Observational Real-World Evidence Update

Prophylaxis of Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

The primary aim of this analysis is to update the prior estimation of the cost-effectiveness of lanadelumab (Takhzyro®, Takeda Pharmaceutical Company, Ltd.) and two C1 esterase inhibitors (Haegarda®, CSL Behring, GmbH; and Cinryze®, Takeda Pharmaceutical Company, Ltd.) for long-term prophylaxis against acute attacks in patients with hereditary angioedema (HAE) using updated model inputs from observational real-world evidence (RWE). The preliminary phase updates will be conducted on clinical model inputs using randomized controlled trial (RCT) literature and economic unit costs to present value. The preliminary phase will be built upon by the RWE phase as outlined in Section 2 of this plan. We will compare both the preliminary and RWE phase findings with the original model results. We note that berotralstat was recently approved for long-term prophylaxis against acute attacks in patients with HAE. However, given the scope of this update that focuses on observational RWE, we opted to not include berotralstat. This update will use the existing model, developed in Microsoft Excel, as described below.

1.1 Preliminary Phase Updates (RCT updates and unit costs to present value)

Procedures for the updated systematic literature review assessing the evidence on lanadelumab, Haegarda, and Cinryze will follow established best methods.[1,2] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[3] We will re-run the search strategy from the 2018 review of HAE in MEDLINE, EMBASE to identify any references published in the time after the final posting of the prior report. The detailed research protocol and search strategy of the prior report can be found here.

After the literature search, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using Distiller (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. Reviewers will screen references in accordance with pre-specified research questions. The findings will be first categorized into randomized controlled trial literature versus real-world evidence to support corresponding updates to the preliminary phase and RWE phase of this research. The preliminary phase literature updates will focus on randomized controlled trials that support / enhance efficacy outcomes (e.g., data on reductions in attack rates), and other clinical model inputs (Table 1.1). Literature from non-randomized sources that include measures consistent with cost-effectiveness model inputs will be categorized as supporting the RWE update phase, alongside the corresponding observational claims analyses.

Table 1.1 Literature shell to organize evidence across update phases

	Full Text RCTs Available at the time of 2018 Report	Preliminary Phase: Randomized Controlled Trial literature to support / enhance:		Observational RWE Phase: RWE literature to support / enhance:
		Efficacy	Other Inputs	Model Inputs
Lanadelumab	0 (HOPE trial identified in abstract form)			
Cinryze	1 (Zuraw 2010)			
Haegarda	1 (COMPACT – Longhurst 2017)			

Finally, in the preliminary phase, where necessary, all unit costs from the 2018 report will be inflated to 2021 US dollars. Healthcare costs will be inflated using the Personal Consumption Expenditure (PCE) price index.[4]

2. Methods: Long-Term Cost Effectiveness Observational RWE Update

2.1 Overview and Model Structure

The HAE model was developed as a Markov model with two health states: "alive with HAE" and "dead" (Figure 2.1). The model used one-month cycles over a lifetime time horizon. Transition from the "alive with HAE" state to "dead" were based on background mortality from US life tables and HAE-specific mortality. Within the "alive with HAE" health state, health-related quality of life, number of acute attacks and time spent in acute attacks were estimated. For each attack, severity of attack, anatomical location of the attack for severe attacks (i.e., laryngeal and non-laryngeal), mortality from asphyxiation due to laryngeal attack, and attack-specific disutility, as well as treatment patterns (setting and drugs), emergency department (ED) visits, hospitalizations and associated costs were considered (Figure 2.2). These outcomes were tracked over time for persons receiving long-term prophylaxis with lanadelumab and the C1 inhibitors, and those not receiving long-term prophylaxis.

The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only) and a lifetime time horizon. As data permit, productivity impacts and other indirect costs will be included in a modified societal perspective scenario analysis, which will be considered as a co-base case if the impact of the HAE prophylaxis on these costs is substantial. This will most

often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses thresholds of $100,000-$150,000 per QALY. A 3% discount rate will be applied for costs and health outcomes.

Figure 2.1. Model Framework

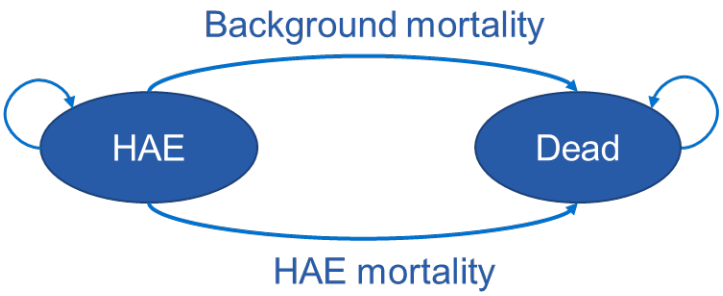
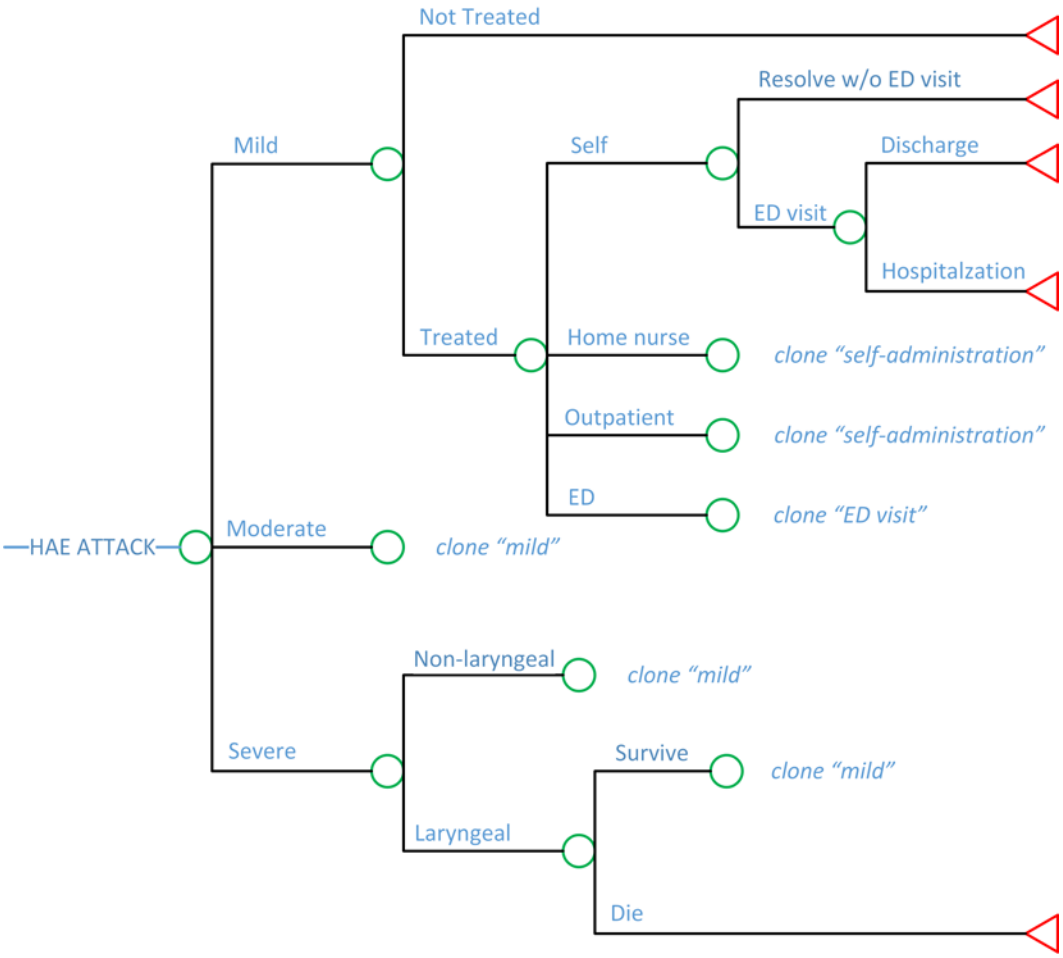


Figure 2.2. HAE Attack Pathway



Legend: This reflects how payoffs (i.e., costs and utilities) associated with the different HAE attack events and outcomes will be weighted. Green circles are chance nodes. Red triangles are terminal nodes. "Clone" refers to

structural replication of a previously described branch of the decision tree (i.e., not replication of probabilities). "ED" refers to emergency department.

2.2 Key Model Choices and Assumptions

Table 2.1. Key Model Assumptions

Assumption	Rationale
Model Choice: Prior model inputs will be supplemented with real-world evidence from published literature and planned analysis (see protocol)	Real world evidence will aid in updating baseline attack rates and other model inputs as denoted in this plan. For the updated base-case, we will continue to rely on randomized controlled trials for comparative efficacy inputs.
HAE-specific mortality results only from asphyxiation following a laryngeal attack; other anatomical locations for acute attacks do not result in death.	Death from HAE attacks primarily results from asphyxiation following a laryngeal attack.[5]
Death due to asphyxiation following a laryngeal attack occurs quickly following the attack; we will assume that these persons do not receive on demand treatment.	The mean (standard deviation) duration of a fatal laryngeal attack is 4.5 (3.6) hours.[5] In Bork et al., 2008,[5] whether on-demand therapy had been administered to persons who died following a laryngeal attack was unclear.
The one-year fatality rate from laryngeal attack is 0.3% (i.e., 3 in 1000 attacks observed over a one-year period result in a death).	Data on the fatality rate due to a laryngeal attack are limited.
All non-fatal moderate and severe acute attacks are treated (varied in sensitivity analysis).	Treatment guidelines and empirical data suggest that moderate and severe attacks are treated.[6]
Only (and all) severe attacks are treated in the ED.	Treatment guidelines and empirical data suggest that severe attacks are typically treated in the ED.[6]
Non-severe attacks do not result in ED visits or hospitalizations.	Treatment guidelines and empirical data suggest that non-severe attacks are not typically treated in the ED nor do they result in hospitalizations.[6]
The durations of mild, moderate, and severe attacks are one, three, and five days, respectively. Untreated attacks last an extra day.	Data on the duration of attacks by severity is limited but attacks generally last between two-five days.[6]
Patients do not discontinue prophylactic therapies over their lifetime.	There is no indication that attack rate declines with age.
As with the original economic assessment, we will not model adverse events (AEs).	There were no serious/treatment-related AEs attributable to the prophylactic therapies in the clinical trials.
We will use consistent health state utility values across treatments evaluated in the model. We do not anticipate updating these estimates for this review	In the original model, health state utilities were derived from publicly available literature and applied to health states. It is not anticipated that new utility values will be identified as part of this RWE update.
Indirect costs (including missed work, childcare, and travel) for acute attacks will be updated based on the mean number of attacks per year estimated by the real-world data analysis.	In the original model, indirect cost per attack were obtained from Wilson et al., 2010[7] and multiplied by the number of attacks per year. In the RWE update, the number of attacks per year will be updated based on analysis of real-world data.
Model outcomes will include total life years (LYs) gained, quality-adjusted life years (QALYs) gained and total costs for each intervention over a lifetime time	Because the difference in LYs gained was minimal in the original evaluation, we do not anticipate calculating evLYG.

horizon. Equal value life years gained (evLYG) will not be calculated.	

2.3 Populations

The population for this analysis will be patients in the US with types I and II HAE who are considered to be candidates for prophylactic treatment. Where possible, the baseline characteristics used in the model will reflect the real-world patient characteristics of patients receiving HAE prophylaxis. (Table 2.1).

Table 2.2. Baseline Values for Patient Population

Variable	Original Value	Source	RWE Update Value
Age in years (mean)	39.6	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[8-11]	Anticipated update based on findings of real-world data analysis
Gender (% female)	68.4%	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[8-11]	Anticipated update based on findings of real-world data analysis
Weight, Female (kg)	76.4 (SD: 30.93)	Fryar et al. 2016[12]	Anticipated update based on findings of real-world data analysis
Weight, Male (kg)	88.8 (SD: 31.11)	Fryar et al. 2016[12]	Anticipated update based on findings of real-world data analysis
Baseline attack frequency (per month)	3.39	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[8-11]	Anticipated update based on findings of real-world data analysis

2.4 Interventions

The interventions assessed in this model are:

- Lanadelumab (Takhzyro®, Takeda Pharmaceutical Company Limited)
- C1 inhibitor, intravenous injection (human) (Cinryze®, Takeda Pharmaceutical Company Limited)
- C1 inhibitor, subcutaneous injection (human) (Haegarda®, CSL Behring GmbH)

Berotralstat (Orladeyo™, BioCryst Pharmaceuticals, Inc.) is an oral treatment that was approved by the FDA December 2020 for HAE prophylaxis. Due to the timing of approval, limited real-world evidence is available for berotralstat, thus inclusion of this new intervention was not considered in scope for the 2021 HAE RWE update.

Comparators

The comparator will be no long-term prophylaxis. Patients in all intervention and comparator groups can receive on-demand treatment for acute attacks.

2.5 Input Parameters

Clinical Inputs

Severity and Anatomical Location of Acute Attacks (no anticipated RWE updates)

In the original evaluation, data on the severity and anatomical location of acute attacks were drawn from the Berinert® (CSL Behring) Patient Registry (Table 2 in Riedl 2016[13]), ignoring the attacks of unknown intensity. The Berinert Patient Registry, a multicenter, observational study, was conducted between 2010 and 2014 at 30 US and seven European sites to obtain both prospective and retrospective safety and usage data on subjects receiving plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH, Berinert). The probability of a severe attack having laryngeal involvement was back-calculated at 11.5%, in order to match the overall proportion of laryngeal attacks in the Berinert Patient Registry, which was 2.0%.

We anticipate that in the RWE update, the number of severe attacks will be informed by the real-world data analysis. This same distribution of severity will be used to estimate the number of mild and moderate attacks.

Table 2.3. Baseline Values for Attack Characteristics

Variable	Original Value	Source	RWE Update Value
Severity of attack (%)		Reidl 2016[13]	No anticipated Update
Mild	36.6%		
Moderate	46.2%		
Severe	17.2%		
Severe attacks that are laryngeal (%)	11.5%	Reidl 2016[13]	

Mortality Due to HAE Attacks (no anticipated RWE updates)

We will assume that only laryngeal attacks could be fatal. The current model assumes that over one year, the fatality rate from a laryngeal attack is 0.3%. Given limitations in capturing complete death data, we do not anticipate updating this estimate based on the findings of the real-world data analysis.

Treatment Patterns, ED Visits, and Hospitalizations for Acute Attacks (anticipated RWE updates)

In the original model, treatment patterns for acute HAE attacks were derived using data from a survey of US physicians (Figure 7 in Reidl et al., 2015 excluding emergency departments [ED] and hospitals).[14] We anticipate updating treatment patterns, ED visits, and the proportion of ED visits which result hospitalizations based on results of the real-world data analysis.

Table 2.4. Treatment Patterns by Attack Severity

Treatment Patterns	Self	Home Nurse	Outpatient	Severe	Proportion of ED Visits Which Result in Hospitalization	Source	RWE Update Value
Mild	64.9%	13.8%	21.3%	0.0%	N/A	[14]	No anticipated Update
Moderate	64.9%	13.8%	21.3%	0.0%	N/A	[14]	No anticipated Update
Severe	0.0%	0.0%	0.0%	0.0%	40.9%	[15]	Anticipated update based on findings of real-world data analysis

Duration of Acute Attacks (no anticipated RWE updates)

The model assumes that the durations of mild, moderate, and severe attacks are one, three, and five days, respectively. Untreated attacks will last an extra day. We will apply a mean (standard deviation) duration of a fatal laryngeal attack of 4.5 (3.6) hours.[5]

Treatment Effects (RWE updates possible in scenario analyses)

Prophylactic therapies reduce the frequency of acute attacks. In the base-case analysis, we will apply treatment effects, measured as the percent reduction in the number of attacks, from the pivotal trials of each of the prophylactic therapies. As a scenario analysis, we may explore the treatment effect observed before and after initiation of HAE prophylaxis based on the results of the real-world data analysis.

Table 2.5. Treatment Effect Estimates

Drug	Base Case Treatment effect (% reduction in number of attacks)	Source	Scenario Analysis (% reduction in number of attacks)
Lanadelumab	86.9%	Banerji et al., 2017[8]	Potential scenario analysis based on findings of real-world data analysis
Cinryze	50.4%	Zuraw et al., 2010[11]	
Haegarda	84.0%	Longhurst et al., 2017[9]	

Discontinuation (RWE updates possible in scenario analyses)

The base-case model will assume that patients do not discontinue prophylactic therapies over their lifetime. As a scenario analysis, we may explore modeling the observed utilization of prophylactic therapies (see Drug Utilization) with further assumptions required to link utilization to treatment effect.

Adverse Events (no anticipated RWE updates)

The model will not consider adverse events, as there were no serious/treatment-related AEs attributable to the prophylactic therapies in the clinical trials.

Heterogeneity and Subgroups (RWE updates possible in scenario analyses)

No subgroup analyses are planned. As in the prior model analyses, we plan to run scenarios by a plausible range of baseline attack rates to characterize part of the heterogeneity of HAE. The plausible range will be informed in part, by the RWE analyses.

Health State Utilities (no anticipated RWE updates)

In the original model, health state utilities were derived from publicly available literature and applied to health states. Utility estimates were derived from a study in Sweden that utilized the EuroQoL 5D (EQ-5D) for valuing health-related quality of life among HAE patients.[16] Patients completed EQ-5D-5L (five-level) for both the attack-free state (EQ-5D today), and the last HAE attack (EQ-5D attack), and collected data on age, sex, and other variables such as attack location and severity. We will use consistent health state utility values across treatments evaluated in the model. We do not anticipate updating these estimates for this review.

Table 2.6. Health State Utilities and Attack Disutility

Parameter	Value (SD)	Source
Attack-free	0.825 (SD 0.207)	Nordenfelt 2014[16]
Mild attack disutility	-0.07	
Moderate attack disutility	-0.369	
Severe attack disutility	-0.486	
Age-related disutility	-0.02205 per 10-year increase	

SD: standard deviation

Drug Utilization (RWE updates possible in scenario analyses)

The following inputs will be used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen
- Protocol/label dosage for the indication

We will assume that prophylactic therapies are taken on a life-long basis. The dosing regimens, schedules, and dose intensity adjustment factors for each therapy are shown in Table 2.5. Depending on data availability, we will consider real-world utilization of prophylactic agents in the calculation of cost and relative treatment effect.

Table 2.7. Treatment Regimen Recommended Dosage

Generic Name	**Lanadelumab**	**C1 inhibitor, intravenous injection (human)**	**C1 inhibitor, subcutaneous injection (human)**
Brand Name	TAKHZYRO®	CINRYZE®	HAEGARDA®
Manufacturer	Takeda	Takeda	CSL Behring
Route of Administration	subcutaneous	intravenous	subcutaneous
Dosing	300 mg every 2 weeks; Dosing every 4 weeks may be considered in some patients	1,000 IU twice a week	60 IU/kg twice a week

Table Footnotes

Cost Inputs (anticipated RWE updates)

Costs will be updated in this review.

Prophylactic Drug Acquisition Costs (unit cost updates)

Prophylactic drug cost inputs are shown in Table 2.6. We will use the wholesale acquisition cost (WAC) price per dose unit for subcutaneously administered drugs and self-administered doses of

intravenously administered drugs. For non-self-administered doses of intravenously administered drugs, because the drug is not being dispensed directly to the patient, we will use the average sales price (ASP) plus a 9% markup representing the mean markup for physicians' offices, home infusion, and hospital outpatient administered dose units (Table 2.6).

Table 2.8. Prophylactic Drug Cost Inputs

Intervention	Administration	Unit	WAC per Unit/Dose*	ASP per Unit/Dose†
Lanadelumab	SC	300 mg	$23,414	-
Haegarda	SC	2,000 IU	$1,994	-
Haegarda	SC	3,000 IU	$2,992	-
Cinryze	IV	1,000 IU	$5,683	$ 6,149

*WAC (wholesale acquisition cost) as of February 22, 2021.

†ASP (Average Selling Price) as of February 18, 2021 plus 9% markup for physicians' offices, home infusion, and hospital outpatient administered dose units.

Administration and Monitoring Costs for Prophylactic Drugs (unit cost updates)

All administration and monitoring costs included in the RWE update will reflect those in the original model, with updates to 2021 payment amounts.

For lanadelumab and Haegarda, which are administered subcutaneously, only the first dose administration was assumed to be performed in a clinic. We will apply the cost of a physician office visit of $131.20 (CPT 99214) and the cost of subcutaneous administration of $14.31 (CPT code 96372). Subsequent doses will be self-administered.

For Cinryze and Ruconest, which are administered intravenously, training for self-administration occurs over the first five physician office visits.[17] Therefore, we will apply the cost of five physician office visits, and a cost of IV drug administration of $$41.87 (CPT code 96374). Based on data from the Berinert registry, we estimate that 95% of patients will self-administer their IV therapies.[13] For the 5% who cannot or choose not to self-administer, we will apply physician visit and drug administration costs in each cycle of the model.

Health Care Utilization Costs for On-Demand Treatment (unit cost updates)

We anticipate generating new cost estimates for cost per home visit/on-demand treatment administration, cost per physician office visit for on-demand treatment administration, cost per ED visit, and cost per hospitalization from the real-world data analysis.

Therapeutic options for on-demand treatment of acute attacks are Cinryze® (20 IU/kg), Berinert (20 IU/kg), ecallantide (Kalbitor® 30 mg, Shire), icatibant (Firazyr® 30 mg, Shire) and Ruconest (50

IU/kg). As a scenario analysis, we will consider use of generic icatibant. We will compute the average costs per attack in each treatment setting as the cost of these drugs weighted by the proportion of attacks treated with each drug in each treatment setting. We plan to derive the proportions of attacks treated with each drug in each treatment setting based on the real-world data analysis. We note that Kalbitor is not approved for home or self-administration.

Table 2.9. Parameters for Costs of on-Demand Treatment for Acute Attacks

	Cinryze®	Berinert®	ecallantide (Kalbitor®)	Firazyr®	Generic icatibant	Ruconest®
Dose schedule	20 units/kg	20 units/kg	30 mg	30 mg	30 mg	50 units/kg
WAC per dose*	-	-	$15,211	$11,147	$2,796	-
ASP per dose	$9,877	$9,512	$16,092			$12,686
% requiring extra dose	10%	1.9%	12%	12.7%	12.7%	6.6%

* WAC (wholesale acquisition cost) price as of February 22, 2021.

§ ASP (Average Selling Price) as of February 18, 2021 plus 9% markup for physicians' offices, home infusion, and hospital outpatient administered dose units.

In Bork et al., 2012[5], 31% of patients with fatal laryngeal attacks did not receive any emergency life-saving care. We will assume that these patients died before making it to the ED. Among those with severe attacks who arrive at the ED, we plan to use real-world data to inform the proportion of patients who receive an emergency cricothyrotomy, intubation, artificial respiration, and cricothyrotomy.

Adverse Event Costs (no anticipated RWE updates)

There were no serious or clinically-relevant AEs attributable to any of the prophylactic therapies in the clinical trials. Unless the RWE analysis suggests significant changes in serious or clinically-relevant AEs, we will not update the corresponding model inputs.

Productivity Costs (anticipated RWE updates)

Indirect costs (including missed work, child care, and travel) for acute attacks (by severity) will be obtained from Wilson et al., 2010[7]: $959, $4,048, and $6,656, adjusted to present value and for the mean number of acute attacks per year, as estimated by the real-world data analysis.

2.6 Model Outcomes (no anticipated RWE updates)

Model outcomes will include total life years (LYs) gained, quality-adjusted life years (QALYs) gained and total costs for each intervention over a lifetime time horizon. Because the difference in LYs gained was minimal in the original evaluation, we do not anticipate calculating equal-value life years gained (evLYG). Total costs, LY's, and QALYs will be reported as discounted values, using a discount rate of 3% per annum. (Undiscounted results will be presented in an Appendix.)

Model outcomes of interest will include:

- By intervention:
    - Total health care costs (undiscounted and discounted)
    - Direct health care costs (undiscounted and discounted)
    - Indirect health care costs (undiscounted and discounted)
    - Number of attacks
    - Life years (undiscounted and discounted)
    - QALYs (undiscounted and discounted)
- Pairwise comparisons:
    - Incremental cost-effectiveness ratios (cost per attack avoided, cost per life-year, and cost per QALY) of each prophylactic therapy versus no long-term prophylaxis.

2.7 Analysis

We will estimate the expected direct and indirect costs for each attack, expected disutility for each attack, expected probability of death per attack, and the expected duration with symptoms per attack.

Each model cycle lasts one month. For each intervention, we will calculate the probability of death given the number of attacks in each cycle, patient survival, the number of attacks, time spent in the "attack free" state, quality-adjusted survival, and health care costs. Outcomes will be summed over a lifetime time horizon for each intervention. Differences in survival, quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analysis will also be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.

Scenario Analyses

We may conduct relevant scenario analyses, including real-world reduction in attack rate with prophylaxis, persistence and utilization based on real-word data (including the impact on cost and efficacy), variations in the baseline attack rate, inclusion of indirect costs, and consideration of the availability of generic icatibant for acute treatment of attacks. Additionally, we will perform

threshold analyses by systematically altering the price of the interventions to estimate the maximum prices that would correspond to commonly cited thresholds.

Model Validation

As the model structure and assumptions were previously validated as part of the initial cost-effectiveness evaluation, we will not perform a validation of the original model structure, methods, and assumptions. Based on feedback from manufacturers, patient groups, and clinical experts, we will refine data inputs used in the model based on real-world data, as available. We will assess the validity of the resulting observational RWE estimates of baseline HAE attack rates and severity in two ways: 1) by comparison of the observational RWE estimates to the expected distribution of attack severity based on published patient surveys and 2) by reviewing observational RWE findings with expert clinicians who have experience treating patients with HAE. If it is determined that the observational RWE estimates for attack rate and severity are not reflective of real-world patients with HAE, we will consider continuing to rely on published estimates for these model inputs. We will compare the RWE updated model results to the original HAE prophylaxis evaluation as well as to other cost-effectiveness models in this therapy area.

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