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Acute Treatments for Migraine: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

This analysis plan details our approach to the cost-effectiveness models evaluating lasmiditan, rimegepant, and ubrogepant for acute treatment of migraine. The primary aim of the models will be to evaluate the cost-effectiveness of lasmiditan, rimegepant, and ubrogepant compared to each other and to three comparators, in two separate analyses representing two distinct populations. The first population will be patients who have migraine attacks that have not responded to non-prescription medicines (population 1). For population 1, the comparators will be sumatriptan and eletriptan. The second population being evaluated will be patients who have 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). The comparator for population 2 will be "usual care," represented by the placebo arm from clinical trials involving lasmiditan, rimegepant, and ubrogepant. The base-case analyses will take 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 losses will be considered in scenario analyses. The model will be developed in Microsoft Excel 2016 (Redmond, WA). Refer to the Research Protocol (https://icer-review.org/material/acute-migraine-research-protocol/) for details on the systematic review of the clinical evidence on this topic.

2. Methods

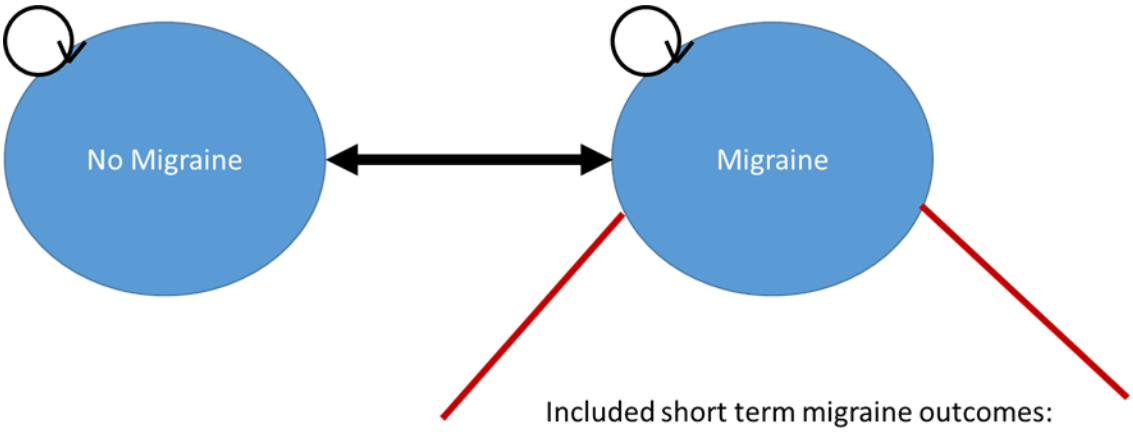
2.1 Overview and Model Structure

For the cost-effectiveness analyses, we will develop a *de novo* decision analytic model informed by key clinical trials, 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 analyses will take a health care sector perspective. Costs and outcomes will be discounted at rate of 3%.

The model will focus on an intention-to-treat analysis, with a hypothetical cohort of patients requiring acute treatment for migraine, being treated with lasmiditan, rimegepant, ubrogepant, sumatriptan, eletriptan, or placebo, in two primary population comparators. Population 1 will compare lasmiditan, rimegepant, and ubrogepant to each other and to two triptans: sumatriptan and eletriptan. Population 2 will compare lasmiditan, rimegepant, and ubrogepant to each other and to no additional migraine-specific acute treatment (i.e. placebo arms from clinical trials). Model cycle length will be 24 hours, based on the typical duration of an acute migraine episode.

As shown in the model schematic, Figure 1, and using definitions shown in Table 1, simulated patients enter the model through either Markov state "No Migraine" or "Migraine," according to the weighted average daily probability of having a migraine in the target population (i.e. 4.8 migraine days per month, a weighted average of 0.157 migraines per day). For those entering "Migraine" Markov state, patients will receive "Acute Treatment" (i.e. lasmiditan, rimegepant, ubrogepant, sumatriptan, eletriptan, or placebo). Initial treatment may result in complete resolution of migraine pain (pain freedom), an improvement in migraine pain without complete resolution (pain relief), or no improvement in migraine pain at two and 24 hours. Patients may also experience nausea and/or vomiting, photophobia, and phonophobia. For those experiencing ongoing migraine pain or nausea/vomiting, there will be some probability that a patient will require treatment in the emergency department. Cost and utility will be summed for each day (i.e. cycle). In the following cycle, patients will move to either the "No Migraine" or "Migraine" state based on the weighted average daily probability of having a migraine.

Figure 1. Model Schematic



Included short term migraine outcomes:

- Initial pain level
- Proportion pain free at 2 hours
- Proportion pain relief at 2 hours
- Proportion pain free at 24 hours
- Proportion pain relief at 24 hours
- Nausea/vomiting free at 2 hours
- Photophobia free at 2 hours
- Phonophobia free at 2 hours
- Physician office visits
- Emergency department visit
- Hospitalization

Table 1. Treatment Response Definitions Used in the Model

Treatment Response Description	Definition	Calculation from Clinical Trials
Pain Freedom at 2 Hours	Reduction of headache pain from 1, 2, or 3 to 0 on a 4-point Likert scale at each time point at 2 hours. or Reduction of headache pain from 1, 2, or 3 to 0 on a 4-point IHS severity rating scale at each time point at 2 hours.	Proportion of all patients with no headache pain at 2 hours.
Pain Freedom at 24 hours	Not completely assessed. Most studies report "sustained" pain freedom at 24 hours	Proportion of all patients with no headache pain at 24 hours.
Pain Relief at 2 Hours	Reduction in initial headache pain of moderate-to-severe intensity to mild or no pain at 2 hours. or Reduction in headache pain severity from moderate (2) or severe (3) at baseline, to mild (1) or none (0), or a reduction in headache severity from mild (1) at baseline, to none (0) at 2 hours.	Proportion of all patients with a decrease in headache pain and symptoms from initial headache pain of moderate to severe intensity to mild or no pain at 2 hours.
Pain Relief at 24 Hours	Not completely assessed. Most studies report "sustained" pain relief at 24 hours	Proportion of all patients with decrease in headache pain and symptoms from initial headache pain of moderate to severe intensity to mild intensity or no headache pain at 24 hours.
No Pain Relief at 2 and 24 Hours	No change in baseline headache pain at 2 and 24 hours post initial treatment. or Recurrence of headache pain at 2 and 24 hours after initial treatment (i.e. moving from 0 to 1, 2, or 3 on a 4-point Likert scale or on a 4-point IHS severity rating scale).	Proportion of all patients with no change in headache pain at 2 and 24 hours. or Proportion of all patients experiencing a relapse in migraine pain at 2 and 24 hours.
Nausea/Vomiting Freedom at 2 Hours	Patient response changed from "yes" to "no" for the presence of baseline nausea/vomiting 2 hours after initial treatment. or Patient response changed from "1" (presence) to "0" (absence) on a binary scale 2 hours after initial treatment when nausea/vomiting was present at baseline.	Proportion of all patients with no nausea/vomiting at 2 hours.

Treatment Response Description	Definition	Calculation from Clinical Trials
Photophobia Freedom at 2 Hours	Photophobia freedom defined as patient response change from "yes" to "no" on a binary scale at 2 hours when photophobia was present at baseline. or Patient response change from "1" (presence) to "0" (absence) on a binary scale at 2 hours when photophobia was present at baseline.	Proportion of all patients with no photophobia at 2 hours.
Phonophobia Freedom at 2 Hours	Phonophobia freedom defined as patient response change from "yes" to "no" at 2 hours when phonophobia was present at baseline. or Patient response change from "1" (presence) to "0" (absence) on a binary scale at 2 hours when phonophobia was present at baseline.	Proportion of all patients with no phonophobia at 2 hours.

Patients will remain in the "No Migraine" Markov state until they experience another acute migraine, upon which they will re-enter the "Migraine" Markov state.

The time horizon of the Markov model will be two years.

2.2 Key Model Choices and Assumptions

Our model includes several assumptions stated in Table 2 below.

Table 2. Model Assumptions and Rationale

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. As such, we believe that a two-year time horizon will be sufficient to estimate a stable incremental cost-effectiveness ratio for the acute 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.

2.3 Populations

The populations of interest for this review will be the prevalent cohort of individuals in the United States (US) aged 18 years and over currently experiencing migraines requiring acute treatment, with or without aura as specified by the International Classification of Headache Disorders (ICHD) 3 diagnostic criteria.[1] Two separate cohorts of patients will be evaluated using different comparators. The first cohort will comprise patients who have migraine attacks that have not responded adequately to non-prescription medicines, such as non-steroidal anti-inflammatory agents. In this cohort, comparisons will be made among lasmiditan, rimegepant, and ubrogepant, and two commonly used oral triptans that may have different effectiveness and cost, sumatriptan and eletriptan, representing a range of triptan medications. The second cohort will comprise patients who have migraine attacks that have not responded to non-prescription medicines and for whom

triptans have not been effective, are not tolerated, or are contraindicated. The general characteristics of the population in each model will reflect the average patient who experiences acute migraine in the US and are shown in Table 3.

Table 3: Baseline Population Characteristics

Baseline Characteristics	Lasmiditan	Rimegepant	Ubrogepant	Sources
Mean Age, years (SD)	42.3 (12.4)	40.2 (12.0)	40.5 (11.8) (ACH I) 41.5 (12.3) (ACH II)	Croop 2019[2] Allergan data on file[3] Doty 2019[4]
Female, %	84.0	85.0	88.2 (ACH I) 89.9 (ACH II)	Croop 2019[2] Allergan data on file[3] Doty 2019[4]
Migraine Days per Month at Baseline	5.2 (1.9)	4.6 (1.8)	4.5 (1.8) (ACH I) 4.4 (1.8) (ACH II)	Croop 2019[2] Allergan data on file[3] Doty 2019[4]
Level of Migraine Pain at Baseline, %	**SAMURAI**			Dodick 2019[5] Kuca et al, 2018[6] Goadsby 2019[7]
Mild	1.9	Not reported	0.0	
Moderate	70.6	Not reported	61.9	
Severe	27.5	Not reported	38.1	
	SPARTAN			
Mild	1.5			
Moderate	69.6			
Severe	28.9			

SD: standard deviation; ACH I: ACHIEVE I study; ACH II: ACHIEVE II study

2.4 Interventions and Comparators

The list of interventions and comparators that was developed with input from patient organizations, clinicians, manufacturers, and payers is presented below.

Interventions

- Lasmiditan
- Rimegepant
- Ubrogepant

Comparators

- Sumatriptan
- Eletriptan
- Usual care (represented by the placebo arms of clinical trials)

The comparator strategy will depend on the population assessed. In population 1, interventions will be compared to each other and to two commonly used triptans that may have different effectiveness and cost. In population 2 (i.e. patients in whom prior treatment with non-prescription medicines failed and for whom triptans have not been effective, are not tolerated, or are contraindicated), the interventions will be compared to each other and to usual care (placebo).

2.5 Input Parameters

Clinical Inputs

Short-term clinical inputs for the effectiveness of acute treatments for migraine and the comparators will be derived from a network meta-analysis of clinical trials evaluating lasmiditan, rimegepant, ubrogepant, sumatriptan, and eletriptan compared with usual care (placebo) and/or with each other, where such studies exist.

Transition Probabilities

The decision model will be evaluated over a two-year time horizon with 24-hour cycles. The probability of having a migraine in each cycle will be determined by the incidence of having a migraine each day, estimated using the number of migraine days per month from patients enrolled in clinical trials. Within each cycle, the probability of being pain-free at 2 and at 24 hours, having pain relief at 2 and 24 hours, and being free from nausea/vomiting, photophobia, and phonophobia at 2 hours for each treatment will be determined from a network meta-analysis of clinical trials for

the new treatments and comparators. For reference, the unadjusted treatment dependent probabilities from clinical trials evaluating the new treatments is shown in Table 4.

Table 4. Unadjusted Treatment Dependent Probabilities From Clinical Trials

Model Input	Lasmiditan/ Placebo	Rimegepant/ Placebo	Ubrogepant/ Placebo	Source
Pain-Free at 2 Hours, %	**SAMURAI** 100 mg: 28.2 200 mg: 32.2 PLB: 15.3 **SPARTAN** 50 mg: 28.6 100 mg: 31.4 200 mg: 38.8 PLB: 21.3	75 mg: 21.2 PLB: 10.9	**ACHIEVE I** 50 mg: 19.2 100 mg: 21.2 PLB: 11.8 **ACHIEVE II** 50 mg: 21.8 PLB: 14.3	Croop 2019[2] Allergan data on file[3] Kuca 2018[6] Goadsby 2019[7]
Pain-Free at 24 Hours, %	Not reported	Not reported	Not reported	
Pain-Relief at 2 Hours, %	**SAMURAI** 100 mg: 59.4 200 mg: 59.5 PLB: 42.2 **SPARTAN** 50 mg: 59.0 100 mg: 64.8 200 mg: 65.0 PLB: 47.7	75 mg: 59.3 PLB: 43.3	**ACHIEVE I** 50 mg: 60.7 100 mg: 61.4 PLB: 49.1 **ACHIEVE II** 50 mg: 62.7 PLB: 48.2	Croop 2019[2] Allergan data on file[3] Kuca 2018[6] Goadsby 2019[7]
Pain-Relief at 24 Hours, %	Not reported	Not reported	Not reported	
Nausea and/or Vomiting Free at 2 Hours*	**SAMURAI** *Nausea-free* 100 mg: 97.7 200 mg: 80.9 PLB: 77.1 *Vomiting-free* 100mg: 97.7 200 mg: 98.4 PLB: 98.6 **SPARTAN** *Nausea-free* 50 mg: 79.1 100 mg: 82.0 200 mg: 81.4 PLB: 80.7 *Vomiting-free* 50 mg: 98.3 100 mg: 99.3	75 mg: 51.0 PLB: 45.2	**ACHIEVE I** *Nausea-free* 50mg: 70.2 100mg: 69.2 PLB: 62.3 **ACHIEVE II** *Nausea-free* 50mg: 71.3 PLB: 70.0	Croop 2019[2] Allergan data on file[3] Kuca 2018[6] Goadsby 2019[7]

Model Input	Lasmiditan/ Placebo	Rimegepant/ Placebo	Ubrogepant/ Placebo	Source
	200 mg: 98.6 PLB: 99.1			
Photophobia Free at 2 Hours*	**SAMURAI** 100 mg: 69.0 200 mg: 68.3 PLB: 53.1 **SPARTAN** 100 mg: 66.5 50 mg: 61.5 200 mg: 69.2 PLB: 53.6	75 mg: 33.4 PLB: 24.5	**ACHIEVE I** 50 mg: 40.7 100 mg: 45.8 PLB: 31.4 **ACHIEVE II** 50 mg: 43.8 PLB: 35.5	Croop 2019[2] Allergan data on file[3] Kuca 2018[6] Goadsby 2019[7]
Phonophobia Free at 2 Hours*	**SAMURAI** 100 mg: 75.8 200 mg: 75.5 PLB: 67.5 **SPARTAN** 50 mg: 71.6 100 mg: 75.0 200 mg: 76.3 PLB: 63.9	75 mg: 41.7 PLB: 30.2	**ACHIEVE I** 50 mg: 57.9 100 mg: 54.5 PLB: 47.1 **ACHIEVE II** 50 mg: 54.1 PLB: 46.3	Croop 2019[2] Allergan data on file[3] Kuca 2018[6] Goadsby 2019[7]

*Some studies reported freedom from symptom at two hours, while other studies reported freedom from symptoms at two hours among those who had symptoms at baseline.

The probability of having migraine-related provider office visits or of being admitted to the emergency department or hospital will be determined for patients with persistent pain, derived from Silberstein et al.[8] To estimate the probability of having a migraine-related provider office, emergency, or hospital visit during a migraine these rates will be divided by the baseline number of migraines with severe headache pain per year. In the model, provider office, emergency department, and hospital visits will only occur in patients who have severe headache pain lasting more than two hours. Therefore, more effective therapies reducing headache pain will result in fewer health care visits than less effective therapies. A risk ratio may be used to modify the probability of being admitted to the emergency department only for patients with persistent nausea and vomiting, using data derived from Gajria et al.[9]

Table 5. Non-Treatment Dependent Values Used to Calculate Model Event Probabilities

Model Input	Value	Source
Mean Number of Migraine-Related Health Care Provider Visits in 12 Months	5.07	Silberstein 2018[8]
Mean Number of Migraine-Related Emergency Department Visits in 12 Months	0.56	Silberstein 2018[8]
Mean Number of Migraine-Related Hospitalizations in 12 Months	0.05	Silberstein 2018[8]
Risk Ratio for Hospitalization in Patients with Nausea and Vomiting	1.26	Gajria 2019[9]

Discontinuation

Treatment discontinuation due to an adverse event at one year was 12.8% with lasmiditan,[10] 2.7% with rimegepant,[11] and 2-3% with ubrogepant.[12] The high discontinuation rate among lasmiditan patients was primarily due to dizziness, and patients were most likely to discontinue therapy after the first or second treated migraine attacks. Given that these treatments are used as symptomatic treatment of an acute condition, the likelihood of discontinuation or switching to another medication is difficult to predict and was not assessed in the single-dose clinical trials or in long-term, open-label, safety studies. As a result, treatment discontinuation and drug switching will not be modeled. Therefore, the modeled population will represent only patients who continue on treatment.

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, we will be modeling a short time horizon of two years to generate the incremental cost-effectiveness estimates for the new therapy. Given the relatively young age of the population being evaluated and associated low mortality rate, mortality will not be included in the model.

Adverse Events

Sumatriptan, eletriptan, lasmiditan, rimegepant, and ubrogepant are all well tolerated, with adverse events typically being minor when they occur. In open-label continuation studies, serious treatment-emergent adverse events were experienced by 0.5% of lasmiditan[10] patients and 2-3% of patients treated with ubrogepant[12] over a 1-year period. An interim analysis of rimegepant patients showed that 2.5% of patients had serious adverse events (not necessarily treatment-related) at 12 weeks.[11] Adverse events determined to be treatment related were generally of mild or moderate severity and were evaluated in an open-label, non-controlled setting. Inclusion of adverse events is

unlikely to measurably impact costs or utilities of the therapies and therefore treatment for adverse events will not be included in the models.

Health State Utilities

Health state utilities will be derived from published literature. For patients without migraine, we will use a utility associated with "no pain" derived from Xu et al.[13] For patients in the "Migraine" Markov state, we will weight the utilities for each migraine day based on a combined distribution of baseline migraine severity derived from clinical trials evaluating the efficacy of lasmiditan, rimegepant, and ubrogepant. These baseline estimates are shown for each study in Table 4. Throughout the course of the migraine episode, the severity distribution of the migraine episode within the cohort and corresponding utility will be calculated to reflect the impact of treatment, or natural progression of migraine in those in whom the treatment is not effective, on pain. Table 6 shows the proposed migraine-specific utility values to be used for a severe, moderate, mild, and pain-free migraine day. The utility weights were estimated using the EQ-5D and stratified by the severity of the migraine.

In addition, and if data is available, we will incorporate a disutility score based on the proportion of patients who suffer from nausea and/or vomiting, photophobia, and phonophobia and for those who require emergency treatment of their migraine symptoms.

Table 6. 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[13]
Moderate Pain	0.773	(0.755, 0.789)	EQ-5D	Xu 2011[13]
Mild Pain	0.835	(0.790, 0.883)	EQ-5D	Xu 2011[13]
Pain free	0.959	(0.896, 0.967)	EQ-5D	Xu 2011[13]
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	
Emergency Department Visit	Estimate not found in literature search	Estimate not found in literature search	Estimate not found in literature search	

Drug Utilization

Drug utilization for acute treatments for migraine evaluated in this model, used to determine costs, are shown in Table 7. The following inputs will be used to model drug utilization and associated costs:

- Protocol dosage for the indication
- Number of repeat doses required per migraine
- Maximum number of doses allowed per month (if limited)

Table 7. Treatment Regimen Recommended Dosage

Generic Name	Lasmiditan	Rimegepant	Ubrogepant	Sumatriptan	Eletriptan	Source
Brand name	Investigational	Investigational	Investigational			
Manufacturer	Eli Lilly	Biohaven	Allergan			
Route of Administration	Oral	Oral	Oral	Oral	Oral	
Dosing	Dosing information not available	Dosing information not available	Dosing information not available	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	Micromedex

Cost Inputs

Drug Costs

Pricing for ubrogepant, rimegepant and lasmiditan are unknown because they are still under FDA review and prices have not been announced by the manufacturers. If pricing is not available at the time of the analysis, we will calculate annual prices required to reach thresholds of between $50,000 and $150,000 per QALY gained. Costs for sumatriptan and eletriptan will be derived using Wholesale Acquisition Cost (WAC) from Redbook and shown in Table 8.[14] Aligning with the ICER Reference Case (http://icer-review.org/wp-content/uploads/2018/07/ICER_Reference_Case_July-2018.pdf), we will use the WAC to price treatments which are available in their generic forms.

Table 8. Drug Cost per Dose

Drug	WAC	Source
Sumatriptan, Oral tablets 50 mg 100 mg	$1.04	Redbook Online from Micromedex[14]
Eletriptan 40 mg	$11.95	Redbook Online from Micromedex[14]

Non-Drug Health Care Costs

The non-drug health care costs for the acute treatment of migraine will include only those costs demonstrated to be associated with treatment. We will include provider office visits, emergency department visits, and hospitalizations as a rapid decrease in pain and other migraine symptoms are likely to be associated with a lower risk of requiring these resources. We will use utilization data from Silberstein et al. combined with cost estimates from physician fee schedules and CMS to estimate the costs of migraine-related office visits, emergency department visits, and hospitalizations.[8] These costs are shown in Table 5. Data have not yet been identified showing an association between physician office visits and better-treated migraine pain. If data are identified showing such an association, they will be included in the base-case analysis.

We will be including the potential impact of therapies for migraine on productivity losses in a scenario analysis. We will use the productivity costs 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.[15] The total productivity costs for acute migraines will be $245 per month.

2.6 Model Outcomes

Model outcomes will include total costs, total QALYs, cost per QALY gained, total life-years, equal value of life years gained (evLYG), and hours of migraine pain avoided for each treatment strategy over a two-year time horizon. We anticipate that the incremental cost-effectiveness ratio will be stable at two years due to the acuteness of migraine attack, rapid resolution of migraine symptoms, and corresponding short model cycle length of one day. Costs and QALYs will also be reported by health state to better describe the costs and benefits of effective acute migraine treatment. All of the costs, QALYs, life years, and evLYG will be reported as discounted values, using a discount rate of 3% per annum.

2.7 Model Analysis

Cost-effectiveness will be estimated using incremental cost-effectiveness ratios, with incremental analyses comparing the new acute treatments for migraine to each other and to either sumatriptan and eletriptan (population 1) or usual care (population 2). The analyses will be conducted from a health care sector perspective in the base-case analyses. Additionally, we will present a cost per hour of migraine pain avoided. A two-year time horizon will be used.

Sensitivity Analyses

We will conduct one-way sensitivity analyses on all model inputs to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying sensitive model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

We plan to conduct scenario analyses that include:

1) Modified societal perspective that includes productivity losses.
2) Extension of the time horizon to five years

Model Validation

We will use several approaches to validate the model. First, we will present our preliminary methods to manufacturers and share methods and results with expert reviewers. Based on feedback from these different stakeholders, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with interested manufacturers included in this review for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-effectiveness models in this treatment area. The outputs from the model will be validated against the trial/study data of the interventions and also any relevant observational datasets.

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