

## **Acute Treatments for Migraine: Effectiveness and Value**

*Draft Background and Scope*

June 28, 2019

### **Background**

Migraine is a common, episodic cause of disabling headache often associated with nausea and sensitivity to light and sound. Overall, 12-15% of adults in the United States (US) have reported migraine or severe headaches.<sup>1,2</sup> The hallmark of migraine is recurrent attacks characterized by headache that is typically 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.<sup>3</sup> Patients with migraine have increased use of health care resources including visits to health care providers and emergency departments.<sup>4,5</sup> Overall cost of health care for those with migraine are estimated to be \$11-50 billion dollars in the US.<sup>4,6</sup> Direct health care costs as well as indirect costs associated with work loss and disability claims are higher for those with migraine,<sup>7-9</sup> and migraine is one of the most common causes of disability worldwide.<sup>10</sup>

Diagnosis of migraine is based upon patient-reported symptoms, history, and physical examination findings; there is no test available that confirms the diagnosis.<sup>11</sup> 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. The most common aura are visual symptoms such as seeing bright lines, shapes, or objects. 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. Migraines are more common in women than men,<sup>12</sup> and in those aged 18 to 44 years.<sup>1,2</sup> 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.<sup>13</sup> Predisposing factors associated with acute migraine attacks include emotional stress, menstruation, visual stimuli, changes in weather, and certain foods and activities.<sup>14</sup>

Treatment of migraine focuses on quickly aborting episodic symptoms and is usually more effective the sooner it is given.<sup>15</sup> These treatments are referred to by a number of terms including “acute treatment,” “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 precede 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. They are often used in combination preparations along with caffeine. Other strategies such as lying down in a quiet and dark room are also helpful, and a nap or sleep is often associated with 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 migraine treatment.<sup>13</sup> 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. Other medications, less commonly used since the introduction of triptans, include ergotamine preparations, barbiturates, and opioids. Side effects and limited efficacy of these drugs, as well as tolerance and misuse for opioids and barbiturates, have led to their being reserved for patient 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, but for about a quarter to a third of patients with severe and frequent attacks, medications to prevent migraine attacks are recommended.<sup>15</sup> This is important because medication overuse headache can result from frequent administration of all medications for acute migraine, especially with nonspecific pain medications such as opioids, barbiturates, and combination agents.

Despite available acute treatments, many individuals do not respond to multiple different medications which demonstrates the need for new acute treatment options. For example, studies of triptans often demonstrate response rates of 40-75%,<sup>16</sup> and decreased response over time can also be seen in some individuals. 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.<sup>17,18</sup> Two new CGRP antagonists, ubrogepant and rimegepant, are under review by the FDA for treatment of acute migraine. Another potential new acute treatment for migraine is lasmiditan, a selective 5-HT 1f agonist.

## Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A final scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments.

## Report Aim

This project will evaluate the health and economic outcomes of lasmiditan, rimegepant, and ubrogepant for acute migraine. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

## Scope of Clinical Evidence Review

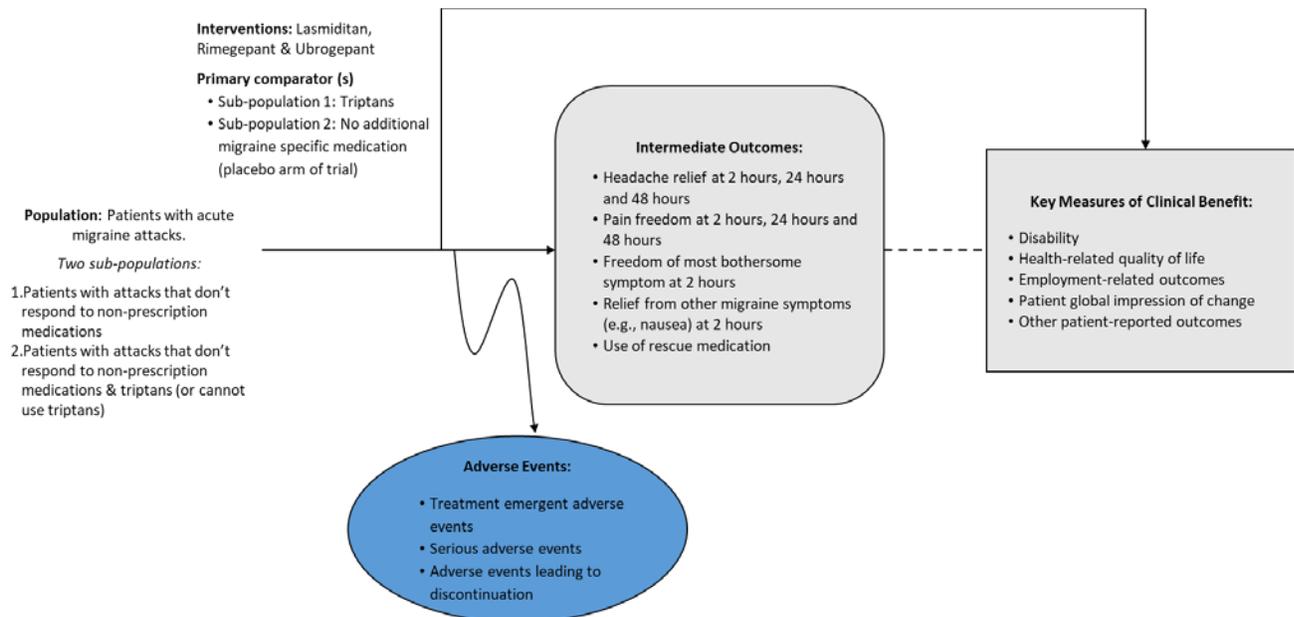
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from 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/grey-literature-policy/>).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

## Analytic Framework

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

**Figure 1.1. Analytic Framework: Anabolic Therapies for Acute 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 health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., remission), and those within the squared-off boxes are key measures of benefit (e.g., mortality). The key measures of 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 treatment which are listed within the blue ellipse.<sup>19</sup>

### Populations

The population of focus for this review will be adults ages 18 years and older with a diagnosis of migraine that is not considered to be chronic (<15 headache days per month), with or without aura as specified by the ICHD diagnostic criteria. We will plan to evaluate two sub-populations of patients with migraine:

1. Patients who have attacks that have not responded to non-prescription medicines.

2. Patients who have attacks that have not responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated.

### ***Interventions***

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Lasmiditan
- Rimegepant
- Ubrogapant

### ***Comparators***

Data permitting, we intend to compare lasmiditan, rimegepant, and ubrogapant to each other and to triptans for sub-population 1. For sub-population 2, we intend to compare lasmiditan, rimegepant, and ubrogapant to each other and to no additional migraine-specific medication (as estimated by the placebo arms of the clinical trials). Since these new agents under review are all orally available, we will focus our comparison of triptans on the oral formulations. We will also consider comparing to other commonly used acute migraine therapies such as NSAIDs, ergot compounds, opioids, and barbiturates.

### ***Outcomes***

The outcomes of interest are described in the table below.

#### **Table 1.1. Key Outcomes and Harms**

The outcomes of interest include:

- 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
- 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)
- Serious adverse events
- Treatment-emergent adverse events
- Adverse events leading to discontinuation

### ***Timing***

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

### ***Settings***

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

### **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 Table 1.2 on the following page.

**Table 1.2. Potential Other Benefits and Contextual Considerations**

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.
Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “the comparator,” 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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

### Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a Markov simulation model to assess the cost-effectiveness of lasmiditan, rimegepant, and ubrogepant compared with each other and with oral triptans (e.g. almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) in sub-population 1, and with each other and with no additional migraine-specific medication as estimated by the placebo arms of the clinical trials in sub-population 2, as defined in the analytical framework. The model will have a short cycle length (one day) and time horizon (e.g. two years) due to the relative acuteness of migraine attack onset and resolution. We anticipate that this time horizon will be sufficient for estimating the long-term cost-effectiveness of these acute treatments for migraine. The model structure will be based in part on models identified through a systematic review of the acute migraine literature. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate analysis conducted from a societal perspective. The target population will consist of adults ages 18 years and older with acute migraine with or

without aura as specified by the ICHD diagnostic criteria and less than 15 headache days per month. The model will consist of Markov health states including presence of migraine and no migraine in each one-day period. Transition states will include treatment outcomes of migraine including resolution and recurrence of migraine. If data are available appropriately linking most bothersome symptoms other than pain to patient quality of life, these symptoms will also be included as an outcome in the model. Treatment-emergent serious adverse events, if any, will also be included as a transition state in the model. A cohort of patients will transition between states during predetermined one-day cycles over a two-year time horizon.

Key model inputs will include clinical probabilities, quality of life values, and health care costs (drug and non-drug treatment costs) associated with the modeled health states. The effects of lasmiditan, rimegepant, ubrogepant, and the comparators will be modeled by altering probabilities, costs, and other inputs to reflect comparative responses to those therapies from clinical trials. Treatment effectiveness of lasmiditan, rimegepant, ubrogepant, and the comparators will be estimated using network meta-analyses, if feasible.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and the associated direct medical costs and utility (expressed as quality-adjusted life years [QALYs]) assigned to each state. Quality-of-life weights will be applied to each health state, including quality-of-life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug, condition-related care, and serious adverse events. In addition, productivity losses associated with migraine and gains from treatment will be included in a separate analysis if data allow. All costs and outcomes will be discounted by a rate of 3%. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY gained. If indicated, threshold analyses will be conducted using cost per QALY gained to assess cost and benefit thresholds needed for a variety of willingness to pay cost-effectiveness thresholds. Additionally, we will conduct a cost per consequence analysis such as a cost per half-day or full day of migraine relief, pending data availability. One-way sensitivity analyses will be conducted on all model inputs, including the time horizon length, to assess their individual impact on outcomes. Probabilistic sensitivity analyses will be conducted to assess the impact of important model parameters simultaneously. Other scenario analyses accounting for specific parametric uncertainties will also be conducted, as appropriate.

In separate analyses, we will explore the potential health system budgetary impact of lasmiditan, rimegepant, and ubrogepant over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: <http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf>.

### ***Identification of Low-Value Services***

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see <https://icer-review.org/material/final-vaf-2017-2019/>). These services are ones that would not be directly affected by the new acute treatments (e.g., emergency department visits for migraine attacks/attacks), 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. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

## References

1. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-349.
2. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache*. 2015;55(1):21-34.
3. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain*. 2018;19(1):82-82.
4. Hawkins K, Wang S, Rupnow M. Direct cost burden among insured US employees with migraine. *Headache*. 2008;48(4):553-563.
5. Stokes M, Becker WJ, Lipton RB, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). *Headache*. 2011;51(7):1058-1077.
6. Ford JH, Ye W, Nichols RM, Foster SA, Nelson DR. Treatment patterns and predictors of costs among patients with migraine: evidence from the United States medical expenditure panel survey. *Journal of medical economics*. 2019:1-10.
7. Messali A, Sanderson JC, Blumenfeld AM, et al. Direct and Indirect Costs of Chronic and Episodic Migraine in the United States: A Web-Based Survey. *Headache*. 2016;56(2):306-322.
8. Raval AD, Shah A. National Trends in Direct Health Care Expenditures Among US Adults With Migraine: 2004 to 2013. *The journal of pain : official journal of the American Pain Society*. 2017;18(1):96-107.
9. Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and Indirect Healthcare Resource Utilization and Costs Among Migraine Patients in the United States. *Headache*. 2018;58(5):700-714.
10. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2018;17(11):954-976.
11. Headache Classification Committee of the International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia : an international journal of headache*. 2018;38(1):1-211.
12. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the subtypes of migraine. *International journal of epidemiology*. 1995;24(3):612-618.
13. Loder E. Triptan therapy in migraine. *The New England journal of medicine*. 2010;363(1):63-70.
14. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia : an international journal of headache*. 2007;27(5):394-402.
15. Charles A. Migraine. *The New England journal of medicine*. 2017;377(17):1698-1699.
16. 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.
17. Eftekhari S, Salvatore CA, Calamari A, Kane SA, Tajti J, Edvinsson L. Differential distribution of calcitonin gene-related peptide and its receptor components in the human trigeminal ganglion. *Neuroscience*. 2010;169(2):683-696.
18. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia : an international journal of headache*. 2010;30(10):1179-1186.

19. Woolf S. An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale. *Clinical Practice Guideline Development: Methodology Perspectives AHCPR Pub.* 1994(95-0009):105-113.