.0)							0.0041
	Lasmiditan 50mg	79	18 (23.0)							n.s.
	Placebo	81	13 (16.0)							---
Rimegepant										
Study 301[28]	Rimegepant 75mg	543	NR							
	Placebo	541								
Study 302[27]	Rimegepant 75mg	537	NR							
	Placebo	535								
Study 303[29]	Rimegepant 75mg	669	NR							
	Placebo	682								
Marcus 2014[30]	Rimegepant 75mg	91	NR							
	Sumatriptan 100mg	109								
	Placebo	229								
Ubrogepant										
ACHIEVE I[32]	Ubrogepant 100mg	297	102 (34.3)	NR						<0.001
	Ubrogepant 50mg	299	103 (34.4)							<0.001
	Placebo	313	69 (22.0)							---

Trial	Arms	N	Global Impression of Change at 2 Hours, n (%)							
			Very Much Better	Much Better	A Little Better	No Change	A Little Worse	Much Worse	Very Much Worse	p-Value vs. Placebo
ACHIEVE II[31]	Ubrogepant 50mg	392	131 (33.4)		NR					<0.001
	Ubrogepant 25mg	435	148 (34.1)							<0.001
	Placebo	376	78 (20.7)							---
Voss 2016[33]	Ubrogepant 100mg	102	NR							
	Ubrogepant 50mg	106								
	Ubrogepant 25mg	104								
	Placebo	113								

mg: milligram, n: number of participants, N: total number of participants, NR: not reported, n.s.: not significant.

Table D10. Adverse Events

Trial	Arms	N	AE Leading to D/C, n (%)	SAEs, n (%)	Death, n (%)	Any AEs, n (%)	TEAEs, n (%)	Dizziness, n (%)	Somnolence, n (%)	Paresthesia, n (%)	Serum AST or ALT Above ULN, n (%)
Lasmiditan											
SAMURAI[25]	Lasmiditan 200mg	609	0 (0)	2 (0.3)	0 (0)	260 (42.7)	237 (38.9)	99 (16.3)	33 (5.4)	48 (7.9)	NR
	Lasmiditan 100mg	630	0 (0)	0 (0)	0 (0)	229 (36.3)	205 (32.5)	79 (12.5)	36 (5.7)	36 (5.7)	
	Placebo	617	0 (0)	1 (0.2)	0 (0)	101 (16.4)	78 (12.6)	21 (3.4)	14 (2.3)	13 (2.1)	
SPARTAN[24]	Lasmiditan 200mg	649	1 (0.2)	1 (0.2)	0 (0)	253 (39.0)	676 (93.2)	117 (18.0)	42 (6.5)	43 (6.6)	NR
	Lasmiditan 100mg	635	0 (0)	1 (0.2)	0 (0)	230 (36.2)		115 (18.1)	29 (4.6)	37 (5.8)	
	Lasmiditan 50mg	654	0 (0)	0 (0)	0 (0)	167 (25.5)		56 (8.6)	35 (5.4)	16 (2.4)	
	Placebo	645	0 (0)	0 (0)	0 (0)	75 (11.6)		16 (2.5)	13 (2.0)	6 (0.9)	
Farkkila 2012[26]	Lasmiditan 200mg	71	NR	28 (39.0)	0 (0)	NR	61 (86.0)	27 (38.0)	8 (11.3)	12 (17.0)	NR
	Lasmiditan 100mg	82	NR	23 (28.0)	0 (0)	NR	59 (72.0)	21 (26.0)	10 (12.2)	9 (11.0)	
	Lasmiditan 50mg	82	NR	16 (20.0)	0 (0)	NR	53 (65.0)	19 (23.0)	8 (9.8)	2 (2.0)	
	Placebo	86	NR	5 (6.0)	0 (0)	NR	19 (22.0)	0 (0)	2 (2.3)	2 (2.3)	
Rimegepant											
Study 301[28]	Rimegepant 75mg	546	0 (0)	2 (0.4)	NR	69 (12.6)	3 (0.5)	4 (0.7)	NR	NR	11 (2.0)
	Placebo	549	0 (0)	1 (0.2)	NR	59 (10.7)	1 (0.2)	2 (0.4)			20 (3.6)
Study 302[27]	Rimegepant 75mg	537	0 (0)	1 (0.2)	0 (0)	93 (17.3)	NR	NR	NR	NR	13 (2.4)
	Placebo	535	0 (0)	2 (0.4)	0 (0)	77 (14.4)					12 (2.2)
Study 303[29]	Rimegepant 75mg	682	0 (0)	0 (0)	0 (0)	90 (13.5)	47 (6.9)	6 (0.9)	NR	NR	1 (0.1)

Trial	Arms	N	AE Leading to D/C, n (%)	SAEs, n (%)	Death, n (%)	Any AEs, n (%)	TEAEs, n (%)	Dizziness, n (%)	Somnolence, n (%)	Paresthesia, n (%)	Serum AST or ALT Above ULN, n (%)
	Placebo	693	0 (0)	0 (0)	0 (0)	73 (10.5)	36 (5.2)	7 (1.0)			1 (0.1)
Marcus 2014[30]	Rimegepant 75mg	86	0 (0)	0 (0)	0 (0)	NR	NR	1 (1.2)	NR	0 (0)	NR
	Sumatriptan 100mg	100	0 (0)	0 (0)	0 (0)			1 (1.0)		2 (2.0)	
	Placebo	209	0 (0)	0 (0)	0 (0)			2 (1.0)		2 (1.0)	
Ubrogepant											
ACHIEVE I[32]	Ubrogepant 100mg	485	1 (0.2)	2 (0.4)	0 (0)	79 (16.3)	58 (12.0)	7 (1.4)	12 (2.5)	NR	62 (12.9)
	Ubrogepant 50mg	466	1 (0.2)	3 (0.6)	0 (0)	44 (9.4)	27 (5.8)	4 (0.9)	3 (0.6)		NR
	Placebo	485	3 (0.6)	0 (0)	0 (0)	62 (12.8)	41 (8.5)	3 (0.6)	4 (0.8)		NR
ACHIEVE II[31]	Ubrogepant 50mg	488	2 (0.4)	0 (0)	0 (0)	63 (12.9)	42 (8.6)	7 (1.4)	4 (0.8)	NR	NR
	Ubrogepant 25mg	478	1 (0.2)	0 (0)	0 (0)	44 (9.2)	30 (6.3)	10 (2.1)	4 (0.8)		53 (11.2)
	Placebo	499	1 (0.2)	0 (0)	0 (0)	51 (10.2)	30 (6.0)	8 (1.6)	2 (0.4)		NR
Voss 2016[33]	Ubrogepant 100mg	102	0 (0)	0 (0)	0 (0)	30 (29.4)	25 (24.5)	6 (5.9)	4 (3.9)	NR	0 (0)
	Ubrogepant 50mg	107	0 (0)	2 (1.9)	0 (0)	23 (21.5)	18 (16.8)	2 (1.9)	3 (2.8)		1 (0.9)
	Ubrogepant 25mg	103	0 (0)	0 (0)	0 (0)	21 (20.4)	14 (13.6)	3 (2.9)	5 (4.9)		0 (0)
	Placebo	113	0 (0)	0 (0)	0 (0)	28 (24.8)	23 (20.4)	1 (0.9)	6 (5.3)		0 (0)

AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, D/C: discontinuation, mg: milligram, n: number of participants, N: total number of participants, NR: not reported, TEAE: treatment-emergent adverse event, ULN: upper limit of normal.

Table D11. Open-Label Extension Studies for Lasmiditan, Rimegepant, and Ubrogepant – Baseline Characteristics

Trial	Arms	N (Treated Attacks)	Headache Pain Intensity of Treated Migraine Attacks, n (%)				Baseline Symptoms of Treated Attacks, n (%)					MBS of Treated Attacks, n (%)		
			Severe	Moderate	Mild	None	Phono-phobia	Photo-phobia	Nausea	Vomiting	None	Phono-phobia	Photo-phobia	Nausea
Lasmiditan														
GLADIATOR[57]	Lasmiditan 200mg	1015 (8513)	2848 (33.4)	5546 (65.1)	115 (1.4)	6 (0.1)	4988 (58.6)	6322 (74.3)	3188 (37.4)	302 (3.5)	962 (11.3)	1726 (22.9)	4141/ 7550 (54.9)	1683/ 7550 (22.3)
	Lasmiditan 100mg	963 (8782)	2872 (32.7)	5762 (65.6)	141 (1.6)	7 (0.7)	5609 (63.9)	6741 (76.8)	3527 (40.2)	275 (3.1)	792 (9.0)	1970/ 7987 (24.7)	4307/ 7987 (53.9)	1710/ 7987 (21.4)
Rimegepant														
Study 201[90]	NR													
Ubrogepant														
NCT 02873221[91,95,96]	NR													

mg: milligram, n: number of participants, N: total number of participants, NR: not reported.

Table D12. Open-Label Extension Studies for Lasmiditan, Rimegepant, and Ubrogepant – Efficacy Outcomes

Trial	Arms	Headache Pain Freedom at 2 Hours		Free of MBS at 2 Hours		Number of Attacks Treated with Second Dose, n/N (%)	Reduction in Mean Migraine Days per Month, Mean
		n/N (%)	p-value	n/N (%)	p-value		
Ubrogepant							
GLADIATOR[57]	Lasmiditan 200mg	2668/8232 (32.4)	<0.001	2963/7298 (40.6)	<0.001	2776/8513 (32.6)	NR
	Lasmiditan 100mg	2296/8532 (26.9)		2909/7758 (37.5)		3627/8782 (41.3)	NR
Rimegepant							
Study 201*[90]	Rimegepant 75mg PRN (2-8)	NR		NR		NR	NR
	Rimegepant 75mg PRN (9-14)						
	Rimegepant 75mg QOD + PRN	NR		NR		NR	-6.0 (at 52 weeks)†
	Rimegepant 75mg Total	NR		NR		NR	
Ubrogepant							
NCT 02873221[91,95,96]	Ubrogepant 100mg	105/420 (25.0)	NR	NR		NR	NR
	Ubrogepant 50mg	96/417 (23.0)	NR				
	Usual care						

mg: milligram, n: number of participants, N: total number of participants, NR: not reported, PRN: as needed, QOD: every other day.
*based on interim analysis at three months,
†in patients with ≥14 headache days/month.

Table D13. Open Label Extension Studies for Lasmiditan, Rimegepant, and Ubrogepant – Adverse Events I

Trial	Arms	N	Any AE, n (%)	TEAE, n (%)	SAEs, n (%)	Treatment-Emergent SAEs, n (%)	AE Leading to D/C, n (%)	Death, n (%)
Lasmiditan								
GLADIATOR	Lasmiditan 200mg	1015	731 (72.0)	528 (52.0)	32 (3.2)	3 (0.3)	146 (14.4)	0 (0)
	Lasmiditan 100mg	963	636 (66.0)	434 (45.1)	28 (2.9)	6 (0.6)	108 (11.2)	0 (0)
Rimegepant								
Study 201*[90]	Rimegepant 75mg PRN (2-8)	1017	659 (64.8)	NR	NR	NR	24 (2.4)	0 (0)
	Rimegepant 75mg PRN (9-14)	481	294 (61.1)				15 (3.1)	0 (0)
	Rimegepant 75mg QOD + PRN	109	109 (38.1)				9 (3.1)	0 (0)
	Rimegepant 75mg Total	1784	1062 (59.5)		45 (2.5)	9 (0.5)	48 (2.7)	0 (0)
Ubrogepant								
NCT 02873221[91,95,96]	Ubrogepant 100mg	409	297 (72.6)	43 (10.5)	12 (2.9)	NR	11 (2.7)	0 (0)
	Ubrogepant 50mg	417	268 (66.3)	42 (10.4)	9 (2.2)		9 (2.2)	0 (0)
	usual care	417	271 (65.0)	65 (15.6)	17 (4.1)		NR	0 (0)

AE: adverse event, D/C: discontinuation, n: number of participants, N: total number of participants, PRN: as needed, QOD: every other day, SAE: serious adverse events, TEAE: treatment-emergent adverse event.
*based on interim analysis at three months

Table D14. Open Label Extension Studies for Lasmiditan, Rimegepant, and Ubrogepant – Adverse Events II

Trial	Arms	N	Dizziness, n (%)	Somnolence, n (%)	Paresthesia, n (%)	Fatigue, n (%)	Nausea, n (%)	Upper Respiratory Tract Infection, n (%)
Lasmiditan								
GLADIATOR[57]	Lasmiditan 200mg	1015	217 (21.3)	95 (9.3)	85 (8.3)	63 (6.2)	53 (5.2)	NR
	Lasmiditan 100mg	963	153 (15.8)	76 (7.8)	51 (5.3)	46 (4.7)	41 (4.2)	
Rimegepant								
Study 201*[90]	Rimegepant 75mg PRN (2-8)	1017	25 (2.5)	NR	NR	NR	33 (3.2)	108 (10.6)
	Rimegepant 75mg PRN (9-14)	481	11 (2.3)				15 (3.1)	31 (6.4)
	Rimegepant 75mg QOD + PRN	109	3 (1.0)				3 (1.0)	12 (4.2)
	Rimegepant 75mg Total	1784	39 (2.2)				51 (2.9)	151 (8.5)
Ubrogepant								
NCT 02873221[91,95,96]	Ubrogepant 100mg	409	12 (2.9)	NR	NR	NR	19 (4.6)	44 (10.8)
	Ubrogepant 50mg	417	5 (1.2)	NR	NR	NR	19 (4.7)	47 (11.6)
	usual care	417	4 (1.0)	NR	NR	NR		48 (11.5)

mg: milligrams, n: number of participants, N: total number of participants, NR: not reported, PRN: as needed, QOD: every other day.
*based on interim analysis at three months

Supplemental NMA Methods

As described in the report, we conducted random effect network meta-analyses (NMAs) where feasible. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[128,129]

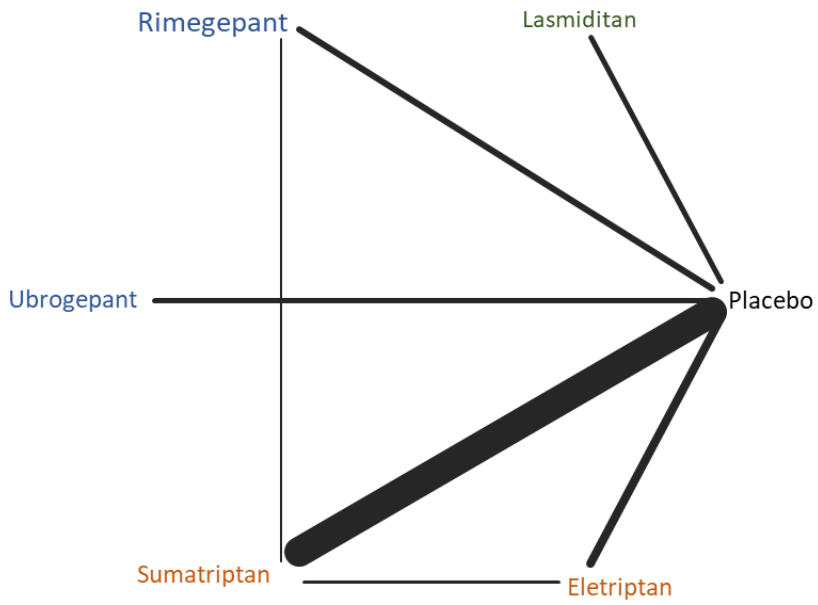
NMAs were conducted using a Bayesian framework. For continuous outcomes, the NMA model corresponds to a generalized linear model with identity link.[89] For binary outcomes (e.g., proportion of patients pain-free at 2 hours), the NMA model corresponds to a generalized linear model with a logit link.[89] For all analyses, we included random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) was assumed constant across all treatment comparisons. We used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was assessed visually using trace plots.

Furthermore, for any network where there were "loops" in evidence, we empirically compared the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[130] As there was no evidence of inconsistency, we present the full NMA results in the report. All analyses were conducted in R using the gemtc package.

Supplemental NMA Results

We provide three network diagrams that represents the NMAs in the report (Figure D2, D3 and D4). To interpret the network figures, note that the lines indicate the presence of a trial directly assessing the connecting interventions, with the thickness of the line corresponding to the number of trials. The location of treatments and the distances between them does not have any meaning. The gepants are depicted in blue, lasmiditan in green, triptans in orange, and placebo in black.

Figure D2. Network of Studies Included in the NMA of 2-hours Pain Relief (see Legend)



Legend: Figure D2 is a network of studies included in the NMA of 2-hours Pain Relief, with the thickness of the connecting lines related to the number of trials available for each pair of treatments. The NMAs of 2-hours Pain Freedom, 24 hours Sustained Pain Freedom, Any AE, TEAE, and dizziness all have a similar network diagram (not shown), with less studies contributing to the sumatriptan versus placebo connection.

Figure D3. Network of Studies Included in the NMAs of Freedom from MBS and Disability

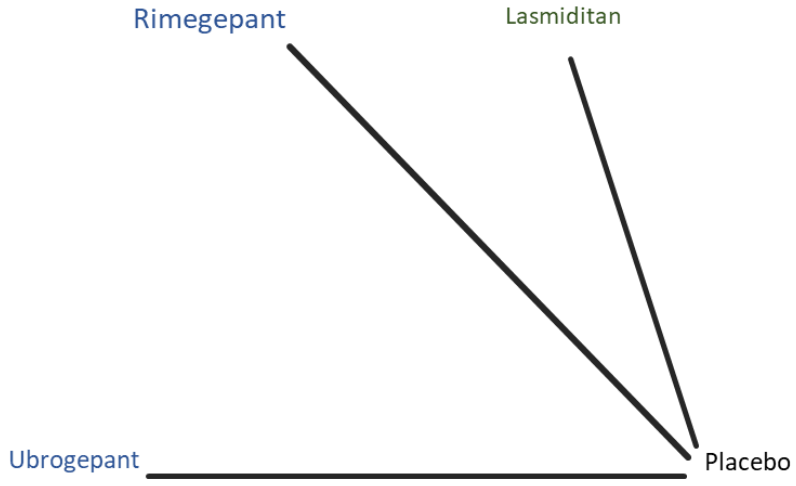
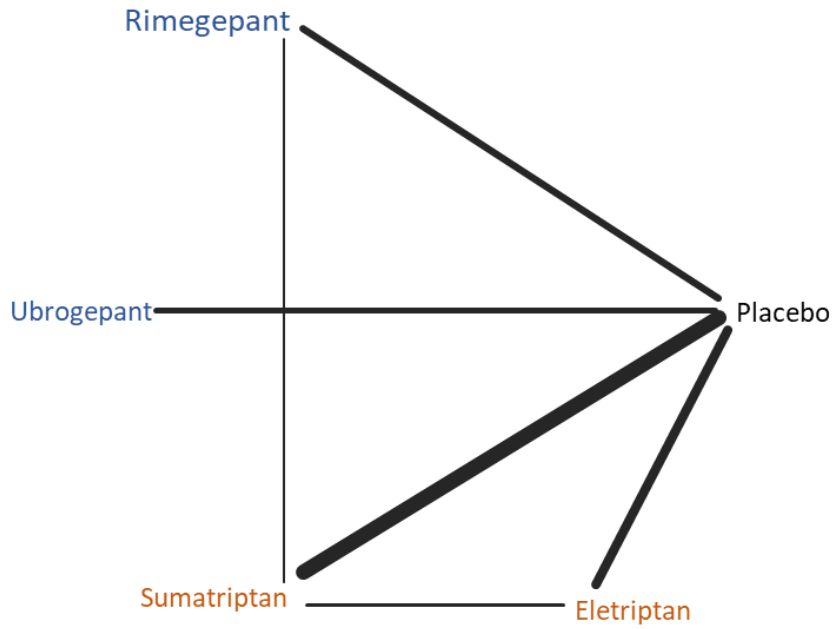


Figure D4. Network of Studies Included in the NMAs of Sustained Pain Freedom at 24 hours



Additional league tables that were not provided in the report are presented below. As stated in the report, 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.

Table D15. All Interventions and Comparators. Pain Freedom at 2 Hours (unadjusted NMA)

Lasmiditan					
1.14 (0.69, 1.84)	**Rimegepant**				
1.12 (0.65, 1.9)	0.99 (0.6, 1.61)	**Ubrogepant**			
0.56 (0.37, 0.88)	**0.5 (0.35, 0.73)**	**0.5 (0.33, 0.8)**	**Sumatriptan**		
0.37 (0.23, 0.63)	**0.33 (0.21, 0.53)**	**0.33 (0.21, 0.57)**	**0.66 (0.47, 0.93)**	**Eletriptan**	
2.21 (1.53, 3.25)	**1.95 (1.45, 2.69)**	**1.97 (1.37, 2.95)**	**3.91 (3.19, 4.76)**	**5.89 (4.23, 8.14)**	**Placebo**

Table D16. All Interventions and Comparators. Pain Relief at 2 Hours (unadjusted NMA)

Lasmiditan					
1.19 (0.86, 1.70)	Rimegepant				
1.28 (0.91, 1.91)	1.08 (0.77, 1.54)	Ubrogepant			
0.72 (0.55, 1.00)	**0.6 (0.48, 0.79)**	**0.56 (0.42, 0.75)**	Sumatriptan		
0.46 (0.33, 0.67)	**0.39 (0.29, 0.54)**	**0.36 (0.25, 0.51)**	**0.64 (0.5, 0.81)**	Eletriptan	
2.2 (1.74, 2.94)	**1.84 (1.5, 2.33)**	**1.71 (1.31, 2.22)**	**3.05 (2.68, 3.45)**	**4.75 (3.78, 5.99)**	Placebo

Table D17. All Interventions and Comparators. Sustained Pain Freedom at 24 Hours (unadjusted NMA)

Lasmiditan					
0.78 (0.33, 1.75)	Rimegepant				
0.96 (0.38, 2.27)	1.23 (0.56, 2.62)	Ubrogepant			
0.59 (0.26, 1.36)	0.76 (0.4, 1.49)	0.62 (0.29, 1.38)	Sumatriptan		
0.41 (0.15, 1.06)	0.53 (0.22, 1.24)	0.43 (0.17, 1.08)	0.7 (0.28, 1.63)	Eletriptan	
1.99 (1.03, 3.9)	**2.57 (1.61, 4.26)**	**2.09 (1.19, 3.9)**	**3.39 (2.05, 5.59)**	**4.86 (2.43, 10.48)**	Placebo

Tables D18. All Interventions and Comparators. Sustained Pain Relief at 24 Hours

a) Baseline-risk Adjusted NMA

Rimegepant				
1.08 (0.77, 1.56)	Ubrogepant			
0.94 (0.72, 1.28)	0.87 (0.64, 1.21)	Sumatriptan		
0.62 (0.43, 0.92)	**0.57 (0.39, 0.85)**	**0.66 (0.48, 0.88)**	Eletriptan	
2.39 (1.93, 3.05)	**2.2 (1.69, 2.88)**	**2.53 (2.1, 3.02)**	**3.84 (2.9, 5.15)**	Placebo

b) Unadjusted NMA

Rimegepant				
0.99 (0.63, 1.61)	Ubrogepant			
0.87 (0.62, 1.31)	0.88 (0.59, 1.39)	Sumatriptan		
0.47 (0.3, 0.74)	**0.48 (0.28, 0.77)**	**0.54 (0.35, 0.77)**	Eletriptan	
2.18 (1.64, 2.99)	**2.21 (1.53, 3.17)**	**2.49 (1.93, 3.1)**	**4.59 (3.31, 6.66)**	Placebo

Table D19. NMA results. All Interventions and Comparators. Any Adverse Event

Lasmiditan					
3.13 (1.69, 5.82)	Rimegepant				
3.51 (1.86, 6.61)	1.12 (0.62, 2.02)	Ubrogepant			
2.16 (1.27, 3.56)	0.69 (0.43, 1.08)	0.61 (0.38, 0.98)	Sumatriptan		
3.66 (2.03, 6.51)	1.17 (0.68, 1.97)	1.04 (0.6, 1.79)	1.7 (1.18, 2.47)	Eletriptan	
3.91 (2.45, 6.25)	1.25 (0.83, 1.87)	1.11 (0.73, 1.71)	1.82 (1.48, 2.27)	1.07 (0.76, 1.52)	Placebo

NMA: network meta-analysis

Table D20. NMA results. All Interventions and Comparators. Treatment Emergent Adverse Events

Lasmiditan					
4 (1.38, 12.04)	Rimegepant				
5.1 (2.31, 12.95)	1.28 (0.48, 3.68)	Ubrogepant			
2.57 (1.3, 6.07)	0.64 (0.27, 1.76)	0.5 (0.27, 1)	Sumatriptan		
3.27 (1, 11.83)	0.82 (0.22, 3.25)	0.64 (0.2, 2.06)	1.27 (0.41, 3.72)	Eletriptan	
5.99 (3.3, 12.52)	1.5 (0.67, 3.71)	1.17 (0.68, 2.03)	**2.33 (1.58, 3.29)**	1.83 (0.65, 5.24)	Placebo

NMA: network meta-analysis

Table D21. NMA results. All Interventions and Comparators. Dizziness

Lasmiditan					
7.02 (2.2, 25.63)	Rimegepant				
4.95 (1.67, 15.92)	0.7 (0.18, 2.72)	Ubrogepant			
4.09 (2, 10.6)	0.59 (0.2, 1.82)	0.83 (0.31, 2.42)	Sumatriptan		
3.97 (1.44, 12.41)	0.57 (0.15, 2.12)	0.81 (0.24, 2.78)	0.97 (0.38, 2.34)	Eletriptan	
8.43 (4.88, 19.35)	1.22 (0.44, 3.48)	1.73 (0.73, 4.52)	2.07 (1.3, 3.34)	2.14 (0.96, 5.11)	Placebo

NMA: network meta-analysis

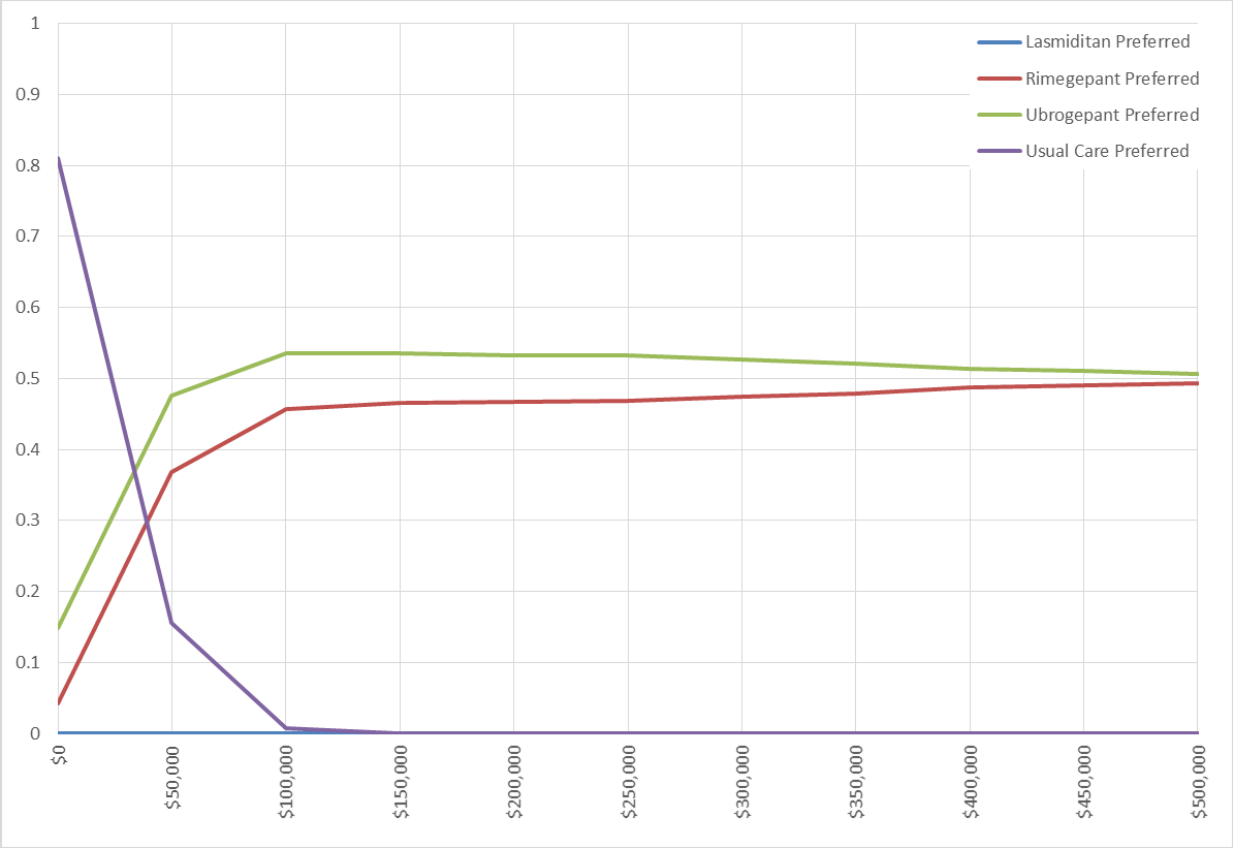
Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	N/A	☐	
	Unpaid caregiver-time costs	N/A	☐	
	Transportation costs	N/A	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	N/A	X	
	Cost of unpaid lost productivity due to illness	N/A	X	
	Cost of uncompensated household production	N/A	☐	
Consumption	Future consumption unrelated to health	N/A	☐	
Social services	Cost of social services as part of intervention	N/A	☐	
Legal/Criminal justice	Number of crimes related to intervention	N/A	☐	
	Cost of crimes related to intervention	N/A	☐	
Education	Impact of intervention on educational achievement of population	N/A	☐	
Housing	Cost of home improvements, remediation	N/A	☐	
Environment	Production of toxic waste pollution by intervention	N/A	☐	
Other	Other impacts (if relevant)	N/A	☐	

N/A: not applicable
Adapted from Sanders et al.[131]

Figure E1. Probabilistic Sensitivity Analysis Results: Acceptability Curve Comparing Lasmiditan, Rimegepant, Ubrogepant, and Usual Care



QALY: quality-adjusted life year

Scenario Analysis 1: Modified Societal Perspective

Labor costs were included in scenario analysis 1. A productivity gain of $51 per migraine was granted to patients who had "no pain" or "mild pain" at 2 hours. No productivity gain was granted to patients who had "moderate pain" or "severe pain" at 2 hours, even if they achieved a lower pain state beyond 2 hours.

Table E2. Costs, QALYs, and Cost-Effectiveness of Treatments Including Productivity Gains

Treatment	Total Cost**	QALYs	Hours of Pain	Cost per QALY Gained (Compared with Usual Care)
Lasmiditan	$8,670	1.8252	1,740	$57,500
Rimegepant*	$7,570	1.8295	1,570	Rimegepant dominates
Ubrogepant	$7,570	1.8295	1,580	Ubrogepant dominates
Usual Care	$8,040	1.8142	2,100	Comparator

QALY(s) = quality-adjusted life-year(s) gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

**Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

Scenario Analysis 2: Decreasing Frequency of Migraines Over Time

Data from a long-term open label safety study suggested that the frequency of migraines decreased over time. However, this single arm trial was not designed to evaluate whether the same effect was observed in a control population. The potential for regression to the mean and a high rate of patient drop-out could reasonably be the source of these observed changes in migraine frequency over time. However, decreasing migraine frequency could have a significant impact on budget impact analyses. Therefore, we conducted a scenario analysis evaluating the impact of decreasing migraine frequency over time, resulting in lower total costs, higher QALYs, and fewer hours of pain for all therapies, including usual care. The cost-effectiveness ratios were similar to the base-case. The full results are shown below.

Table E4. Costs, QALYs, and Cost-Effectiveness of Treatments Including Decreasing Migraine Frequency Over Time

Treatment	Total Cost**	QALYs	Hours of Pain	Cost per QALY Gained (Compared with Usual Care)
Lasmiditan	$8,510	1.8379	1,230	$177,800
Rimegepant*	$7,530	1.8409	1,110	$39,900
Ubrogepant	$7,531	1.8408	1,110	$40,100
Usual Care	$7,092	1.8299	1,480	Comparator

QALY(s) = quality-adjusted life-year(s) gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

**Drug costs per year were calculated without accounting for discontinuation of the drug. Total costs take into account discontinuation and costs of alternative treatments.

Scenario Analysis 3: Five-Year Time Horizon

When evaluating treatments for acute migraine over a longer time horizon, very small differences were observed in the incremental cost-effectiveness ratios. The full results are shown in Tables E5 and E6.

Table E5. Cost per QALY Gained and Cost per Additional Hour of Pain Avoided for Lasmiditan, Rimegepant, and Ubrogepant versus Usual Care in Population 1, with a 5-Year Time Horizon

Intervention	Total Cost	QALYs	Hours of Pain	ICER Compared with Usual Care (cost per additional QALY)	ICER Compared with Usual Care (cost per additional hour of pain avoided)
Lasmiditan	$28,150	4.3607	4,160	$176,700	$4.82
Rimegepant*	$25,400	4.3722	3,750	$39,500	$1.09
Ubrogepant	$25,400	4.3721	3,760	$39,700	$1.09
Usual Care	$24,020	4.3373	5,020	Comparator	Comparator

QALY(s) = quality-adjusted life-year(s) gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

Table E6. Cost per QALY Gained and Cost per Additional Hour of Pain Avoided for Lasmiditan, Rimegepant, and Ubrogepant versus Sumatriptan and Eletriptan in Population 2, with a 5-Year Time Horizon

Intervention	Total Cost	QALYs	Hours of Pain	ICER Compared with Usual Care (cost per additional QALY)
Lasmiditan	$28,150	4.3607	4,162	Sumatriptan and eletriptan dominate
Rimegepant*	$30,740	4.3556	4,466	Sumatriptan and eletriptan dominate
Ubrogepant	$30,760	4.3553	4,481	Sumatriptan and eletriptan dominate
Sumatriptan	$16,490	4.3643	3,843	Comparator
Eletriptan	$16,830	4.3708	3,539	Comparator

QALY(s) = quality-adjusted life-year(s) gained

*Using assumed placeholder price for rimegepant (i.e. same as WAC for ubrogepant)

Description of the evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[132]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on January 23, 2020, in Chicago, IL. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here, beginning at minute 01:51.

Erin Doty, MD
Senior Medical Advisor, Migraine and Headache Disorders, Eli Lilly

Lilly appreciates the recognition the ICER report brings to the need for new acute treatments for migraine. REYVOW™ (lasmiditan) C-V is an innovative medicine with a mechanism of action that is different from any other acute treatment for migraine and is believed to act both centrally and peripherally. In our phase 3 program, statistically significantly more patients than placebo achieved complete elimination of pain and their most bothersome symptom in only 2 hours and with a single dose of lasmiditan. We are pleased with ICER's network meta-analysis finding that lasmiditan may be slightly more efficacious than rimegepant or ubrogepant. Additionally, recent guidance issued by both the FDA and the American Headache Society raised the bar for acute treatment efficacy in clinical trials by recommending pain freedom and freedom from the most bothersome symptom as the primary endpoints, rather than just pain relief. REYVOW is the first FDA-approved acute treatment for migraine to meet this new standard and the first new class approved by the FDA in over two decades.

Migraine is a complex neurologic disease, no two people with migraine are the same, and no two attacks are the same. Therefore, there is no one size fits all approach to treating a migraine. That is why patients and doctors need treatment choices. Lilly advocates for patient and practitioner choice and is committed to making our medicines accessible so that patients can get the right treatment at the right time.

REYVOW offers a new acute treatment option for adult patients with migraine, with and without aura. We look forward to being able to offer REYVOW to patients. Everyone deserves a chance at freedom from the pain and the most bothersome symptoms of migraine.

Gilbert L'Italien, PhD
Senior Vice President of GHEOR and Epidemiology

We're here today to raise concerns regarding the results and conclusions described in the ICER Evidence Review. Our concern pertains to the fact that the evaluation is based on a total population of patients, (your population 1 and 2) and is not focused on the treatment-eligible patient population for the newer agents: i.e. patients who are refractory/intolerant to triptans, or who have a cardiovascular complication. It is not our intent to replace triptan use in patients who are benefitting from triptans or who are triptan naïve.

Who are these eligible patients? Very recent research suggests that 35% of migraine patients have failed 1 triptan, and 25% of patient failed 2 triptans. Research based on assessments using the Migraine Treatment Optimization Questionnaire (MTOQ) suggest around 50% of patients on their first oral triptans report poor or very poor effectiveness of their current treatment, and 56% report the same on their second triptan. A large percentage of such patients use non-preferred treatments (e.g. opioids, barbiturates) and seek emergency room care.

We also know from an extensive literature that ineffective acute treatment with triptans may increase the risk for Medication Overuse Headache and the risk for Chronic Migraine. These are serious public health issues pertaining to inadequate treatment that we feel the new agents can help ameliorate. You rightly highlighted both the debilitating nature of migraine and the high unmet need due to the inadequacies of existing therapies in your Evidence Report. But you also need to appropriately cost these sequelae and embed them into your economic model.

We maintain that your conclusions pertaining to the comparative effectiveness of generic triptans versus the new agents are in error, and we base this opinion on decades old differences between the triptan trials and the new agents, wherein the placebo response is greatly changed. The network meta-analytic approach seems insensitive to account for these differences, even with placebo adjustment. Further you maintain that randomized trials are the only acceptable level of evidence but then use indirect methods to compare them which is an acknowledged lower level of evidence. We provided one active comparator study (Marcus et al) as evidence to the contrary. The study includes rimegepant, sumatriptan and most importantly, a concurrent placebo arm. We would argue that this study has unique value because it is the only active comparator study available, and it suggests similar, not inferior, efficacy between rimegepant and sumatriptan at the two-hour pain endpoint. However, we all know that there is more to treating a migraine than the two-hour endpoint. Important differentiation exists between rimegepant and triptans in that rimegepant can be used in those patients who can't take triptans or those who have failed triptans. Additionally, rimegepant's unique ODT is also associated with a fast onset of action, return to normal functioning by 1 hour, and is not associated with rebound headaches or side effects common to triptans. Lastly, rimegepant's long half life has also shown durable effects to 48 hours

with the vast majority of patients not using other rescue medications. Patients suffering from migraine deserve novel and differentiated treatment options such as rimegepant.

Further, the 2018 American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice reflects our position.

The AHS position statement maintains that cost-effective care can be ensured by limiting new agent access to patients who have contraindications to the use of triptans or who have failed to respond to or tolerate oral triptans, as determined by healthcare provider attestation, or other measures such as the MTOQ. They further maintain that once approved, continued coverage with the new agents should be based on monitoring for monthly migraine frequency, measures such as the MTOQ, or clinical assessment of improvement by the healthcare provider to determine efficacy and tolerability. We agree that these evidence-based measures can be used to fairly assess the value of the newer agents. Positive data from our long-term safety study (i.e. reduction in MMDs, improvements in disability/QOL) increases in health state utilities) provides confidence that patient's therapeutic course will be optimal.

In conclusion we propose that the cost effectiveness analysis (and recommendations so derived) should thus be limited to the new agents (i.e. population 1), with the triptan refractory/intolerant CV contraindicated population, as referent. Further and in contrast to the current analysis, the high humanistic and economic burden among these patients (e.g. ER visits, MOH, Opioid Use, Disability, Lost Productivity, utility decrements) should be included to provide a fair and real world estimate of both the effectiveness and cost for this referent group. This alternative then places the burden of proof on developers of the new agents to demonstrate their real-world comparative value as per the AHS Position Statement. These patients have few alternatives, and the newer agents offer the hope that they can work, care for their loved ones, and play without restriction.

Mitchell Mathis, MD
Vice President, Chief Medical Officer, CNS, Allergan

My name is Dr. Mitchell Mathis. I am Allergan's Chief Medical Officer for neuroscience. I am trained in family medicine and psychiatry. I see patients in private practice, and I came to Allergan after serving 16 years at FDA, where I was Director of the Division of Psychiatry Products in the Center for Drug Evaluation.

Many of my patients have migraine. It prevents these highly-productive people from living their lives, doing their jobs, and caring for their families— indeed migraine is recognized as the 2nd leading cause of disability worldwide.

My thanks to the ICER Staff and patient representatives here today. I would like to speak about three points for ubrogepant:

1) unmet medical need
2) net health benefit
3) long-term value for money

Point 1 – The Unmet Need

- Approximately 30% of patients who try triptans do not have an adequate response or cannot tolerate their adverse reactions.
- About 50% of patients new to triptans DO NOT refill their prescription, and alarmingly, half of these fill an opioid.
- And lastly, for patients with cardiovascular disease, triptans are contraindicated.

Point 2 – The Clinical Value of Ubrogepant

Ubrogepant is the first approved oral CGRP receptor antagonist (gepant), indicated for the acute treatment of migraine. The approval package consisted of the usual two phase 3 registration trials, and a 1-year long-term safety study. The safety of the drug has been demonstrated; the most common adverse events were nausea and somnolence and no adverse event occurred at more than 4%.

The long-term study demonstrated efficacy and safety results consistent with the single-dose studies. In the LT study, discontinuations due to AE's were reported for less than 3% of ubrogepant-treated patients, demonstrating the real-world, long-term tolerability of the drug.

Unlike triptans, Ubrogepant is not expected to cause Medication Overuse Headache (MOH) and is the only oral acute treatment without that warning in its label. In fact, ubrogepant has no Warnings or Precautions in its label, and has many fewer adverse reactions than triptans--this very clean side effect profile makes it easy for patients to continue to use their medication.

Comparing efficacy between triptans and ubrogepant, developed decades apart, is feasible. However, such comparisons should comprehensively adjust for the increasing placebo response over time, and, include **all** triptans. When this approach is taken, the conclusion that ubrogepant is less effective than oral triptans is not supported.

Therefore, when considering ubrogepant's efficacy, obvious safety benefits, and no warnings for MOH, it is reasonable to conclude that the net health benefit for ubrogepant is favorable compared to oral triptans.

Point 3 - Long-term Value for Money

A migraine may last 48 to 72 hours; when ubrogepant's randomized data are examined past the 2-hour time point, it provides compelling evidence that treatment benefits continue to increase after 2 hours and are maximal for pain endpoints at approximately 8 hours following a single dose.

I raise this because the ICER economic model base-case does not include the efficacy increases beyond 2 hours. Increasing efficacy gains beyond 2 hours are, of course, very important to patients. Not including these benefits has a significant impact on the model results.

Allergan has had ongoing discussions with ICER related to this topic. We appreciate ICER including a scenario within the report where efficacy gains beyond 2 hours are included. In triptan insufficient responders as defined by ICER as Population 1, this yields a cost effectiveness result of $138,000 per QALY. This translates to > $78 value based priced per pill. When you add-in ICER's calculated productivity gain of $7/pill, the result is $85 per pill, consistent with Allergan's value-based list price.

Further value may be added with the following considerations noted in the ICER report:

- A favorable side effect profile that reduces complexity and improves outcomes
- No identified risk of MOH
- Novel mechanism of action for acute treatment
- Reducing use of opioids
- Increasing quality of life and productivity for patients and their families

In summary, my 3 key points:
1) unmet need exists
2) Ubrogepant has demonstrated a positive net health benefit
3) Ubrogepant provides high long-term value for money

Thank you.

Nim Lalvani, MA, MPH
Director, American Migraine Foundation (AMF)

Good morning, my name is Nirmala Singh Lalvani (professionally known as Nim Lalvani), I am the Executive Director of the American Migraine Foundation and I am a person impacted by migraine. The American Migraine Foundation (AMF) is the patient-focused organization founded by the experts of the American Headache Society (AHS). I am honored to be here today representing both the patient perspective and the clinical perspective of the American Headache Society. Today, I would like to emphasize the following:

The Patient Population: ICER's Evidence Report broadly addresses the unmet need of the patient population that would benefit from the new acute treatments; however, that focus is lost as the historical triptan data is analyzed. Both AHS and AMF believe that there should be stronger acknowledgement and consideration that although the currently available acute medications are effective for some patients, they are ineffective, poorly tolerated and/or contraindicated in a great majority of other patients. In addition, triptans remain contraindicated in patients with established cardiovascular and cerebrovascular disease (CV) and any suggestion that "decades of use" has in any way changed this contraindication or relaxed patient or clinicians' concerns of the potential for serious adverse CV events is misleading and not in the best interest of patients. Further, triptan medications and NSAIDs are not recommended for those with a history of cardiovascular disease. Additionally, over 2 million people in the US have migraine and a history of greater than or equal to 1 cardiovascular event/disease that may limit their use of triptans. The unmet need in this vulnerable population results in pain, disability, and high individual, family, societal, and economic burden. This population of patients may remain on disability and having to rely on medications such as opioids, butalbital-containing, and caffeine-containing medication. Opioids, butalbital and caffeine-containing medication contribute to medication overuse headache (MOH), suboptimal acute treatment of migraine, and development of disease progression with functional and structural brain alterations. Further, with the US being in an opioid epidemic, we must reduce the use of opioid medications to save lives. Further, according to a report released by the NIDA (National Institute on Drug Abuse), 130 people will die today, and every day, from opioid overdose. Additionally, according to a 2019 report in the American Journal of Medicine, 1 out of every 7 (14%) of opioid prescriptions are written for headache. We must do better.

New effective acute treatment options are opioid-sparing medications. Comparing the new acute treatments for migraine to triptans should not be viewed as a replacement for triptans, but these new therapies are filling a gap of unmet need for a vulnerable patient population without an effective and safe treatment option for migraine attacks. Ethically, we cannot leave these vulnerable patients in pain, disability, and an unfortunate path to disease progression to chronic migraine, medication overuse headache, and possible opioid dependence and its complications.

On behalf of the American Headache Society, the American Migraine Foundation and the patient community connected to AMF, I would like to thank ICER for taking the time to review these new therapies. As someone impacted by migraine, I know how important options are for patients who have for so long been debilitated.

1. According to a report released by NIDA (National Institute on Drug Abuse) yesterday, 130 people will die today, and every day, from opioid overdose.

2. 1 out of every 7 (14%) of opioid prescriptions are written for Headache according to a 2019 report in the American journal of medicine. See reference below.

Angie Glaser
Content Editor, Migraine Again

I am a person with Chronic Migraine, content editor for Migraine Again, and a patient advocate with the World Health Education Foundation. I want to begin by thanking ICER for bringing me here to speak on behalf of people impacted by Migraine.

I think it is really important for you to see human faces - and not just numbers - today. The decisions that you make will have a real impact on real lives, and I urge you to try to remember our humanity.

How much is your ability to think clearly and move without pain worth to you? What does your health mean to you?

This is what it means to me: Migraine - and Migraine medicine - have been a part of my life for as long as I can remember. I was diagnosed as a toddler and again at age 12 when, for the first time, I was disabled for days by the symptoms of a Migraine attack.

The Imitrex my doctor gave me made my Migraine worse. **I thought I was broken because the migraine medicine didn't help my migraine but I learned later that my experience was actually incredibly common.**

After graduating from college and entering the job force, I very quickly went from driven and healthy to disabled by Chronic Migraine. I was 24 years old.

Chronic migraine forced me to leave my job and move back in with my parents. I barely left my dark bedroom for the better part of three years. I applied for temporary disability insurance and then permanent disability insurance.

I now work from home, part-time, as an editor for a Migraine patient website. Every day I interact with desperate and strong people who are intent on living a little better with this unpredictable disease. I have interacted with thousands of people, mostly women, who have lost promotions, dreams, careers, and relationships to Migraine.

Even those whose attacks respond to triptans have to deal with side effects and limited quantities. Triptans come with the potential for medication overuse. There is very good data that shows if you take triptans for more than 12 days a month, you're at an increased risk of having more Migraine attacks in the following 12 months.

Medication overuse is one of the main factors that reliably predict episodic Migraine transforming to Chronic Migraine.

Studies also show that step therapy and inadequate treatment contribute directly to disability and disease progression. I believe, in my case, that a lack of effective options for acute Migraine attacks contributed to me becoming disabled by Chronic Migraine. Even now, access to a medication that, within 2 hours, would make me more functional could mean the difference between financial independence and living in my parents' extra bedroom.

Triptans were a double-edged sword for me – not only did they not treat my attacks, they came with awful side effects. I still tried them over and over again, for more than 10 years, because they offered hope to get me back to myself when Migraine attacks made me feel less than human.

We deserve better. We deserve a life without pain, fatigue, and nausea. Most importantly, we deserve the dignity of making a decision about what is best our health with our healthcare providers. We deserve a chance.

Sharol Klise

Good Morning & Thank you for having me here today & for your attention. What makes my testimony here today different is, to my understanding, I am the only one speaking here today who has taken any of the agents being considered. My name is Sharol Klise I am a 51-year-old post-menopausal Mortgage professional from the Seattle area & I have been a migraine sufferer for over 35 years. In that time, I have been episodic & chronic. I have experienced symptoms ranging from moderate pain to auditory disturbance & sensitivity, vision impairment including temporary blindness, nausea, projectile vomiting to debilitating pain.

I have over the past 35 years tried a myriad of medication including narcotics, anticonvulsants & triptans none of which worked for me. I have tried nearly every combination of therapies available just to mitigate the migraines or their symptoms in order to function & do the tasks most people take for granted like go to work every day, drive, go for a walk, plan for a dinner party or attend events. I have lost opportunities for job advancement because of the perception of not being reliable & relationships over being flaky & canceling at the last minute. Since being a part of one of the research studies my life is completely different. For me this agent works every single time & have reduced the number of migraines I have in a month significantly which has changed life for the better in many ways. I am able to work consistently which means no stress about paying bills & becoming an employee who is effective & worthy of promotion. I can make plans with family & friends & be confident I can follow through with them. Last year I was able to go to 2 concerts that required purchasing tickets 6 or more months in advance which I could not have done with migraines. Before this drug I would not have been able to commit to coming here today. I understand, based on reading the report, that these agents are not currently viewed as the most cost effective treatment based on other treatments being available. I would like to state that if the other treatments work for people then by all means that is what they should use but for those of us for whom the treatments do not work having lower cost drugs is not the point. There are a few things that are not being addressed or addressed in an incomplete manner in the documents I have seen thus far.

1. Quality of life & income loss for those for whom the other available treatments do not work – the loss of productivity numbers are low at best, particularly for those of us for whom triptans are ineffective. I will tell you the cost to me not having consistent ability to work cost me hundreds of thousands of dollars & seeming unavailable or unreliable has cost relationships including my marriage for which there is no dollar value

2. Insurance costs & patient out of pocket costs – before taking this agent I had multiple trips to neurologists, emergency rooms & far more primary care visits which cost both the insurance company & me a significant amount of money.

3. Cost to society – If I was unable to work I would also not have healthcare coverage. At some point both of these circumstances would mean I would fall to disability & medicare for support which is a cost not just to my quality of life but also a tangible cost of being on a public welfare system rather than contributing member of society. In conclusion, your mindful consideration of cost of quality of life, productivity as well as insurance & patient costs is appreciated. Most importantly please consider those of us that the products on the market do not serve, we have given up friends, family, careers & general participation in life & the possibility of restoring our lives or preventing others from getting to that point is the intangible benefit for which there is cost benefit analysis but rather quality of life

Eileen Brewer
President, Clusterbusters

My name is Eileen Brewer and I live with chronic migraine. Yesterday, it was a challenge getting here because my disease caused cognitive impairment. I tried to get on the wrong plane, which was bound for Houston. Then I waited at the wrong gate and almost didn't get on the plane. Sometimes having migraine disease means that something as simple as reading a few signs becomes a difficult and near impossible task. If it weren't for the kindness of strangers who helped me, I may not have made it here.

You may be thinking I haven't attempted to manage my disease well. I have. I've been attempting to manage it since 1990. In 30 years I have tried 29 different medications to treat attacks. This does not include the medications I've tried to prevent attacks or the countless alternative treatments and therapies. I've tried to cope with pain. Not a single one of them has aborted an attack for me. Ever. That should be all I need to say to convince you that people need access to more options. Sadly it isn't. Experts have told you that these medications work less well than others. They have told you that triptans are better treatments based on data that is 30 years old. This analysis ignores real world experience with triptans over the past few decades, including a better understanding of their limited efficacy and significant side-effects. There is little head-to-head data, but the one study we do have shows that these classes of drugs work equally as well as triptans. Importantly, these new medicines don't cause Medication Overuse Headache like triptans can. You can not vote that triptans are better than these new medicines. The evidence does not support this conclusion.

Our understanding of migraine is not yet complete. But we increasingly understand that it happens on multiple pathways. Triptans affect one of these pathways. So this is great for people that can use these and for whose migraine is related to this pathway. Mine is not. I'm not some anomaly because triptans make my head hurt worse, make my heart feel like it is going to explode out of my chest, and make my pulse accelerate to as much as 180 beats per minute. This happens to others. Others also have other negative side-effects. Your data says 10-18% do not respond well to triptans. 10-18% of 40 million is still a lot of people. Overall, this population represents 36 billion dollars in costs annually in the US. We represent lost productivity, increased burden on our healthcare system, and increased burden on our families, friends, and communities. When you calculate the value of these drugs, it is important to consider those things.

I'm here to tell you that I need something in my life to change and so do millions of other people. I used to think I was crazy or strange with doctors writing me off as a tough case, or accusing me of being a drug seeker. I don't even like the drugs they were accusing me of being addicted to. They didn't work. They made things worse. What's great about being itchy and more nauseous on top of having all the symptoms of a migraine attack? I'm not saying that opioids are not appropriate for some people. Some people find them to be a great rescue medication, but they certainly are not and should not be a first line treatment. Still, opiates continue to be

prescribed for migraine at unnecessarily high rates, often as a first line treatment. We have an opportunity to offer another approach and more options. We have an opportunity to fight the opioid epidemic in a new way. We are always talking about novel approaches to treating pain, but we seem to be hesitant to recognize these when we are looking at them.

Triptans work best when you take them at the start of an attack. I wake up every morning with a migraine attack. I throw up almost every day, sometimes multiple times a day. I go to sleep every night with a migraine attack. Some days I function reasonably well. I have learned to live with pain. There is this piece of my brain devoted to coping with pain. It's job is to remind me to relax, think around it, and survive. Some days that's my whole brain because things are just so intense. Some days I wander around my house desperately searching for something, anything that will make it stop. I open cabinets, the fridge, the pantry, the vanity, but nothing is ever there. There is no escape.

I'm not alone. I represent millions of people with the same story. I often wonder what I could do if I didn't have to factor in pain. I am productive but I could be better. I could have a clean house. I could reliably take my kids to activities. I could work a 40/hr a week job. There wouldn't be days when my husband had to work, care for the kids, cook, clean, do dishes and care for me. I could do everything I dreamed.

When you consider advising on coverage for these medications, please consider the totality of the people you are affecting. Your analysis MUST fully capture the benefits of these medicines and NOT make a flawed comparison with 30-year-old data.

I don't care if a treatment is less effective than another treatment I know doesn't work for me. I care that I have the potential of a new option. If insurance won't cover it though, it won't matter what is out there. I'll just have to continue waiting and hoping for a better life than this one. This really isn't any kind of life at all. But you have the power to make it a better one

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

Thank you for inviting me to speak here today regarding acute treatments for migraine. I stand before you today, a 41-year-old woman, who lives with daily intractable chronic migraine. Since the age of eight, migraine has been a constant part of my life. Over thirty-three years, episodic migraine became chronic, then intractable. Through this evolution I have needed and used many preventives and acute medications to treat my disease and symptoms.

On my journey with migraine I have found that I am allergic to sumatriptan, cannot tolerate other triptans, have an allergic reaction to most NSAIDs, and cannot tolerate home administration of DHE. The pain management options I am left with are very limited, and while I also live with anxiety and depression, this reality only exacerbates feelings of hopelessness and defeat.

Despite quarterly botulinum neurotoxin injections, bilateral occipital, supraorbital and sphenoganglion blocks, acupuncture, massage therapy, and four preventive medications, I am still in pain. My acute treatments are oral ketoralac, promethazine or ondancetrom for nausea, and chlorpromazine to sleep off the really bad attacks. My rescue medication is nasal ketamine spray, which I have to pay out of pocket for, and have shipped from a compounding pharmacy out of state. When those fail me, I can take a steroid taper but 95% of the time it just interrupts my sleep and eating patterns.

More often than I would prefer, I find myself in my local urgent care center for a specific treatment protocol written up by my headache specialist due to long bouts of intractable migraine. If that also fails the next step is a three-day admission to the hospital for DHE infusions. Not only is this a huge burden on me physically and emotionally, it deeply affects my family. In order to care for me my husband needs to take off from work, days at a time. My children see their mother unable to function most days. The hours and days spent in urgent cares and hospital rooms are times I cannot get back.

My life with migraine could change drastically with these new acute medications for migraine. I now have a viable pain management option that could potentially work for me, unlike the triptans. I am barely getting by on my current regiment and need something better. It is disheartening that ICER finds these new therapies to be less effective overall than triptans.

I find ICER's rating to be concerning because it could mean that for someone like myself who is allergic to and cannot tolerate triptans, there is a real possibility that I will not have access to any of these new therapies. Since these outcomes are mostly based on limited trial data and the use of the QALY or quality adjusted life year, the decisions based on those outcomes can adversely affect patients. Methodologies used to measure value, such as the QALY, rarely evolve enough to truly provide the strongest view of a therapy's value. Many therapy value analyses take place around the

time of marketing approval. Nonetheless, applicable research pertaining to the treatment, the disease it addresses, and other therapies are still emerging. Also, this collection of facts over time gives the clearest interpretation of the value of a treatment.

QALY can also discriminate against people with disabilities and serious chronic conditions. These disability weights reduces the value of life-sustaining properties of a medication if it is also not possible to return a patient to full health. For someone like myself, a drug may not seem valuable to cover due to my diagnosis of chronic migraine which, on the Migraine Disability Assessment Test, my score would reflect a level of moderate to severe disability.

There should be a sufficient integration of the tangible benefits of good health, including considerations related to quality of life such as, being able to physically carry out a task or attend an event or meeting, as well as having the mental well-being to interact with family or friends at work or in community activities. Overall, the impact these value assessments have on patients is extremely monumental in how we can live quality lives.

Patient input, updated use of QALY's to also address disabilities and chronic conditions and proper representation on the voting panel to include clinical experts who are within the medical specialty they are assessing are strongly recommended.

It is my hope that through the engagement of patient advocacy groups and their reach on platforms like social media, the inclusion of the patient voice will be a permanent piece of future value assessments.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the New England CEPAC Public Meeting on January 23, 2020 in Chicago, IL.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Foluso Agboola, MBBS, MPH	Institute for Clinical and Economic Review	*
Steven Atlas, MD, MPH-DF/HCC	Harvard Medical School, Massachusetts General Hospital	*
Todd A. Lee, PharmD, PhD	University of Illinois at Chicago	*
Zunelly Odhiambo, MPH	Institute for Clinical and Economic Review	*
Steven D. Pearson, MD, MSc	Institute for Clinical and Economic Review	*
Michelle Poulin, BA	Institute for Clinical and Economic Review	*
David M. Rind, MD, MSc	Institute for Clinical and Economic Review	*
Matt Seidner, BS	Institute for Clinical and Economic Review	*
Daniel Touchette, PharmD, MA, FCCP	Institute for Clinical and Economic Review	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	Associate Professor, Saint Louis University Center for Health Outcomes Research, School of Medicine, and College for Public Health & Social Justice	*
Nicholas Bagley, JD	Professor of Law, University of Michigan Law School	*
Bijan Borah, PhD	Professor of Health Services Research, Mayo Clinic College of Medicine and Science	*
Aaron Carroll, MD, MS	Professor of Pediatrics; Associate Dean for Research Mentoring; Director, Center for Health Policy and Professionalism Research, Indiana University School of Medicine	*
Don Casey, MD, MPH, MBA	Principal, IPO4Health; Senior Vice President and Chief of Clinical Affairs, Medecision	*
Gregory Curfman, MD	Deputy Editor, Journal of the American Medical Association (JAMA)	*
Stacie B. Dusetzina, PhD	Associate Professor of Health Policy, Ingram Associate Professor of Cancer Research, Vanderbilt University School of Medicine	*
Jill Johnson, PharmD	Professor, College of Pharmacy, University of Arkansas for Medical Sciences	*
Reem Mustafa, MD, MPH, PhD	Associate Professor of Medicine, Division of Nephrology and Hypertension, and Director, Outcomes and Implementation Research, University of Kansas Medical Center	*
Rachel Sachs, JD, MPH	Associate Professor of Law, Washington University in St. Louis	*
Kurt Vanden Bosch, PharmD	System Formulary Manager, St. Luke's Health System, Idaho	*
Stuart Winston, DO	Physician Lead: Patient Experience, Quality Improvement, Integrated Health Associates, St. Joseph Mercy Health System	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participants and COI Disclosures

Participant	Affiliation	Disclosure
Harold Carter, PharmD	Senior Director, Clinical Solutions, Express Scripts	Full-time employee of Express Scripts.
Erin G. Doty, MD	Senior Medical Advisor, Migraine and Headache Disorders, Eli Lilly	Full-time employee of Eli Lilly.
Katie Golden, BA	Director of Patient Relations, Immediate Past Steering Committee Member, CHAMP	Received compensation from the following organizations which receive at least 25% funding from pharmaceutical companies: CHAMP, Miles for Migraine, and US Pain Foundation (sponsorship includes Allergan, Biohaven, and Eli Lilly)
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. 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.
Gil L'Italien, PhD	Senior Vice President of GHEOR and Epidemiology, Biohaven Pharmaceuticals	Full-time employee of Biohaven Pharmaceuticals.
Mitchell Mathis, MD	Vice President, Chief Medical Officer, CNS, Allergan	Full-time employee of Allergan.
Travis Tacheny, PharmD	Clinical Pharmacy Program Consultant, HealthPartners	Full-Time Employee of HealthPartners.
Sarah Wells Kocsis, MBA	Vice President of Public Policy, Society for Women's Health Research	Held senior positions at three different health care companies (Amgen, Boston Scientific, and Hologic) and has stock holdings in excess of $10,000 in each of these 3 companies.

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.