Observational Real-World Evidence Update

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

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About ICER

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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 the development of the original 2018 report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. For this report update, ICER consulted with the manufacturers of prophylactic HAE therapies and a clinical expert, Dr. Kevin Yee-Bien Tse. Dr. Tse is not responsible for the final contents of this report, nor should it be assumed that he supports any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input during the original 2018 assessment, please visit: *https://icer.org/wp-content/uploads/2020/10/ICER_HAE_Key_Stakeholders_041218-1.pdf*

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List of Acronyms and Abbreviations Used in this Report

ACE	Angiotensin-converting enzyme
AE	Adverse event
AEP	Aetion Evidence Platform
AHRQ	Agency for Healthcare Research and Quality
ARB	Angiotensin II receptor blocker
ASP	Average sales price
CDC	Centers for Disease Control and Prevention
DPP4	Dipeptidyl-peptidase 4
ED	Emergency department
evLYG	Equal value of life years gained
HAE	Hereditary angioedema
HRQoL	Health-related quality of life
ICER	Institute for Clinical and Economic Review
IQR	Interquartile range
IV	Intravenous
NEP	Neutral endopeptidase inhibitor
PCE	Personal consumption expenditure
PDC	Proportion of days covered
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RWD	Real-world data
RWE	Real-world evidence
SAE	Severe adverse event
SD	Standard deviation
WAC	Wholesale acquisition cost

1. Background

This section incorporates information and language from the 2018 ICER assessment of prophylactic treatments for hereditary angioedema (HAE).

In 2018, The Institute for Clinical and Economic Review (ICER) conducted a review of lanadelumab (Takhzyro®, Takeda Pharmaceutical Company, Ltd.) and two C1 inhibitors (Haegarda®, CSL Behring, GmbH; and Cinryze®, Takeda Pharmaceutical Company, Ltd.) for long-term prophylaxis against acute attacks in patients with hereditary angioedema (HAE). The primary objective of this analysis is to update the prior estimation of the cost effectiveness of Takhzyro, Haegarda, and Cinryze using recent observational real-world evidence (RWE). This work is a pilot project to explore how ICER can update review topics using observational RWE, with an emphasis on therapies that have been approved through accelerated approval pathways and are in use for over two years.

HAE is a rare genetic disorder that causes painful attacks of swelling in the face, hands, feet, and stomach, as well as potentially life-threatening swelling of the throat. Most HAE is caused by a deficiency (Type I HAE) or dysfunction (Type II HAE) of a protein called C1 inhibitor (C1 esterase inhibitor, C1-INH). Attacks can last for up to five days, and can be spontaneous or triggered by stress, medical procedures, and certain medications like oral contraceptives or ACE inhibitors. Attacks can occur rarely or as often as once every few days. Because of their severity and unpredictability, attacks can significantly reduce a patient's functioning and ability to perform activities of daily living.

The goal of HAE treatment is to reduce the duration, frequency, and severity of attacks. On-demand treatments are used to reduce the duration and severity of a single attack. Long-term prophylactic treatments, the focus of the 2018 report[1] and this update, are taken regularly to prevent attacks and reduce attack severity. ICER's 2018 report found that long-term prophylaxis with either of the C1 inhibitors or Takhzyro resulted in fewer acute attacks and improved quality of life for people living with HAE, but 2018 pricing of all three treatments exceeded traditional cost-effectiveness thresholds. The 2018 report identified uncertainties in the evidence and key model assumptions that influenced the cost-effectiveness findings. One of the most consequential uncertainties in the 2018 model was the frequency and severity of attacks at baseline among patients who would be prescribed prophylactic treatment. As demonstrated in the 2018 report, small differences in the assumed attack rate resulted in a wide range of cost-effectiveness results.

As a first step, the 2018 economic model was assessed for inputs influential to the results that could be reliably and validly analyzed in an observational claims analysis. The observational RWE contributions to cost-effectiveness updates were identified *a priori* in an observational claims analysis protocol. The primary contribution from observational RWE centers on estimating the baseline monthly attack rate and health care resource use (i.e., severity) of attacks in individuals

who initiated prophylactic therapy of Takhzyro, Haegarda, or Cinryze, that had a large impact on the incremental cost-effectiveness ratio in the 2018 report. Additional inputs from the observational claims analysis included other baseline patient characteristics (age, gender, weight), the percentage of patients who reduced Takhzyro dosing (i.e., one dose every four weeks instead of every two weeks), and other health care resource use and unit cost estimates.

The updated cost-effectiveness analysis continues to rely on the pivotal randomized controlled trial (RCT) evidence to quantify the relative reductions in attacks attributed to prophylactic treatment (i.e., treatment efficacy). Treatment effectiveness was not considered to be reliably assessed within the available claims data due to small sample size, limited duration of follow-up, and lack of ability to identify an appropriate comparator due to the potential for unmeasured confounding. Therefore, real-world treatment effectiveness was explored as a descriptive pre-post analysis but did not replace RCT treatment efficacy in the updated cost-effectiveness analysis.

This report was developed specifically to pilot-test the impact of leveraging observational RWE to update ICER reviews of drugs initially approved through the accelerated approval pathway. This report does not include an assessment of berotralstat, a recently approved prophylactic treatment that was not included in the 2018 Report.

2. Methods

2.1 Overview

The primary aim of this analysis was to update our 2018 cost-effectiveness analysis of Haegarda, Cinryze, and Takhzyro for long-term prophylaxis against acute attacks in patients with HAE. We started with the existing 2018 report economic model, developed in Microsoft Excel, as described in the Supplement. The update was then conducted in two phases. The first (preliminary phase), focused on incorporating new model inputs based on an updated review of the RCT literature. The preliminary phase literature update and supporting studies are detailed in Supplement Section A. The subsequent observational RWE phase addresses the primary aim. In the observational RWE phase, we used real-world data (RWD) analyses to provide new inputs for model assumptions regarding baseline attack frequency and utilization costs related to severity of attack. In addition, where necessary, all unit costs from the 2018 report and 2020 US Dollars from the *de novo* RWE analysis were inflated to 2021 US dollars using the Personal Consumption Expenditure (PCE) price index.[2]

This two-phase update approach was taken to help make transparent the separate incremental effects of updating the model with new RCT evidence and with RWE. This report emphasizes the observational RWE phase whereas the preliminary phase RCT literature update may be found in the Supplement. Consistent with the 2018 Report, the primary measure of cost effectiveness was the incremental cost per quality-adjusted life years (QALYs) gained. Equal value of life years gained (evLYG) as a measure of health gain was introduced after the 2018 Report and therefore is not featured within this update.

2.2 Real-World Data Analysis

Full descriptions of the RWE protocol, including details of the approach used to identify patients, can be found in Supplemental Appendix B. We performed our RWE analyses using Optum's de-identified Clinformatics® Data Mart Database. This database is comprised of administrative health claims for members of large commercial and Medicare Advantage health plans and includes approximately 65 million lives. These data allowed for the identification of HAE patients and the capture of key study elements including prescription claims, costs, emergency department (ED) visits and other health care resource utilization from April 13, 2008 through March 31, 2020. Optum's standard costs are based on algorithms that reflect the intensity of care provided, including quantity of services, relative resource costs, and the nature of utilization. Standard cost is an estimate of the allowed amount (i.e., the total cost of service) and is validated by Optum against the paid amount. Analyses of this database were performed within the Aetion Evidence Platform® (AEP).

In order to explore uncertainties raised in the November 2018 report,[1] the real-world data (RWD) analysis had the following primary objective: to describe baseline demographic characteristics, attack rates, and attack-related medical service utilization among patients initiating treatment with Takhzyro, Haegarda, or Cinryze, identified via prescription claims. HAE attack rates were calculated in total and by severity. Severe attacks were defined as an ED visit or hospitalization due to HAE (please see protocol for algorithms and code lists). Non-severe attacks were defined as treatment with on-demand therapy administered in an outpatient visit, home nurse visit, or self-administered by the patient. Data on the duration of attacks by severity is limited, however attacks generally last between two and five days.[3] Thus, on-demand therapy administered by a health care professional in an outpatient or home setting, during an ED visit, and during inpatient hospitalizations occurring within five days of each other were considered part of a single attack episode. Secondary objectives were to explore attack rates and utilization following long-term prophylaxis initiation with Takhzyro, Haegarda, or Cinryze and to explore the percentage of Takhzyro initiators who moved to less frequent dosing after six months attack free. All other cohort, exposure, and outcome definitions, and statistical and sensitivity analysis were detailed in the pre-defined study protocol.

The design, study execution, analysis, and reporting (across the report, supplement, and protocol) of this RWE study met published good practices guidelines.[4] In addition, we sought public comment from stakeholders on the research protocol. Based on comments received from the manufacturers and clinical experts, we included descriptive information on therapies that may be associated with increased risk of HAE attacks and added suggested limitations and interpretations to the study.

2.3 Cost-Effectiveness Analysis

All updated model assumptions and inputs are listed in Supplement Section C2 and further detailed in the model analysis plan. The key assumption related to incorporation of new RWE was that attacks were counted through claims for attack-related prescriptions and/or ED visits or hospitalizations coded as due to HAE. Thus, all attacks were assumed to be treated. Patients might have experienced some form of episode but if they did not seek and receive medical care it would not have been counted in our RWE analysis.

In the observational RWE phase, the preliminary phase model was updated to include data from the *de novo* RWE claims analysis. Supplement Section C2 presents a comparison of model inputs that were updated for this effort versus the inputs used in the 2018 assessment. A complete listing of all original model inputs can be found in the 2018 Final Report.[1] We performed both one-way and probabilistic sensitivity analyses according to standard methodologies in the field.

3. Results

3.1 Observational RWE Findings

As shown in Supplement Table B1, during the 12-year timespan covered by the RWE analysis, 158 patients initiated prophylactic treatment with Cinryze (49.4%), Haegarda (24.0%), or Takhzyro (26.6%).

In the six months prior to initiation of prophylaxis therapy, 136 of these 158 patients (86%) had evidence of at least one attack episode (note: attacks occurring within five days of each other were considered part of a single attack episode). Out of 1,783 total attack episodes observed for all patients in the six months prior to initiation of prophylaxis therapy, 5.7% were severe, and 94.3% were non-severe (Table 3.1).

On average, the 158 patients had 1.88 HAE attacks per month prior to initiation of prophylaxis therapy.

Table 3.1. Baseline HAE Attack Rates over Six Months

	Attacks N (%)	Mean Attack Rate (per Patient per Month)
Severe HAE attack episodes	102 (5.7%)	0.11
Non-severe HAE attack episodes	1,681 (94.3%)	1.77
Total attacks (severe and non-severe)	**1,783 (100%)**	**1.88**

Supplement Section C4 provides details on the results of sensitivity analyses of attack rates and other utilization, cost, and exploratory analyses. Sensitivity analyses were conducted varying the definition of HAE attacks. Data on the precise timing of self-administered treatment is not available. Rather, the number of treatments administered was estimated from pharmacy dispensing data, including date and quantity dispensed, and dosing guidelines. In estimating the number of self-treated attacks, we assumed, based on clinical guidelines, that patients would have on-demand treatment on hand to treat up to two attacks. These two on-hand doses were subtracted out in the calculation of self-administered doses in the primary analysis. In sensitivity analysis, each prescription dose was counted as an attack. This increased the non-severe attacks to 1,871 and total attacks to 1,973 and resulted in 2.08 attacks per patient per month.

In the primary analysis we treated attack-related visits within five days of each other to be part of the same attack. In sensitivity analyses, we reduced the assumed attack duration to two days and then to one day, treating events on distinct days as separate attacks in the one-day duration analysis. Estimated attack rates increased to 1.90 and 1.96 in these analyses, respectively.

For non-severe episodes the most common on-demand therapy used was Firazyr, used in 61.0% of episodes, followed by Berinert (19.6%). Of 102 severe attack episodes, 19 (18.6%) included a hospitalization. The average cost per ED visit was $2,940 and average cost per hospitalization was $20,957 (2021 USD). An analysis of Takhzyro initiators suggested that 48% (20/42) reduced dosing to every four weeks. Although not used in the cost-effectiveness analysis updates, descriptive analyses of severe attack rates pre versus post prophylaxis initiation suggested a post period mean severe attack rate of 0.0389 severe attack episodes per patient per month (vs. 0.1076 in the pre period).

3.2 Observational RWE Updated Cost-Effectiveness Findings

Key results of the RWE analysis which were used in the observational RWE updated cost-effectiveness model included baseline attack rate, unit costs for health care resource use, distribution of attack severity, market share for on-demand drugs, and proportion of Takhzyro patients who switch to every four week dosing (Supplement Tables C3 – C9). Table 3.2 presents the observational RWE update results on discounted costs and outcomes for prophylaxis and no prophylaxis.

Table 3.2. Results for the Observational RWE Update Base Case for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Prophylaxis Drug Cost*	Total Cost*	Attacks	QALYs	Life Years
No prophylaxis	$0	$6,780,000	926	18.00	23.30
Haegarda	$12,890,000	$13,950,000	148	18.53	23.31
Cinryze	$13,520,000	$16,880,000	458	18.33	23.30
Takhzyro	$12,660,000	$13,490,000	114	18.54	23.31

QALY: quality-adjusted life year

*Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

With the inclusion of RWE alongside the other model inputs, long-term prophylaxis continued to result in a lower number of acute attacks, higher costs, and higher QALYs compared to no long-term prophylaxis, but with fewer QALYs gained than the prior base-case analyses. The influence of these new model assumptions on cost effectiveness was dramatic, increasing the incremental cost-effectiveness ratios for all drugs to figures above $10 million per QALY gained (Table 3.3).

Table 3.3. Comparison of 2018 and Observational RWE Update Base-Case Results for HAE Prophylaxis versus no Prophylaxis

Treatment	2018 Report Cost per QALY gained	Observational RWE Update Cost per QALY gained
Cinryze	$5,950,000	$30,070,000
Haegarda	$328,000	$13,430,000
Takhzyro	$1,110,000	$12,370,000

QALY: quality-adjusted life year

*Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million. Note: Due to ratio properties of incremental cost-effectiveness ratios, results can become extreme with small denominators.

Sensitivity analysis, scenario analysis, and threshold analysis for the Observational RWE Phase updates are presented in Supplement Section C4.

The incremental contribution of key inputs to the difference in the cost-effectiveness ratios between the original 2018 report, the preliminary phase update, and the observational RWE phase update is presented in Table 3.4 below. The first row presents the incremental cost per QALY of prophylaxis compared with no prophylaxis from the 2018 evaluation. The second row presents the results of the preliminary phase updates (Supplement Tables C10 and C11). Each subsequent row builds upon the previous with the addition of another group of RWE inputs. More detailed tables by drug are provided in Supplement Tables C26, C27, and C28.

Table 3.4. Impact of RWE Update on Incremental Cost per QALY

	Incremental Cost per QALY		
	Haegarda	**Cinryze**	**Takhzyro**
2018 evaluation base-case results	$328,000	$5,954,000	$1,108,000
Preliminary phase literature update results	$461,000	$7,060,000	$1,280,000
Observational RWE Update Steps	**Haegarda**	**Cinryze**	**Takhzyro**
1. Proportion on Takhzyro that switch to every 4-week dosing	N/A	N/A	$199,000
2. Baseline attack rate	$10,390,000	$24,280,000	$10,010,000
3. Population and clinical parameters*	$13,790,000	$30,360,000	$12,730,000
4. Cost parameters†	$13,430,000	$30,070,000	$12,370,000
Final RWE Update Results	$13,430,000	$30,070,000	$12,370,000

QALY: quality-adjusted life year, RWE: real-world evidence

* Population parameters, pretreatment attack severity, treatment pathway (proportion of mild and moderate attacks treated with home self-administration, home nurse, or outpatient; proportion of severe attacks which result in hospitalization, hospitalization resource utilization mortality)

† Direct cost of emergency department visits and hospitalization, cost of administration, market shares of on demand drugs

3.3 New Health Benefit Price Benchmarks Based on Observational RWE Update

As shown in Table 3.5 below, based on the Observational RWE Phase updates, all the HAE prophylaxis agents would need to be priced significantly lower than the current list prices to reach health-benefit price benchmarks (HBPBs). Discounts needed to reach cost-effectiveness thresholds are more substantial than those suggested in the original 2018 report.

Table 3.5. Observational RWE Update HBPBs for HAE Prophylactic Therapies

	Annual WAC	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Discount from List Price to Reach Threshold Prices	Discounts from List Price to Reach 2018 Report Threshold Prices
Haegarda	$536,694	$247,669	$248,779	53.6% to 53.9%	27.7% to 28.2%
Cinryze	$548,563	$139,742	$140,550	74.5% to 75.4%	59.7% to 60.0%
Takhzyro	$461,611*	$218,858*	$219,844*	52.4% to 52.6%	33.7% to 34.2%

QALY: quality-adjusted life year

*Considers proportion with dose reduction

4. Discussion

The goal of this update to the 2018 ICER report on prophylactic treatments for HAE was to evaluate the impact of integrating new inputs based on observational RWE. We were aware from our 2018 model and corresponding sensitivity analyses that cost effectiveness of prophylaxis was sensitive to the baseline rate of HAE attacks. This sensitivity is because the cost of rescue treatment is high and because attacks are common so that even a small change in baseline rates, higher or lower, could determine whether prophylaxis was highly cost-effective or highly overpriced for the absolute benefit to patients. This analysis aimed to address these key assumptions in the model and update them, given that these treatments have all been available on the market for two years since the original report was issued.

In the observational RWE update, the most influential new finding was a reduction in the assumed baseline rate of HAE attacks from 3.39 per month in the 2018 report, which was based on data from the pivotal trials of these agents, to 1.88 per month in the RWE cohort of 158 patients newly initiating Takhzyro, Haegarda, or Cinryze. RWE findings for population parameters (e.g., age and weight), and pre-treatment attack severity further increased the incremental cost per QALY whereas RWE findings for health care utilization by attack severity, costs associated with attacks, and the market share distribution of on-demand drugs reduced the incremental cost per QALY.

We note several limitations to the observational RWE analysis. This analysis uses one primary evidence source, insurance claims. Other potential sources, such as patient registries that include patient reported outcomes, could provide updates to other domains (e.g., quality of life) of comparative effectiveness and cost effectiveness. The claims-based analysis was not able to differentiate between HAE patient sub-types which might have different underlying risks of attacks. However, clinical expert input indicated that practice is not generally targeted based on patient subtypes, thus we believe the inability to differentiate by subtype in the claims analysis does not substantially impact the findings.

Importantly, there are currently no published consensus algorithms for measuring HAE attack rates in claims data. We sought information from a clinical expert, treatment guidelines, and published literature to create operational definitions for severe and non-severe HAE attacks, but alternative definitions may be suggested that would change the number of baseline attacks counted in this dataset. While we are confident that claims data can validly capture severe attacks treated via ED and inpatient hospitalizations, using prescription claims for measuring non-severe attacks could either under- or overestimate attack rates. For example, 22 patients did not have any evidence of attacks in the six months prior to initiating prophylactic treatment. In a sample of coverage policies for health plans included in the Optum data, the plans require that at least one attack is documented every four weeks in order to qualify for prophylactic therapy (Takhzyro), or that prescriber attests that patient experiences attacks and would benefit from prophylactic therapy

(Cinryze and Haegarda).[5-7] These discrepancies suggest that our definition of non-severe attack may not be sensitive enough to capture all attacks and that attacks may be underestimated. However, using dispenses of on-demand therapies may overestimate non-severe attack counts. The relatively short shelf life of on-demand treatments may cause patients to refill without using previously filled prescriptions. Ultimately, even when we evaluated results using more relaxed definitions for non-severe attacks, the attack rates observed in the real-world data were far lower than those documented for patients participating in the pivotal RCTs for these three treatments.

As with the 2018 analysis, our estimates of long-term comparative clinical effectiveness of prophylaxis remain uncertain due to a lack of data on the natural history of attack rates over patients' lifetimes and by the sample sizes and the short duration of the available clinical trials and claims data. We also note continued uncertainty in the proportion of patients who require re-dosing of acute treatment for HAE attacks, with wide ranges reported in published literature. Due to limitations of claims data to capture self-administered treatment, we were unable to update these model inputs in the observational RWE phase updates. Higher rates of re-dosing than assumed in this analysis may lead to more favorable cost-effectiveness findings for prophylaxis than in our updated base-case analysis.

Cost-effectiveness analyses should be considered alongside other potential benefits and contextual considerations, described in the 2018 report, for the purposes of judging a treatment's overall value. Further, patient heterogeneity and individual management goals should be considered alongside population estimates of cost effectiveness.

This pilot, a collaboration between researchers at ICER, Aetion, and the University of Washington, demonstrates the feasibility of using observational RWE to address uncertainties in aspects of cost-effectiveness findings and corresponding health-benefit price benchmarks. In this case, the observational RWE findings suggest that patients initiating prophylactic treatment do not have as many attacks as was previously assumed from clinical trial data. The addition of observational RWE confirms the conclusions of the 2018 HAE review that at current drug prices, prophylactic treatment for HAE does not meet traditional cost-effectiveness thresholds. HAE prophylactic agents are effective, but real-world experience suggests that patients being treated are less severely affected by HAE than those in clinical trials, and thus prophylaxis with these treatments is far less cost-effective in a real-world patient population than was suggested in our first report.

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Supplemental Materials

A. Literature Review Update: Supplemental Information

A1. Methods Overview

Procedures for the updated systematic literature review assessing the evidence on Takhzyro, Haegarda, and Cinryze followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and other established best practice guidelines.[8-10] The search strategy from the 2018 review of HAE was re-run in MEDLINE and 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 was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. Reviewers screened references in accordance with pre-specified research questions. The findings were 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 focused on randomized controlled trials that support/enhance efficacy outcomes (e.g., data on reductions in attack rates) and other clinical model inputs (Table 2.1). Literature from non-randomized sources that include measures consistent with cost-effectiveness model inputs were categorized as supporting the RWE update phase, alongside the corresponding observational claims analyses.

A2. Results

Study Selection

Our literature search identified 563 potentially relevant references (see Supplement Figure A1), of which 17 references related to three drugs met our inclusion criteria. Primary reasons for study exclusion included outcomes out of scope of pre-specified research questions, duplicate/previously known information, and interventions not of interest. At the time of the 2018 report, full text RCTs were available for Cinryze (Zuraw 2010[11]) and Haegarda (Longhurst 2017[12]). The HELP trial for Takhzyro was available in abstract form. The nine included publications are categorized in Table A1 and described in further detail below. The remaining eight abstracts were evaluated and determined to not influence the cost-effectiveness analyses summarized in Chapter 4.

Table A1. New Literature to Inform Updates Across 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
Takhzyro	0 (HELP trial abstract)	1 (Banerji 2018)	2 (Lumry 2021, Riedl 2020)	0
Cinryze	1 (Zuraw 2010)	0	0	0
Haegarda	1 (COMPACT – Longhurst 2017)	1 (Lumry 2019 – out of scope)	4 (Craig 2019, Li 2019, Lumry 2018, Lumry 2021)	1 (Riedl 2018)

Cinryze

No references relating to either efficacy / other model inputs (first phase) or supporting RWE literature (observational RWE phase) were identified in the updated literature search.

Haegarda

Five references were identified relating to either the previously published Phase III COMPACT trial or a new Phase III RCT (SAHARA) focused on a fixed-dose subcutaneous Haegarda treatment.[13-17] Craig 2019[13] is the open-label extension of the COMPACT RCT, and Li 2019[14] is a pre-specified exploratory subgroup analysis of patients in the COMPACT study. Both references do not add any new evidence to inform subsequent phases of this report but support current model assumptions. Two references (Lumry 2018[15] and Lumry 2021[17]) reported on long-term health-related quality of life (HRQoL) in patients enrolled in the main COMPACT trial and the COMPACT open-label extension trial. The SAHARA randomized study (Lumry 2019[16]) was identified as a new RCT that compares a fixed-dose of subcutaneous plasma-derived C1-INH versus placebo. We view the fixed-dose efficacy evidence as outside the scope of this review given the weight-based dosing schedule per the Food and Drug Administration label.[18]

Takhzyro

Three references relating to one Phase III RCT were identified.[19-21] Banerji 2018[19] was identified as the main publication of the Phase III HELP study, which informed updates to baseline characteristics and efficacy rates of Takhzyro in the model. Lumry 2021[20] is a health-related quality of life (HRQoL) analysis of the HELP study that reports endpoints such as EQ-5D-5L score. Riedl 2020[21] was identified as an exploratory analysis with a focus on time to onset of effect and long-term efficacy of Takhzyro. Results from this study support current model assumptions.

Literature to Support RWE Phase

One reference was identified as literature to support the RWE phase of this report, specifically in the phase of protocol development. Riedl 2018[22] is a retrospective study looking at treatment patterns and health care resource utilization in the HAE patient population in the US.

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Hereditary Angioedema

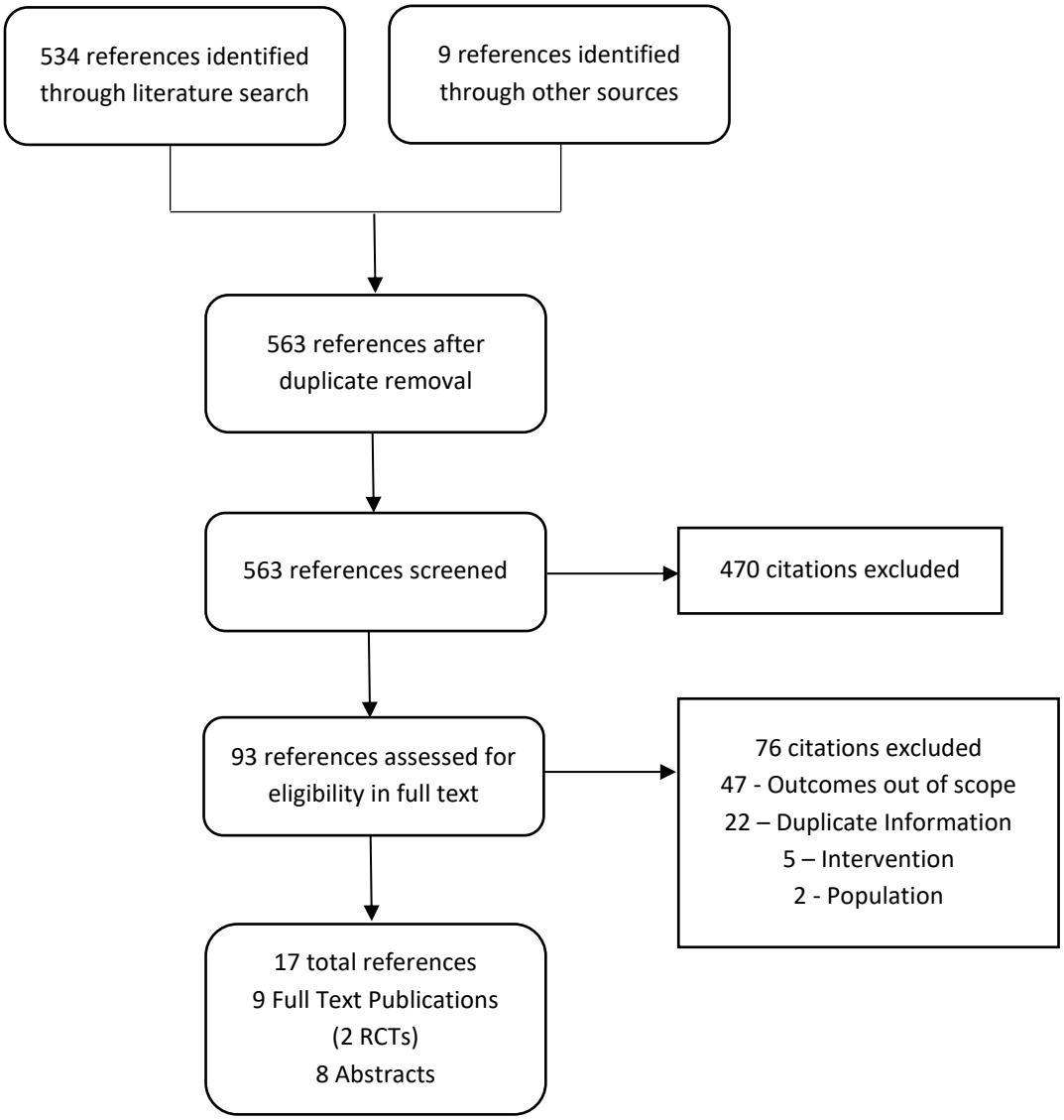


Table A2. Evidence Table for Included References (N=9)

<table>
<tr><th>Drug</th><th>Trial</th><th>Main Outcomes</th></tr>
<tr><td colspan="3">To Support: Efficacy</td></tr>
<tr><td>Takhzyro</td><td>Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. [HELP Study]

Banerji, A. JAMA. 2018.[19]</td><td>Main Outcomes:
Mean rate ratio relative to placebo (95%CI):
0.24 (0.15, 0.39) in 150-mg every-4-week arm
0.27 (0.18 to 0.41) in 300-mg every-4-week arm
0.13 (0.07 to 0.24) in 300-mg every-2-week arm
adjusted P < 0.001 for all comparisons.</td></tr>
<tr><td>Haegarda</td><td>Fixed-Dose Subcutaneous C1-Inhibitor Liquid for Prophylactic Treatment of C1-INH-HAE: SAHARA Randomized Study.

Lumry, W. The Journal of Allergy & Clinical Immunology in Practice. 2019.[16]</td><td>Main Outcomes:
From Day 1, LS means of NNA reduced from 3.9 with placebo to 1.6 with pdC1-INH (P < 0.0001).
From Day 1, median 79.5% reduction in HAE attacks v. placebo (mean [SD] 59.52% [69.06])
From Day 15, mean 84.6% reduction in HAE attacks v. placebo (mean [SD] 63.48% [58.45]).
Most patients had >50% NNA reduction with pdC1-INH (from day 1, 78%).
Of patients with data in both treatment periods, 77.6% and 76.6% receiving pdC1-INH liquid from days 1 and 15, respectively, were clinical responders (P < 0.0001).
Provides evidence on severity % post Haegarda
8.8% of placebo-treated patients were attack-free
5.3%, 22.8%, and 63.2% of placebo-treated patients had mild, moderate, and severe attacks
37.5% of pdC1-INH treated patients were attack free
8.9%, 26.8%, and 26.8% of pdC1-INH treated patients had mild, moderate, and severe attacks, respectively.</td></tr>
<tr><td colspan="3">To Support: Economic Inputs and Assumptions</td></tr>
<tr><td>Takhzyro</td><td>Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP Study

Lumry, W. Allergy. 2021.[20]</td><td>Main Outcomes:
Day 0: Mean EQ-5D-5L scores were high in all groups – no significant changes observed at day 182
<table>
<tr><th>Arm</th><th>Timeframe</th><th>Mean Index Scores</th><th>Mean VAS Scores</th></tr>
<tr><td rowspan="2">Placebo</td><td>Day 0</td><td>0.89</td><td>81.9</td></tr>
<tr><td>Day 182</td><td>0.88</td><td>84.2</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td rowspan="2">LANA 150 mg q4w</td><td>Day 0</td><td>0.84</td><td>78.4</td></tr>
<tr><td>Day 182</td><td>0.89</td><td>83.3</td></tr>
<tr><td rowspan="2">LANA 300 mg q4w</td><td>Day 0</td><td>0.87</td><td>82.8</td></tr>
<tr><td>Day 182</td><td>0.87</td><td>82.5</td></tr>
<tr><td rowspan="2">LANA 300 mg q2w</td><td>Day 0</td><td>0.89</td><td>81.2</td></tr>
<tr><td>Day 182</td><td>0.88</td><td>83.2</td></tr>
</table>
Index and VAS scores from day 0 to 182: mean change was not statistically significant for any arm.
</td></tr>
<tr><td></td><td>Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks

Riedl, M. Allergy. 2020.[21]</td><td>Main Outcomes
Attack Rate (days 0-69)
Lanadelumab: 0.41-0.76
Placebo: 2.04
Attacks requiring acute treatment
Lanadelumab: 0.33-0.61
Placebo: 1.66
P ≤ 0.001
Moderate/severe attacks
Lanadelumab: 0.31-0.48
Placebo: 1.33
P ≤ 0.001
Attack-Free
Lanadelumab: 37.9-48.1%
Placebo: 7.3%
Lanadelumab efficacy was considered durable as attacks rates presented lower than placebo consistently through treatment end, beginning as early as the first 2 weeks of treatment.</td></tr>
<tr><td>Haegarda</td><td>Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks.

Craig, T. The Journal of Allergy & Clinical Immunology in Practice. 2019.[13]</td><td>Main Outcomes
Monthly attack rate: 4.3 in 3 months before entry to trials (N=126), treated for mean of 1.5 years
Steady-state C1-INH functional activity: increase to 66.6% in 60 IU/kg arm
Adverse events: 11.3 events per patient-year in 40 IU/kg arm vs. 8.5 in 60 IU/kg arm
Median annualized attack rates
40 IU/kg: 1.30
60 IU/kg: 1.0</td></tr>
</table>

		Median Rescue Medication Use • 49 IU/kg: 0.2 times per year • 60 IU/kg: 0.0 times per year 23 patients received 60 IU/kg for over 2 years. Nineteen of these patients were attack-free during months 25 to 30 of treatment.
	Subcutaneous C1 inhibitor for prevention of attacks of hereditary angioedema: Additional outcomes and subgroup analysis of a placebo-controlled randomized study. Li, H. Allergy, Asthma, and Clinical Immunology. 2019.[14]	**Main Outcomes** Attacks of any severity • 60 UI/kg: 10.43 (23.0%) • Placebo: 34/42 (81%) Need for Rescue Medicine • 60 UI/kg: 35 treated attacks • Placebo: 358 treated attacks **Conclusion:** Consistent treatment effect was observed with C1-INH (SC) 60 UI/kg dosing in all subgroups of patients with type I/II HAE across different measures.
	Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema. Lumry, W. Journal of Allergy and Clinical Immunology. 2018.[15]	***[Week 32]*** Reports Mean difference of HRQoL scores (EQ-5D, HADS, WPAI, TSQM) between both doses of Haegarda and placebo treatments (Lumry 2021 has more updated estimates)
	Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study Lumry, W. Orphanet Journal of Rare Diseases. 2021.[17]	**Main Outcomes** ***[Week 88]*** EQ-5D, mean change from baseline (SD) • Health state value: 0.05 (0.153) • VAS: 5.83 (14.601) WPAI, mean change from baseline (SD) • Absenteeism: -4.89 (23.296) • Presenteeism: -14.31 (31.765) • Work Productivity: -15.97 (34.946) • Activity Impairment: -14.35 (32.013) C1-INH(SC) 60 IU/kg arm: significant improvements from baseline for 3 domains • presenteeism (mean change [95% CI], − 23.33%[− 34.86, − 11.81]), • work productivity loss (− 26.68% [− 39.92, − 13.44]), • activity impairment (− 16.14% [− 26.36, − 5.91])

		C1-INH(SC) 40 IU/kg group: significant improvement from baseline in only activity impairment: mean change [95% CI], − 12.71 [− 21.63, − 3.79]
To Support: RWE Phase		
Haegarda	Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States Riedl, M. Orphanet Journal of Rare Diseases. 2018[22]	**Main Outcomes:** • Out of 631 patients, 68.8% reported C1-INH(IV) use and 62.8% reported using ecallantide and/or icatibant • 306 episodes of prophylactic use of C1-INH(IV) in 155 patients • Use of ≥ on-demand rescue medication was used during 53% (163/306) of those episodes • Sixty-eight (20.2%) of 336 C1-INH(IV) users eligible for the HCRU analysis were hospitalized at least once • Eighteen patients had a central venous access device (CVAD); of these, 5 required hospitalization and 14 required an emergency department visit • Adjusted relative risk of hospitalization and/or ED visits for patients with a CVAD was 2.6 (95% CI: 0.17, 39.23) compared to C1-INH(IV) users without a CVAD

B. Real-World Data Analysis: Supplemental Information

The objective of the observational RWE study is to generate relevant and timely inputs to the cost-effectiveness model and address key uncertainties identified in the 2018 report that were appropriate to evaluate in real world evidence, including:

- Describing baseline demographic characteristics, attack rates, and attack-related medical service utilization among initiators of one of the three treatments for long-term prophylaxis use (Takhzyro, Haegarda, or Cinryze)
- Exploring attack rates and utilization following long-term prophylaxis initiation, including the percentage of patients who receive less frequent dosing for Takhzyro in clinical practice.

A retrospective descriptive claims study was completed (please see protocol for additional details on data source, study design, patient populations, measure definitions/code lists, and analytic methods).

B1. Baseline Analysis

Methods

In the baseline analysis, patients newly initiating Takhzyro, Haegarda, or Cinryze (identified by prescription claims) between October 10, 2008 through October 3, 2019 were eligible to enter the cohort. These patients were required to have at least 180 days of baseline enrollment and no evidence of prophylactic treatment during this period (see protocol for more details). Using this cohort, we evaluated baseline outcomes: patient characteristics, HAE attack rates, attack-related medical service utilization, and costs.

HAE attacks were separated into two categories. Severe attacks were defined as an HAE specific ED visit or hospitalization (see protocol for algorithms and code lists). Non-severe attacks were defined as treatment with on-demand therapy administered in an outpatient visit, home nurse visit, or self-administered by the patient. Data on the duration of attacks by severity is limited, however attacks generally last between two and five days.[3] Thus, on-demand therapy administered by a health care professional in an outpatient or home setting, during an ED visit, and during inpatient hospitalizations occurring within five days of each other were considered part of a single attack.

Costs were estimated for HAE attack episodes by severity and treatment location (ED only vs. inpatient for severe attacks and home vs. office for non-severe attacks). Cost analyses were

restricted to 2017-2020 in order to estimate the most timely and relevant costs and were inflated to 2021 US dollars (see protocol for more details) Attack costs for ED visits and hospitalizations (Table B5) were estimated by summing costs across the medical services utilized during an attack, then excluding the costs of on-demand therapies, which are included in the cost - effectiveness model separately.

Patient Characteristics

One hundred and fifty-eight (158) patients initiated prophylactic treatment with Cinryze (49.4%), Haegarda (24.0%), or Takhzyro (26.6%; Table B1). The mean age of patients at the time of prophylaxis initiation was 40.7 (SD: 19.0), and 72% of patients were female (Table B2; see modeling section on how results compared to 2018 model inputs). The literature has shown that DPP4 inhibitors, ACE inhibitors, ARBs, and NEP inhibitors can increase the risk of angioedema attacks.[23,24] Of the 158 patients in the prophylaxis treatment cohort, 13% were prescribed a drug within one of these therapy classes in the six months prior to initiation of prophylaxis treatment.

Table B1. Baseline Inclusion/Exclusion Flow Table

Criteria	Less Excluded Patients	Remaining Patients
All patients	-	67,691,644
Patients meeting inclusion criteria (use of Cinryze, Haegarda, or Takhzyro)	-67,691,227	417
Excluded due to < 180 days baseline enrollment	-59	358
Excluded patients initiating Cinryze who do not have evidence of prophylactic use for 90 days post cohort entry	-137	221
Excluded based on prior prophylactic use of Cinryze during the baseline period (dose >= 1500 / week during period 90 days to 1 day prior to cohort entry (13 weeks))	-2	219
Excluded based on prior prophylactic use of Cinryze during baseline period (dose >= 1500/ week during the period 180 days to 91 days prior to cohort entry (13 weeks))	0	219
Excluded based on prior use of Haegarda	-28	191
Excluded based on prior use of Takhzyro	-32	159
Excluded based on prior use of older prophylactic (Berotralstat, Danazol, Oxandrolone, Tranexamic Acid, Aminocaproic Acid, Methyltestosterone, Stanozolol)	-1	158
Final cohort	-	**158**

Table B2. Baseline Cohort Patient Characteristics

Variable	Value
Number of patients	158
Age - mean (SD)	40.65 (19.03)
Age - median [IQR]	39.00 [26.00, 54.00]
Male; n (%)	45 (28.5%)
Female; n (%)	113 (71.5%)

Attack Rates

In the six months prior to initiation of prophylaxis therapy, 86% of patients (N = 136) had evidence of at least one attack episode. Thus, 22 patients were free from an HAE attack before initiating prophylaxis therapy; 10 of these patients initiated Takhzyro, four initiated Haegarda, and eight initiated Cinryze. Eighty-six percent of patients were severe attack-free in the six-month baseline time period.

Out of 1,783 total attack episodes observed for all patients in the six months prior to initiation of Takhzyro, Haegarda, and Cinryze, 5.7% were severe and 94.3% were non-severe (Table B3). On average, patients had 1.88 HAE attacks per month.

Table B3. Six-month Baseline HAE Attack Rates

	Attacks N (%)	Mean attack rate (per patient per month)
Severe HAE attack episodes	102 (5.72%)	0.11
Non-severe HAE attack episodes	1,681 (94.28%)	1.77
Total attacks (severe and non-severe)	**1,783 (100%)**	**1.88**

Sensitivity analyses were conducted on the definition of HAE attacks. Data on the precise timing of self-administered treatment is not available. Rather, the number of treatments administered was estimated from pharmacy dispensing data, including the date and quantity dispensed, and dosing guidelines. In estimating the number of self-treated attacks, we assumed, based on clinical guidelines, that patients would have on-demand treatment on hand to treat up to two attacks. These two on-hand doses were subtracted out in the calculation of self-administered doses in the primary analysis. In sensitivity analysis, each prescription dose was counted as an attack. This increased the non-severe attacks to 1,871 and total attacks to 1,973 and resulted in 2.08 attacks per patient per month.

As noted above, in the primary analysis, we treated attack-related visits within five days of each other as part of the same attack. In sensitivity analyses, we reduced the assumed attack duration to two days and then to one day, treating events on distinct days as separate attacks in the one-day duration analysis. Estimated attack rates increased to 1.90 and 1.96 in these analyses, respectively.

Utilization

We assessed the distribution of care settings for treated attacks. Among hospitalizations, we assessed the prevalence of intubation, cricothyrotomy/tracheotomy, and artificial respiration.

Among 102 severe attack episodes, a total of 19 hospitalizations were observed (Table B4). Intubation occurred in 23.5% (n=4) of these hospitalizations and cricothyrotomy/tracheotomy in 11.8% (n=2). All patients who were intubated or had a cricothyrotomy/tracheotomy were put on mechanical ventilation. Fifteen of the 19 hospitalizations were preceded by an ED visit. We observed a total of 108 ED visits.

Among 1,681 non-severe HAE attack episodes, there were 20 outpatient setting visits where on-demand treatment was administered and 152 home visits with on-demand treatment administered. 1,509 doses of on-demand therapy were administered by the patient. Across all non-severe attacks, the most common on-demand therapy used was Firazyr (61.0%), followed by Berinert (19.6%).

Table B4. Utilization by Severity of Attack

	Total Counts
Severe HAE attack episodes†	
ED visit only	93
Inpatient hospitalizations	19
Non-severe HAE attacks	
Treated in outpatient setting with on-demand therapy	20
Treated at home with on-demand therapy	152
Self-administered on-demand therapy	1,509

†Severe attack episodes were defined as any attack-related hospitalization that happened within a five-day time period. There were on average, 1.05 ED visits per HAE severe attack and 1.12 ED visits per attack with an inpatient hospitalization.

Costs

Average cost per ED visit was $2,940 and average cost per hospitalization was $20,957 (B5).

Table B5. Costs Associated with HAE Attacks

	Costs
Cost per ED visit	$2,940 (SD: $2,901)
Cost per hospitalization	$20,957 (SD: $13,628)

ED: emergency department, SD: standard deviation

B2. Post-Prophylaxis Descriptive Analyses

Methods

As an exploratory and descriptive analysis, we evaluated severe attack rates following prophylactic treatment initiation among a cohort of patients who met the inclusion/exclusion criteria for the baseline analyses and had at least 90 days of continuous enrollment following prophylaxis initiation. Patients were censored upon the first of: maximum follow up of 365 days, disenrollment, end of data, or death.

Patient Characteristics

134 patients were included in the post-prophylaxis exploratory analysis (B6). The majority of patients initiated Cinryze (72), followed by Takhzyro (34) and Haegarda (28; Table B7)

Table B6. Post-Prophylaxis Exploratory Cohort Inclusion/Exclusion Flow Table

Criteria	Less Excluded Patients	Remaining Patients
All patients	-	67,691,644
Patients meeting inclusion criteria (use of Cinryze, Haegarda, or Takhzyro)	-67,691,227	417
Excluded due to < 180 days baseline enrollment	-59	358
Exclude patients initiating Cinryze who don't have prophylactic use for 90 days post cohort entry	-143	215
Excluded based on prior prophylactic use of Cinryze during the baseline period (dose >= 1500 / week during period 90 days to 1 day prior to cohort entry (13 weeks))	-2	213
Excluded based on prior prophylactic use of Cinryze during the baseline period (dose >= 1500/ week during the period 180 days to 91 days prior to cohort entry (13 weeks))	0	213
Excluded based on prior use of Haegarda	-33	180
Excluded based on prior use of Takhzyro	-35	145
Excluded based on Use of older prophylactic (Berotralstat, Danazol, Oxandrolone, Tranexamic Acid, Aminocaproic Acid, Methyltestosterone, Stanozolol)	-1	144
Excluded due to <90 days follow-up	-10	134
Final cohort	-	**134**

Table B7. Post-Prophylaxis Exploratory Cohort Patient Characteristics

Variable	Overall	Takhzyro Initiators	Haegarda Initiators	Cinryze Initiators
Number of patients	134	34	28	72
Age - mean (SD)	39.83 (18.77)	46.53 (15.48)	39.61 (22.31)	36.75 (18.11)
Age - median [IQR]	37.00 [26.00, 54.00]	47.50 [34.00, 58.00]	39.00 [20.25, 57.75]	34.00 [22.00, 48.00]
Male; n (%)	40 (29.9%)	6 (17.6%)	11 (39.3%)	23 (31.9%)
Female; n (%)	94 (70.1%)	28 (82.4%)	17 (60.7%)	49 (68.1%)

IQR: interquartile range, SD: standard deviation

Severe Attack Rates

The average follow-up time in the cohort was 24 months, though this differed by drug. Patients initiating Cinryze, which was the first drug approved, tended to initiate earlier in the study period and thus had more follow-up time available. They were followed for a mean of 33.1 months, as opposed to 9.6 months for Takhzyro and 18.5 months for Haegarda (Table B8). Across all patients in the post-prophylaxis exploratory cohort, patients initiating Takhzyro had the highest percentage of severe attack-free months in the follow-up period (92.3%), followed by Cinryze (73.0%) and Haegarda (69.7%; Table B8).

Table B8. Post-prophylaxis Treatment Initiation Severe Attack Rates

	Number of Patients	Average Follow-up Time per Patient (min, max)	Average Severe Attack-Free Months per Patient	Average Proportion of Months Severe Attack Free
Overall	134	24.1 (4, 119)	16.2	77.0%
Takhzyro	34	9.6 (4, 18)	9.0	92.3%
Cinryze	72	33.1 (4,119)	23.0	73.0%
Haegarda	28	18.5 (5, 32)	12.5	69.7%

Due to the small sample size, there is insufficient power to complete a formal pre/post analysis to detect a meaningful difference in attack rates. Thus, the comparison between baseline and post-prophylaxis exploratory cohorts is descriptive only. Compared to the baseline period, patients had fewer severe HAE attacks per month on average (0.11 vs. 0.04; Table B9). The 64% reduction in severe attacks per month is in line with results from the pivotal RCTs, which measured reduction in all HAE attacks compared with placebo over the entire study period and demonstrated a range of 50%-87% reduction in HAE attacks. While this is not an equal comparison (e.g., difference in severe attacks vs. all attacks) and the RWE results are descriptive, the RWE results appear to be consistent with the RCT estimates.

Table B9. Descriptive Comparison of Severe Attack Rates in Baseline versus Follow-up Period

	Baseline Period	Follow-up Period
Number of patients	158	134
Total number of patient months	948 (fixed, 6 months per patient)	2982 (variable)
Total number of severe HAE attacks	102	116
Severe HAE attacks per patient per month	0.11	0.04

Adherence and Switching

Adherence to prophylaxis therapy could impact the cost and effectiveness of these treatments. To assess real-world patterns, we evaluated adherence using proportion of days covered (PDC). PDC was calculated as the proportion of days covered with any prophylactic medication – not just the medication initiated - for the first six months post initiation of a prophylaxis therapy. The six-month follow-up period was selected to increase comparability across the three therapies. The percentage of patients with PDC greater than 80% during the six months post initiation was highest for Takhzyro patients (70.6%), followed by Cinryze (56.9%) and Haegarda (53.6%).

As noted above, patients switching to a different prophylactic were not censored from follow-up. Of the patients that switched, the majority switched to Takhzyro; 22% of patients that initiated Cinryze and 25% of Haegarda initiators switched to Takhzyro. Only 2.9% and 5.9% of Takhzyro patients switched to Haegarda and Cinryze, respectively.

B3. Exploratory Analysis of Takhzyro Dose Reduction

Methods

According to the FDA-approved label, patients on Takhzyro who are attack free for six months can reduce the frequency of dosing from every two weeks to every four weeks. To assess the frequency of dose reduction in real-world setting, we analyzed refill patterns in a cohort of patients initiating Takhzyro. Patients were required to have a minimum of nine months follow-up: six months to assess eligibility for dose reduction plus 90 days to evaluate whether an actual dose reduction occurred.

Patient Characteristics

Forty-two patients initiating Takhzyro met cohort entry criteria (Table B10). These patients were slightly older and more likely to be female compared to the baseline cohort (Table B11).

Table B10. Takhzyro Dose Reduction Cohort Inclusion/Exclusion Flow Table

	Less Excluded Patients	Remaining Patients
All patients	-	67,691,644
Did not meet cohort entry criteria (use of Takhzyro)	-67,691,570	74
Excluded due to <180 days baseline enrollment	-14	60
Excluded due to prior use of Takhzyro	-16	44
Excluded due to < 270 days of enrollment following cohort entry	-2	42
Final cohort	-	**42**

Table B11. Takhzyro Dose Reduction Cohort Patient Characteristics

Variable	Value
Number of patients	42
Age - mean (SD)	48.55 (15.97)
Age - median [IQR]	48.50 [39.25, 59.50]
Male; n (%)	10 (23.8%)
Female; n (%)	32 (76.2%)

IQR: interquartile range, SD: standard deviation

Dose Reduction

Among 42 patients initiating Takhzyro, 27 patients were both attack free and on bi-weekly dosing during the first six months following initiation. Of these 27 patients eligible for a reduction in dosing, 20 (74%) reduced dosing to every four weeks. Thus, 48% (20/42) of those who initiated Takhzyro were observed to reduce dosing to every four weeks.

B4. Patient Weight

Methods

Patient weight is of interest due to the weight-based dosing of some HAE therapies. A limitation of claims data is incomplete data capture on patient weight, thus we created a separate cohort in Optum's De-identified Integrated Claims-Clinical dataset, which combines adjudicated claims data with Optum's Electronic Health Record data, to obtain a larger sample of HAE patients with weight values. This cohort included all patients with a diagnosis related to HAE or with a prescription for an HAE drug (Table B12).

Table B12. EHR Weight Cohort Inclusion/Exclusion Flow Table

Criteria	Less Excluded Patients	Remaining Patients
Starting patient population	-	102,673,516
Did not meet cohort entry criteria	-	18,086
Excluded due to insufficient enrollment	-2,949	15,137
Exclude if less than 18 years old	-1,775	13,362
	-	**13,362**

Table B13. EHR Weight Cohort Patient Characteristics

Variable	Value
Mean age	48.95
Female, %	65.40%
Mean weight, females	77.44
Mean weight, males	91.77

Weight

The average weight of females with HAE was 77.4 kg (SD: 21.9) and 91.8 kg (SD 22.3) for males. Weight was missing for approximately 20% of HAE patients in the cohort (Table B13).

B5. Firazyr/Icatibant Mix

The first generic versions of icatibant were approved in July 2019. To evaluate the relative frequency of branded versus generic icatibant use in current data, we conducted a supplemental analysis of icatibant prescription fills and administration events in 2020. The analysis included events from January 1, 2020 through end of data, March 31, 2020. No medical service events corresponding to icatibant administration were identified during this period. Among the 183 prescriptions filled, 149 (81.4%) were identified as branded Firazyr and 34 (18.6%) as generic icatibant.

C. Long-Term Cost-Effectiveness: Supplemental Information

C1. Methods Overview

The HAE model was developed as a Markov model with two health states: "alive with HAE" and "dead" (Figure C1). 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 C2). These outcomes were tracked over time for persons receiving long-term prophylaxis with Takhzyro and the C1 inhibitors, and those not receiving long-term prophylaxis.

The base-case analysis took a health care system perspective (i.e., focus on direct medical care costs only) and a lifetime time horizon. Productivity impacts were included in a modified societal perspective scenario analysis. A 3% per year discount rate was applied for future costs and health outcomes. Model output cost-effectiveness summary measures included: cost per attack avoided, cost per quality-adjusted life years (QALYs) gained, and cost per life-year gained. Note that equal value of life years gained (evLYGs) was not included in the 2018 evaluation and therefore was not included within this update.

Figure C1. Model Framework

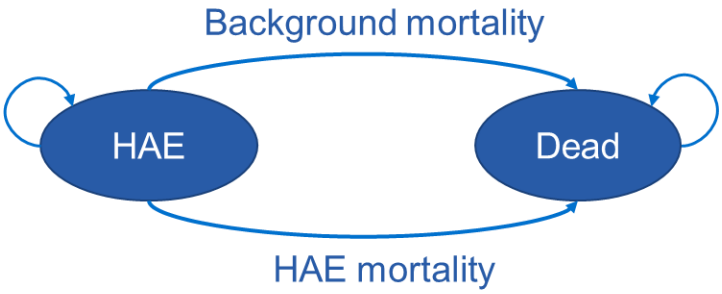
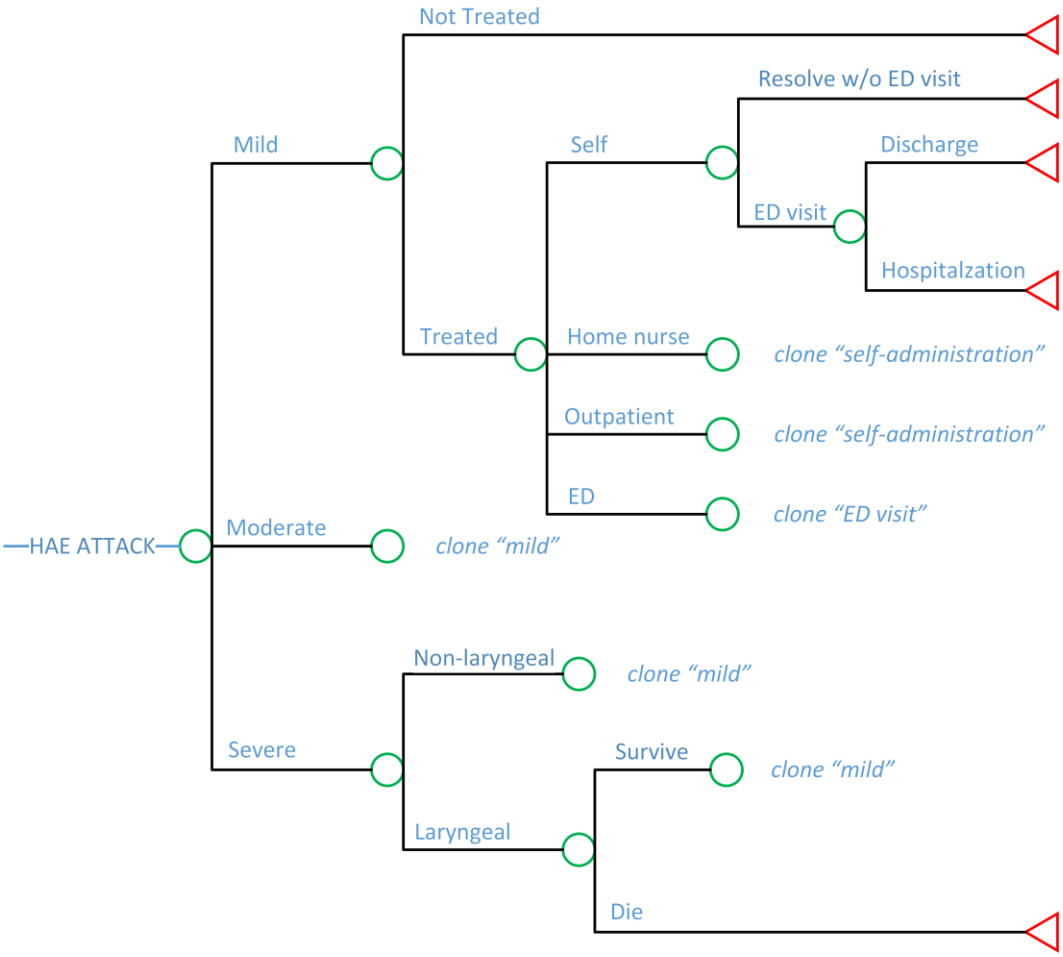


Figure C2. HAE Attack Pathway



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.

Table C1. 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	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[25]

Target Population

Consistent with the original analysis, the population for this analysis consisted of patients in the US with HAE I/II who are candidates for long-term prophylactic treatment.

Treatment Strategies

The interventions assessed in this model were:

- Haegarda (C1-INH, subcutaneous injection [human])
- Cinryze (C-INH, intravenous injection [human])
- Takhzyro (lanadelumab)

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

C2. Model Inputs and Assumptions

Table C2. Key Model Choices and Assumptions

Assumption	Rationale
Model Choice: Prior model inputs will be supplemented with real-world evidence from published literature and real-world evidence analysis	Observational RWE will aid in updating baseline attack rates and other model inputs. For the updated base case, we will continue to rely on randomized controlled trials for comparative efficacy inputs.
All moderate and severe attacks are treated.	Treatment guidelines and empirical data suggest that moderate and severe attacks are treated.[3]
In the RWE Observational Update, all mild, moderate, and severe attacks are treated	The baseline attack rate which is generated from the de novo RWE analysis is based on treated attacks
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.[3]
Market share distribution of on-demand drugs is consistent across treatment settings (e.g., home use, physician, emergency department).	Update of previous assumptions based on real-world evidence of claims data which is not stratified by treatment setting.
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.	In the original model, health state utilities were derived from publicly available literature and applied to health states. No new utility values were identified as part of this RWE update.

The preliminary phase updates focused on randomized controlled trials, updated drug prices, and inflation of unit costs to 2021 US dollars. Key updates to inputs in the preliminary phase were: mean annual baseline attack frequency (from 3.39 in the 2018 Report to 3.81 based on the inclusion of one additional RCT[26]), proportion of patients self-administering on-demand treatment for attacks (64.9% in 2018 Report to 76.3% in preliminary phase update based on recently published data for treatment patterns,[27] and drug acquisition costs (an average of 43% increase from 2018

Report to preliminary phase update [range +10% for Cinryze ASP pricing to +186% for Berinert list price) (Table C7).

Updated inputs from the Observational RWE Phase were applied to the preliminary phase model, with RWE updates overriding the preliminary phase inputs where applicable. Key updates to inputs in the observational RWE phase were the baseline attack rate, now based on real-world data for patients initiating HAE prophylaxis rather than clinical trials, severity of attacks, proportion of patients self-administering on-demand treatment for attacks, market share of acute treatments, and cost of ED and hospitalizations. Original and updated values for model inputs which were updated from the original 2018 cost-effectiveness analysis are shown in the following sections. A complete listing of all original model inputs can be found in the 2018 HAE final report.[1]

Model Inputs

Inputs

Table C3. Source of Key Model Input Updates

	Full Text RCTs Available at the time of 2018 Report	Preliminary Phase: Randomized Controlled Trial literature to support / enhance:		Observational RWE Phase: De novo RWE claims analysis and literature to support / enhance:
		Efficacy	Other Inputs	Model Inputs
Epidemiology	N/A	N/A	Age, gender, baseline attack rate	Age, gender, weight, baseline attack rate, pre-treatment severity of attack distribution
Treatment Pathway	N/A	N/A	Mode of treatment administration for mild and moderate attacks, HAE laryngeal attack mortality rate	Mode of treatment administration for mild and moderate attacks, Proportion of severe attacks that start in the ED that result in hospitalization, proportion of attacks with cricothyrotomy and intubation
Health Care Resource Use and Cost	N/A	N/A	Direct cost of home nurse, physician office visits, ED visits, hospitalizations, indirect cost per mild, moderate, severe attack, other direct costs of treatment (e.g., IV administration), drug acquisition costs for preventive and on-demand treatment	Direct cost of ED visits and hospitalizations, Market share of on-demand drugs
Takhzyro	0 (HELP – Banerji 2017 conference abstract)	% reduction in attack frequency (Banerji 2018)	-	Proportion of patients that switch to every four-week dosing
Cinryze	1 (Zuraw 2010)	-	-	-
Haegarda	1 (COMPACT – Longhurst 2017)	-	-	-

Population Inputs

In the original 2018 analysis, the baseline age, gender, and attack frequency used in the model reflected the weighted average of these baseline characteristics across the three pivotal clinical

trials for the interventions the baseline weight for males and females was obtained from Centers for Disease Control and Prevention (CDC) anthropometric reference data.[11,12,26,28,29] In the preliminary phase updates, inputs for age, gender, and attack frequency were updated with an additional RCT publication to reflect the weighted average across four clinical trials.

Baseline attack rate in the 2018 evaluation was an average of three RCTs: Banerji 2017, Longhurst 2017 and Zuraw 2010).[11,12,30] In the preliminary phase updates, baseline attack rate was updated to the average of four available RCTs: Banerji 2018 (full publication of earlier Banerji 2017 conference presentation), Longhurst 2017, Zuraw 2010, and Riedl 2017.[12,26,30] The baseline attack rate changed from 3.39 per month in the 2018 report to 3.81 per month in the preliminary phase updates. Drug acquisition cost for prophylactic and acute treatments were updated to current WAC or ASP pricing. The market share for acute treatments remained consistent with the 2018 analysis, assuming equal use of Berinert, Firazyr, and Ruconest for mild and moderate attacks and equal use of Berinert, Firazyr, Ruconest, and Kalbitor for severe attacks.

In the Observational RWE Phase, these inputs were updated again to reflect the mean age, gender, weight, and baseline attack frequency in the cohort of HAE patients initiating prophylaxis that were identified in the RWE analysis.

Table C4. Base-Case Model Cohort Characteristics

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value	Source
Age in years (mean)	39.6	Zuraw 2010[11], Longhurst 2017[12], Riedl 2017[26], Banerji 2017[28]	40.8	Zuraw 2010[11], Longhurst 2017[12], Riedl 2017[26], Banerji 2018[31]	40.65	RWE analysis
Gender (% female)	68.4%	Zuraw 2010[11], Longhurst 2017[12], Riedl 2017[26], Banerji 2017[28]	72.1%	Zuraw 2010[11], Longhurst 2017[12], Riedl 2017[26], Banerji 2018[31]	71.5%	RWE analysis
Weight, female (kg)	76.40	Fryar 2016[29]	Same as original value		77.44	RWE analysis
Weight, male (kg)	88.80	Fryar 2016[29]	Same as original value		91.77	RWE analysis
Baseline attack frequency (per month)	3.39	Zuraw 2010[11], Longhurst 2017[12], Riedl 2017[26], Banerji 2017[28]	3.81	Longhurst 2017[12], Riedl 2017[26], Banerji 2018[31]	1.88	RWE analysis

RWE: real-world evidence

Clinical Inputs

In the preliminary phase updates, clinical inputs largely remained the same as the 2018 analysis with the exception of a publication with updated treatment patterns for the proportion of mild-moderate attacks self-treated, treated by a home nurse, or treated in an outpatient setting.[27] For the Observational RWE phase updates, the proportion of attacks which are mild, moderate, and severe was derived using a combination of literature and RWE estimates. First, we identified the proportion of all HAE attacks that resulted in an ED visit with or without hospitalization. These attacks were considered severe (5.7% of attacks). The ratio of mild to moderate attacks from published literature was used to generate the proportion mild vs moderate for the remaining 94.3% of attacks.[32] The proportion of Takhzyro patients who switch to every four week dosing was updated based of RWE estimates of the proportion of Takhzyro initiators who met switched to every four week dosing. No efficacy reduction was assumed for patients who switch to every four-week dosing. Market share for acute treatments was updated based on observed market share in the de novo RWE analysis and applied to both mild/moderate and severe attacks.

Table C5. Key Clinical Model Inputs

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value	Source
Pre-treatment severity of attack Mild Moderate Severe	 36.6% 46.2% 17.2%	Riedl 2016[32]	Same as original value		 41.7% 52.6% 5.7%	RWE analysis
Mild/moderate HAE attack mode of treatment administration: Self Home nurse Outpatient	 64.9% 13.8% 21.3%	Riedl 2015[33]	 76.3% 11.8% 11.9%	Riedl 2020[21]	 89.8% 9.0% 1.2%	RWE analysis
Proportion of severe attacks that start in the ED that result in hospitalization	40.9%	Zilberberg 2011[34]	Same as original value		26.5%	RWE analysis
Proportion of hospitalized patients who receive a cricothyrotomy	69.4%	Bork 2012[35]	Same as original value		7.4%	RWE analysis
Proportion of hospitalized patients who are intubated	40.0%	Bork 2012[35]	Same as original value		18.5%	RWE analysis
Proportion of cricothyrotomy patients who receive artificial respiration	60.0%	Bork 2012[35]	Same as original value		100.0%	RWE analysis
Proportion of intubated patients who receive artificial respiration	40.0%	Bork 2012[35]	Same as original value		100.0%	RWE analysis

Clinical Probabilities/Response to Treatment

During the preliminary phase updates, the reduction in attack frequency was revised for Takhzyro to reflect new RCT data. Other inputs remained the same as the original 2018 analysis. Results of the observational RWE data analysis provided additional evidence on the proportion of patients using Takhzyro who successfully remain attack free and switch to lower dosing.

Table C6. Key Treatment Response Model Inputs

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value	Source
Takhzyro % reduction in attack frequency	86.9%	Banerji 2017[28]	87.7%	Banerji 2018[31]	Same as preliminary updated value	
Proportion of Takhzyro patients who switch to q4w dosing	0% with 44.4% as a scenario	Cook 1997[8]	Same as original value		47.6%	RWE analysis

Mortality

We assumed that only laryngeal attacks could be fatal. The monthly probability of death from a laryngeal attack was applied to background mortality from US life tables.

Utilities

No new utility values were identified to inform model updated. Thus, utility values used within the model remained identical to those in the 2018 HAE evaluation.[1]

Adverse Events

There were no serious or clinically relevant AEs attributable to any of the prophylactic therapies in the clinical trials.

Economic Inputs

Drug Acquisition Costs

Drug cost inputs are shown in Table C7. We used the Wholesale Acquisition Cost (WAC) per dose unit for subcutaneously administered drugs and self-administered doses of intravenously administered drugs. For non-self-administered doses of intravenous drugs, because the drug is not being dispensed directly to the patient, we used the average sales price (ASP) plus a 9% markup representing the mean markup for units administered in physicians' office, home infusion, and hospital outpatient settings. In the base-case analysis, all icatibant was assigned the brand Firazyr WAC price. As a scenario analysis we explored applying the cost of generic icatibant rather than the brand price, assuming no change in the market share for acute treatment.

Table C7. Drug Cost Inputs

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value
Cost of Takhzyro (300 mg dose)	$16,520	FSS*	$23,414	WAC†	Same as preliminary updated value
Cost of Cinryze (500 U)	$2,012	FSS*	$2,842	WAC†	Same as preliminary updated value
	$2,797	ASP	$3,075	ASP (Jan 2021)	Same as preliminary updated value
Cost of Haegarda (2000 UI)‡	$1,393	FSS*	$1,994	WAC†	Same as preliminary updated value
Cost of Berinert	$1,135	FSS*	$3,250	WAC†	Same as preliminary updated value
	$2,447	ASP (June 2018)	$2,713	ASP (Jan 2021)	Same as preliminary updated value
Cost of Kalbitor (30 mg dose)	$11,174	FSS*	$15,211	WAC†	Same as preliminary updated value
	$14,306	ASP (June 2018)	$16,092	ASP (Jan 2021)	Same as preliminary updated value
Cost of Firazyr (30 mg dose)	$7,178	FSS*	$11,147	WAC†	Same as preliminary updated value
Cost of generic icatibant (30 mg dose; *scenario*)	Not included	N/A	$2,796	WAC†	Same as preliminary updated value
Market share of on-demand drugs – self or home nurse Cinryze Berinert Kalbitor Firazyr Ruconest	 0.0% 33.3% 0.0% 33.3% 33.3%	Assumption	Same as original value		 9.97% 19.61% 0.88% 61% 8.54%
Market share of on-demand drugs – physician or ED Cinryze Berinert Kalbitor Firazyr Ruconest	 0% 25.0% 25.0% 25.0% 25.0%	Assumption	Same as original value		 9.97% 19.61% 0.88% 61% 8.54%

*Federal Supply Schedule (FSS) price as of October 1, 2018.

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

Administration and Monitoring Costs

A cost of administration is applied to intravenously and subcutaneously administered medications which are not self-administered. These unit costs were updated to 2021 dollars in the preliminary

phase updates and again using results of the observational RWE for the cost of subcutaneous administration and IV administration.

Table C8. Cost of Administration

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value	Source
Cost of subcutaneous administration	$20.88	CPT 96372	$14.31	CPT 96372	$65.99	RWE analysis inflated to 2021 USD
Cost of IV administration	$47.16	CPT 96374	$41.87	CPT 96374	$157.38	RWE analysis inflated to 2021 USD
Cost of physician office visit	$80.00	CPT 99214	$131.20	CPT 99214	Same as preliminary updated value	

Health Care Utilization Costs

Direct costs of acute attacks included drug costs, costs of a home nurse, and physician office administration of on-demand treatment, costs of ED visits and hospitalizations.

Table C9. Cost of Acute Attacks

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value	Source
Home nurse administration	$179	Graham 2017[36]	$188	Graham 2017[36] inflated to 2021 USD	Same as preliminary updated value	
Physician office visit	$266	Graham 2017[36]	$279	Graham 2017[36] inflated to 2021 USD	Same as preliminary updated value	
ED visit	$1,796	Zilberberg 2011[34]	$1,913	Zilberberg 2011[34] inflated to 2021 USD	$2,940	RWE analysis inflated to 2021 USD
Hospitalization	$5,782	Zilberberg 2011[37]	$6,155	Zilberberg 2011[37] inflated to 2021 USD	$20,957	RWE analysis inflated to 2021 USD
Emergency intubation	$146.00	CPT 31500	$144.81	CPT 31500	Same as preliminary updated value	
Cricothyrotomy	$346.68	CPT 31605	$339.51	CPT 31605	Same as preliminary updated value	
Ventilator support, <96 hours	$14,089	DRG 208	$15,000	DRG 208	Same as preliminary updated value	
Ventilator support >96 hours	$32,709	DRG 207	$34,823	DRG 207	Same as preliminary updated value	

C3. Preliminary Phase Update Results

One new RCT was identified in the updated literature review, and one additional article describing on-demand treatment for attacks.[26,27] Results of these articles were used to update model inputs, along with an update to drug acquisition costs from 2018 to 2021.

Key model input updates generated by inclusion of the two new articles included:

- Mean annual baseline attack frequency of 3.81 (vs. 3.39 in the 2018 Report)
- Proportion of patients self-administering on-demand treatment for attacks of 76.3% (vs. 64.9% in 2018 Report)

Results using the new model inputs from the first update phase are shown in Tables C10 – C12. As can be seen, all incremental cost-effectiveness ratios remain very high, and there was only a modest difference from the results of 2018 to the those in the preliminary phase literature update. Higher baseline attack frequency would make the drugs more cost-effective, but this effect was

more than counter-balanced by the increase in costs related to a higher rate of self-administration of on-demand treatment.

Table C10. Results for the Preliminary Phase Base Case for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Prophylaxis Drug Cost*	Total Cost*	Attacks	QALYs	Life Years
No prophylaxis	$0	$13,950,000	1,871	17.11	23.26
Haegarda	$12,490,000	$14,560,000	299	18.43	23.27
Cinryze	$12,890,000	$19,800,000	926	17.94	23.26
Takhzyro	$11,960,000	$15,660,000	230	18.44	23.27

QALY: quality-adjusted life year

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

Table C11. Incremental Cost-Effectiveness Ratios for the Preliminary Phase Base Case

Treatment	Comparator	Cost per Attack Avoided	Cost per QALY Gained*	2018 Report Cost per QALY Gained
Haegarda	No prophylaxis	$387	$462,000	$328,000
Cinryze	No prophylaxis	$6,188	$7,060,000	$5,950,000
Takhzyro	No prophylaxis	$1,042	$1,280,000	$1,110,000

QALY: quality-adjusted life year

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

Note: Due to ratio properties of incremental cost-effectiveness ratios, results can become extreme with small denominators.

Table C12. Preliminary Phase HBPBs for HAE Prophylactic Therapies

	Annual WAC	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Discount from List Price to Reach Threshold Prices	Discounts from List Price to Reach 2018 Report Threshold Prices
Haegarda	$536,694	$515,969	$518,930	3.3% to 3.9%	27.7% to 28.2%
Cinryze	$548,563	$306,377	$308,114	43.8% to 44.1%	59.7% to 60.0%
Takhzyro	$599,403	$531,665	$534,506	10.8% to 11.3%	33.7% to 34.2%

QALY: quality-adjusted life year.

C4. Sensitivity Analysis

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per addition QALY for Haegarda, Cinryze, and Lanadelumab for both the Preliminary Phase updates and Observational RWE Phase Updates. In both phases, key model inputs were the baseline attack rate, drug cost, and reduction in attack frequency.

Preliminary Phase Sensitivity Analyses

We found that baseline attack rate, prophylactic drug acquisition costs, and the treatment effect (% mean reduction in attack frequency) in most cases had the largest impact on the incremental cost-effectiveness ratio. See Tornado Figures C3, C4, and C5 for each prophylactic agent.

Figure C3. Preliminary Update Tornado Diagram for Haegarda

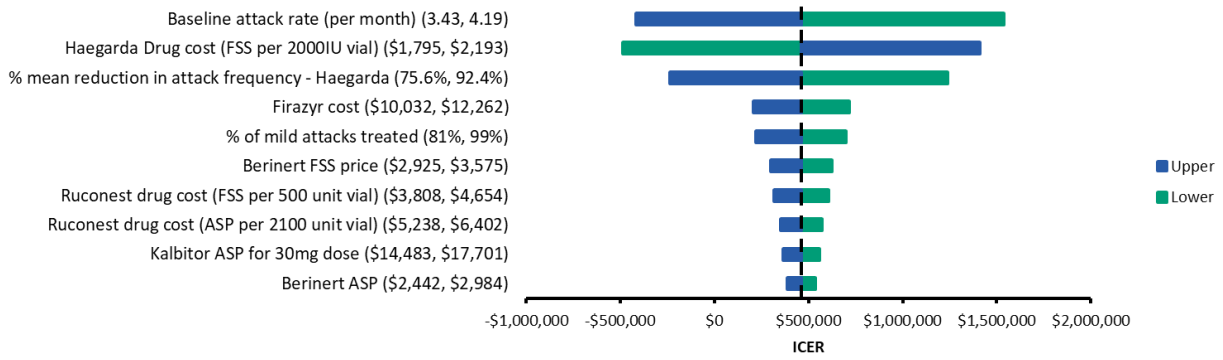


Table C13. Preliminary Update Tornado Diagram Inputs and Results for Haegarda versus no Prophylaxis

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Baseline attack rate (per month)	$1,540,000	-$419,000	3.43	4.19
Haegarda Drug cost (WAC per 2000IU vial)	-$485,000	$1,410,000	$1,795	$2,193
% mean reduction in attack frequency	$1, 2400,000	-$238,000	75.6%	92.4%
Firazyr cost	$716,000	$208,000	$10,032	$12,262
% of mild attacks treated	$701,000	$221,000	81%	99%

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Table limited to top 5 most influential results

Figure C4. Preliminary Update Tornado Diagram for Cinryze

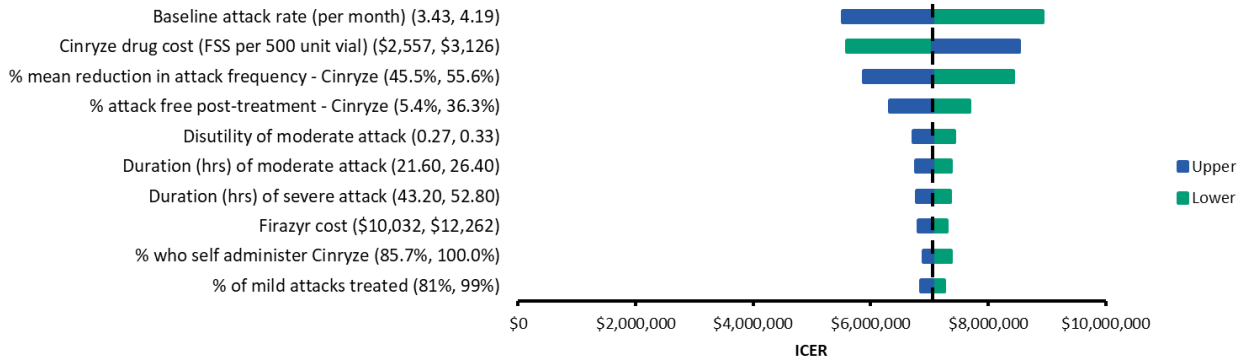


Table C14. Preliminary Update Tornado Diagram Inputs and Results for Cinryze versus no Prophylaxis

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Baseline attack rate (per month)	$8,920,000	$5,5300,000	3.43	4.19
Cinryze drug cost (WAC per 500 unit vial)	$5,600,000	$8,520,000	$2,557	$3,126
% mean reduction in attack frequency	$8,420,000	$5,800,000	45.5%	55.6%
% attack free post-treatment	$7,680,000	$6,324,000	5.4%	36.3%
Disutility of moderate attack	$7,430,000	$6,720,000	0.27	0.33

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Table limited to top five most influential results

Figure C5. Preliminary Update Tornado Diagram for Takhzyro

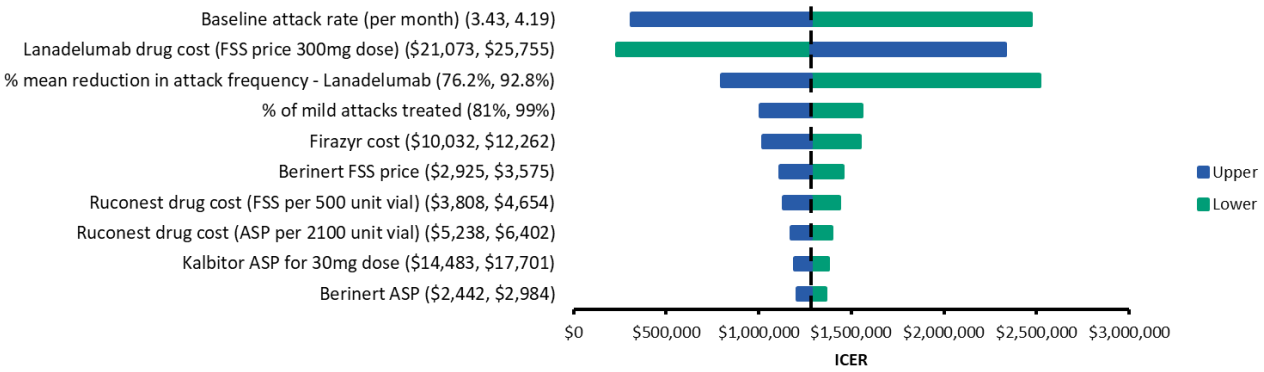


Table C15. Preliminary Update Tornado Diagram Inputs and Results for Takhzyro versus no Prophylaxis

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Baseline attack rate (per month)	$2,470,000	$313,000	3.43	4.19
Cinryze drug cost (WAC per 500 unit vial)	$236,000	$2,330,000	$21,073	$25,755
% mean reduction in attack frequency	$2,520,000	$802,000	76.2%	92.8%
% of mild attacks which are treated	$1,560,000	$1,010,000	81%	99%
Firazyr cost	$1,550,000	$1,020,000	$10,032	$12,262

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Table limited to top 5 most influential results

Table C16. Preliminary Update Results of Probabilistic Sensitivity Analysis for Haegarda versus no Prophylaxis

	Haegarda		No Prophylaxis		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$14,630,000	$13,190,000, $16,470,000	$14,420,000	$13,500,000, $14,920,000	$404,000	-$1,210,000, $2,310,000
Total QALYs	18.39	16.40, 20.09	17.07	15.09, 18.76	1.32	1.21, 1.42
Incremental cost-effectiveness ratio	-	-	-	-	$319,000	-$881,000, $1,830,000

Table C17. Preliminary Update Results of Probabilistic Sensitivity Analysis for Cinryze versus no Prophylaxis

	Cinryze		No Prophylaxis		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$19,920,000	$18,490,000, $21,320,000	$14,420,000	$13,500,000, $14,920,000	$5,700,000	$4,240,000, $7,090,000
Total QALYs	17.90	15.88, 19.60	17.07	15.09, 18.76	0.83	0.72, 0.96
Incremental cost-effectiveness ratio	-	-	-	-	$6,930,000	$4,87,000, $9,130,000

Table C18. Preliminary Update Results of Probabilistic Sensitivity Analysis for Takhzyro versus no Prophylaxis

	Takhzyro		No Prophylaxis		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$15,630,000	$14,040,000, $17,550,000	$14,420,000	$13,500,000, $14,920,000	$1,410,000	-$406,000, $3,350,000
Total QALYs	18.40	16.43, 20.08	17.07	15.09, 18.76	1.33	1.20, 1.44
Incremental cost-effectiveness ratio	-	-	-	-	$1,070,000	-$299,000, $2,640,000

Figure C6. Preliminary Update Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds

This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis.

Observational RWE Phase Sensitivity Analyses

Baseline attack rate, prophylactic drug acquisition costs, and the treatment effect (% mean reduction in attack frequency) remained the most impactful inputs on the incremental cost-effectiveness ratios (See Tornado Figures C7-C9).

Figure C7. Observational RWE Phase Tornado Diagram for Haegarda

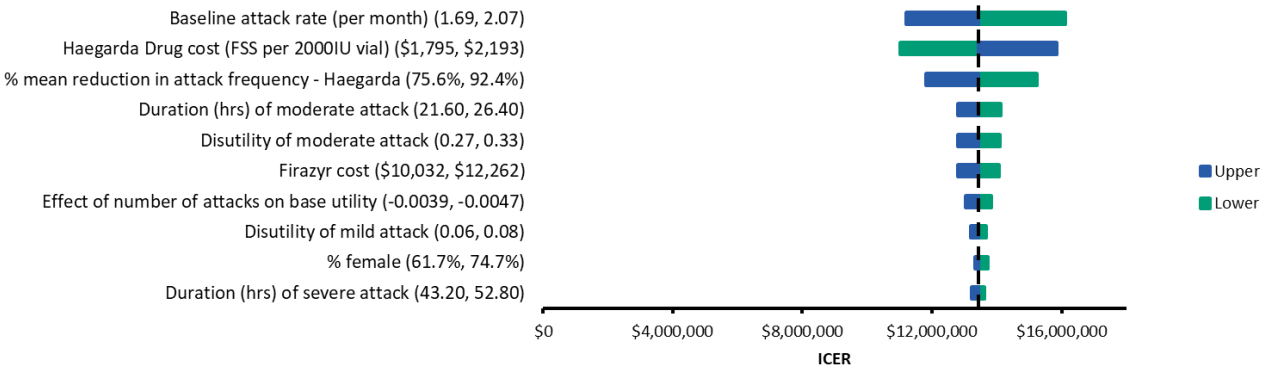


Table C19. Observational RWE Phase Tornado Diagram Inputs and Results for Haegarda versus no Prophylaxis

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Baseline attack rate (per month)	$16,130,000	$11,220,000	1.69	2.07
Haegarda drug cost (WAC per 2000IU vial)	$11,010,000	$15,840,000	$1,795	$2,193
% mean reduction in attack frequency	$15,230,000	$11,820,000	75.6%	92.4%
Duration of a moderate attack (hours)	$14,120,000	$12,800,000	21.6	26.4
Disutility of a moderate attack	$14,110,000	$12,810,000	0.27	0.33

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental cost-effectiveness ratio output.
Table limited to top 5 most influential results

Figure C8. Observational RWE Phase Tornado Diagram for Cinryze

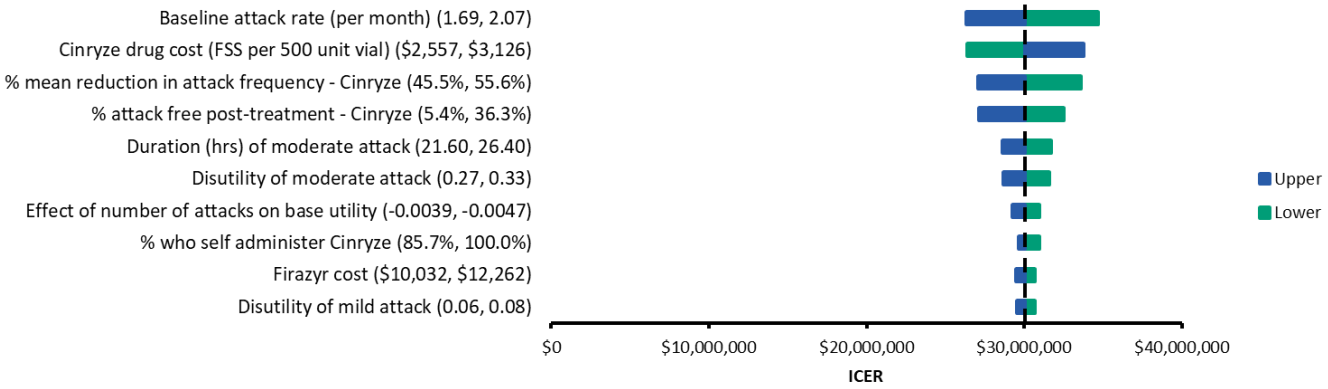


Table C20. Observational RWE Phase Tornado Diagram Inputs and Results for Cinryze versus no Prophylaxis

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Baseline attack rate (per month)	$34,670,000	$26,300,000	1.69	2.07
Cinryze drug cost (WAC per 500 unit vial)	$26,360,000	$33,780,000	$2,557	$3,126
% mean reduction in attack frequency	$33,580,000	$27,070,000	45.5%	55.6%
% attack free post-treatment	$32,520,000	$27,150,000	5.4%	36.3%
Duration of a moderate attack (hours)	$31,710,000	$28,590,000	21.6	26.4

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental cost-effectiveness ratio output.
Table limited to top 5 most influential results

Figure C9. Observational RWE Phase Tornado Diagram for Takhzyro

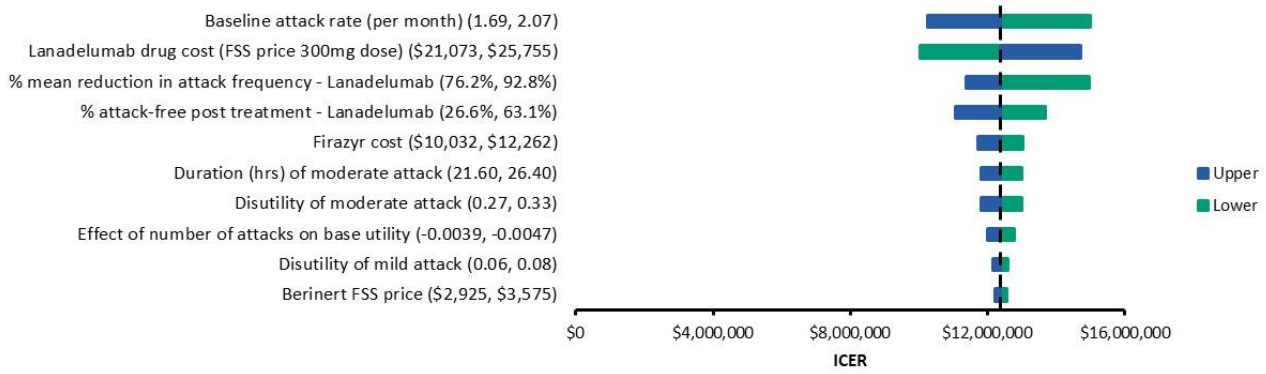


Table C21. Observational RWE Phase Tornado Diagram Inputs and Results for Takhzyro versus no Prophylaxis

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Baseline attack rate (per month)	$14,980,000	$10,240,000	1.69	2.07
Cinryze drug cost (WAC per 500 unit vial)	$10,040,000	$14,710,000	$21,073	$25,755
% mean reduction in attack frequency	$14,950,000	$11,370,000	76.2%	92.8%
% attack-free post treatment	$13,680,000	$11,050,000	26.6%	63.1%
Firazyr cost	$13,020,000	$11,720,000	$10,032	$12,262

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the incremental cost-effectiveness ratio output.
Table limited to top 5 most influential results

None of the prophylactics met a cost-effectiveness threshold up to $200,000 in any of the simulations in probabilistic sensitivity analysis.

Table C22. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: HAE Prophylaxis versus no Prophylaxis, Observational RWE Phase

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Haegarda	0%	0%	0%	0%
Cinryze	0%	0%	0%	0%
Takhzyro	0%	0%	0%	0%

QALY: quality-adjusted life year

Table C23. Observational RWE Phase Results of Probabilistic Sensitivity Analysis for Haegarda versus no Prophylaxis

	Haegarda		No Prophylaxis		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$14,070,000	$13,600,000, $14,660,000	$7,720,000	$7,400,000, $8,040,000	$6,350,000	$5,770,000, $7,010,000
Total QALYs	18.45	16.30, 20.19	17.80	15.67, 19.55	0.65	0.60, 0.70
Incremental cost-effectiveness ratio	-	-	-	-	$9,840,000	$8,470,000, $11,690,000

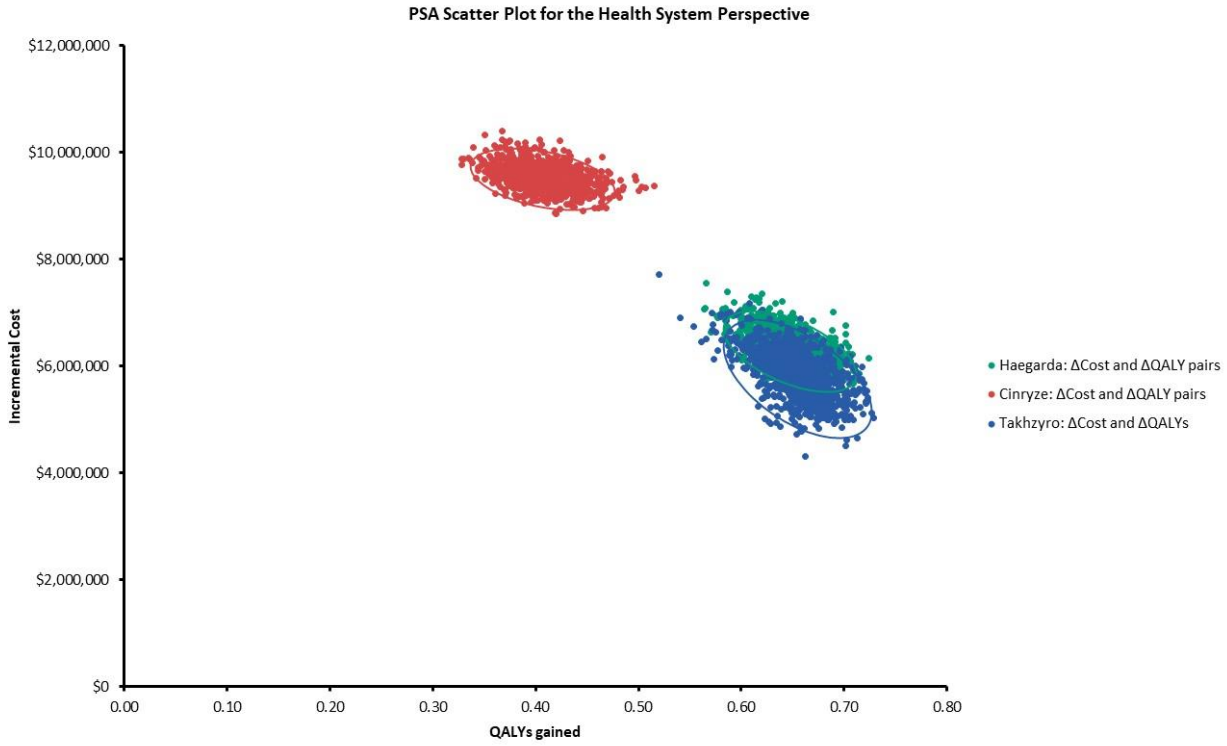
Table C24. Observational RWE Phase Results of Probabilistic Sensitivity Analysis for Cinryze versus no Prophylaxis

	Cinryze		No Prophylaxis		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$17,260,000	$16,860,000, $17,710,000	$7,720,000	$7,400,000, $8,040,000	$9,540,000	$9,100,000, $10,040,000
Total QALYs	18.21	16.07, 19.95	17.80	15.67, 19.55	0.41	0.36, 0.47
Incremental cost-effectiveness ratio	-	-	-	-	$23,570,000	$19,94,000, $27,670,000

Table C25. Observational RWE Phase Results of Probabilistic Sensitivity Analysis for Takhzyro versus no Prophylaxis

	Takhzyro		No Prophylaxis		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$13,560,000	$12,780,000, $14,360,000	$7,720,000	$7,400,000, $8,040,000	$5,840,000	$5,000,000, $6,680,000
Total QALYs	18.46	16.32, 20.21	17.80	15.67, 19.55	0.65	0.59, 0.71
Incremental cost-effectiveness ratio	-	-	-	-	$8,950,000	$7,300,000, $11,000,000

Figure C10. Observational RWE Phase Update Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds



This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis.

In addition to one-way and probabilistic sensitivity analysis, the contribution of key inputs to differences in findings between the preliminary phase update and observational RWE phase is presented in Table C26 for Haegarda, Table C27 for Cinryze, and Table C28 for Takhzyro. In each table, the first row presents the results of the Preliminary Phase Updates for the incremental cost, incremental QALYs, and incremental cost per QALY of prophylaxis compared with no prophylaxis. Each subsequent row builds upon the previous with the addition of another set of RWE data inputs. For each outcome type (incremental cost, incremental QALYs, and incremental cost per QALY), the first column (Result) presents the new result after inclusion of the group of RWE data inputs on that row. The second column (Incremental Impact of RWE Update) presents the absolute difference between the inclusion of that group of RWE Update inputs and the row preceding it. The third column shows the relative impact of the addition, with the percent difference between the new result relative to the preliminary phase results. Results of this sensitivity analysis showed that RWE update of the baseline attack rate resulted in the largest change in model outcomes.

Table C26. Build-up of Incremental Impact of RWE Updates for Haegarda

	Incremental Cost			Incremental QALYs			Incremental Cost per QALY		
Build Step and RWE Input Group	**Result**	**Incremental Impact of RWE Update**	**% Difference from Phase 1**	**Result**	**Incremental Impact of RWE Update**	**% Difference**	**Result**	**Incremental Impact of RWE Update**	**% Difference**
2018 evaluation results	$390,000	N/A	N/A	1.19	N/A	N/A	$328,000	N/A	N/A
Preliminary update results (Reference)	$609,000	N/A	N/A	1.32	N/A	N/A	$462,000	N/A	N/A
1. Baseline attack rate	$6,770,000	$6,160,000	1012%	0.65	-0.67	-51%	$10,390,000	$9,930,000	2149%
2. Population parameters*	$6,950,000	$180,000	1041%	0.65	0.00	-51%	$10,640,000	$250,000	2203%
3. Pretreatment attack severity	$7,380,000	$430,000	1112%	0.54	-0.12	-59%	$13,730,000	$3,090,000	2872%
4. Treatment pathway†	$7,360,000	($20,000)	1109%	0.53	0.00	-60%	$13,790,000	$60,000	2885%
5. Direct cost of ED visits and hospitalization	$7,220,000	($140,000)	1086%	0.53	0.00	-60%	$13,520,000	($270,000)	2826%
6. Cost of administration	$7,220,000	$0	1086%	0.53	0.00	-60%	$13,520,000	$0	2826%
7. Market shares of on demand drugs	$7,170,000	($50,000)	1077%	0.53	0.00	-60%	$13,430,000	($90,000)	2807%
Final RWE Update Results	$7,170,000	$6,560,000	1077%	0.53	-0.79	-60%	$13,430,000	$12,970,000	2807%

ED: emergency department, QALY: quality-adjusted life year, RWE: real-world evidence.

*Baseline age, sex, weight.

†Proportion of mild and moderate attacks treated with home self-administration, home nurse, or outpatient; proportion of severe attacks which result in hospitalization, hospitalization resource utilization mortality.

Table C27. Build-up of Incremental Impact of RWE Updates for Cinryze

	Incremental Cost			Incremental QALYs			Incremental Cost per QALY		
Build Step and RWE Input Group	**Result**	**Incremental Impact of RWE Update**	**% Difference**	**Result**	**Incremental Impact of RWE Update**	**% Difference**	**Result**	**Incremental Impact of RWE Update**	**% Difference**
2018 evaluation results	$4,443,000	N/A	N/A	0.75	N/A	N/A	$5,954,000	N/A	N/A
Preliminary update results (Reference)	$5,850,000	N/A	N/A	0.83	N/A	N/A	$7,060,000	N/A	N/A
1. Baseline attack rate	$9,940,000	$4,090,000	70%	0.41	-0.42	-51%	$24,280,000	$17,220,000	244%
2. Population parameters*	$9,930,000	($10,000)	70%	0.41	0.00	-50%	$24,210,000	($70,000)	243%
3. Pretreatment attack severity	$10,200,000	$270,000	75%	0.34	-0.07	-59%	$30,160,000	$5,950,000	327%
4. Treatment pathway†	$10,190,000	($10,000)	74%	0.34	0.00	-59%	$30,360,000	$200,000	330%
5. Direct cost of ED visits and hospitalization	$10,120,000	($70,000)	73%	0.34	0.00	-59%	$30,140,000	($220,000)	327%
6. Cost of administration	$10,130,000	$10,000	73%	0.34	0.00	-59%	$30,180,000	$40,000	328%
7. Market shares of on demand drugs	$10,100,000	($30,000)	73%	0.34	0.00	-59%	$30,070,000	($110,000)	326%
Final RWE Update Results	$10,100,000	$4,250,000	73%	0.34	-0.49	-59%	$30,070,000	$23,010,000	326%

ED: emergency department, QALY: quality-adjusted life year, RWE: real-world evidence.

*Baseline age, sex, weight.

†Proportion of mild and moderate attacks treated with home self-administration, home nurse, or outpatient; proportion of severe attacks which result in hospitalization, hospitalization resource utilization mortality.

Table C28. Build-up of Incremental Impact of RWE Updates for Takhzyro

	Incremental Cost			Incremental QALYs			Incremental Cost per QALY		
Build Step and RWE Input Group	**Result**	**Incremental Impact of RWE Update**	**% Difference**	**Result**	**Incremental Impact of RWE Update**	**% Difference**	**Result**	**Incremental Impact of RWE Update**	**% Difference**
2018 evaluation results	$1,321,000	N/A	N/A	1.19	N/A	N/A	$1,108,000	N/A	N/A
Preliminary update results (Reference)	$1,710,000	N/A	N/A	1.33	N/A	N/A	$1,280,000	N/A	N/A
1. Baseline attack rate	$8,040,000	$6,330,000	370%	0.66	-0.67	-51%	$12,230,000	$10,950,000	852%
2. Population parameters*	$8,000,000	($40,000)	368%	0.66	0.00	-50%	$12,140,000	($90,000)	845%
3. Pretreatment attack severity	$8,410,000	$410,000	392%	0.55	-0.11	-59%	$15,390,000	$3,250,000	1098%
4. Treatment pathway†	$8,370,000	($40,000)	390%	0.54	0.00	-59%	$15,430,000	$40,000	1101%
5. Direct cost of ED visits and hospitalization	$8,240,000	($130,000)	382%	0.54	0.00	-59%	$15,190,000	($240,000)	1082%
6. Cost of administration	$8,240,000	$0	382%	0.54	0.00	-59%	$15,190,000	$0	1082%
7. Market shares of on demand drugs	$8,170,000	($70,000)	378%	0.54	0.00	-59%	$15,070,000	($120,000)	1073%
8. Proportion that switch to every 4 week dosing	$6,710,000	($1,460,000)	293%	0.54	0.00	-59%	$12,370,000	($2,700,000)	863%
Final RWE Update Results	$6,710,000	$5,000,000	293%	0.54	-0.79	-59%	$12,370,000	$11,090,000	863%

ED: emergency department, QALY: quality-adjusted life year, RWE: real-world evidence.

*Baseline age, sex, weight.

†Proportion of mild and moderate attacks treated with home self-administration, home nurse, or outpatient; proportion of severe attacks which result in hospitalization, hospitalization resource utilization mortality.

‡ lower cost and higher QALYs compared with prophylaxis

C5. Scenario Analyses

No scenario analyses resulted in an incremental cost per QALY ratio which changed the conclusions of the analysis relative to the base case. The detailed methods are presented following the summary of findings across two scenarios. A modified societal perspective considering indirect costs associated with HAE attacks results in lower cost per QALY for all prophylaxis drugs, although all remain well above $200,000 per QALY gained. A scenario assuming 100% use of generic icatibant rather than branded Firazyr for the treatment of acute HAE attacks, keeping the overall market basket of acute treatments constant, results in substantially lower cost of no prophylaxis owing to reduced cost of acute treatment. This also translates into reduced cost-offsets from avoiding acute attacks with prophylactic treatment and higher incremental cost per QALY ratios.

Table C29. Preliminary Phase Scenario Analysis Results

Treatment	Base-Case Results	Modified Societal Perspective	Generic Icatibant
Haegarda	$462,000	$343,000	$2,370,000
Cinryze	$7,060,000	$6,950,000	$8,880,000
Takhzyro	$1,280,000	$1,170,000	$3,260,000

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

Table C30. Observational RWE Phase Scenario Analysis Results

Treatment	Base-Case Results	Modified Societal Perspective	Generic Icatibant
Haegarda	$13,430,000	$13,300,000	$18,180,000
Cinryze	$30,070,000	$29,960,000	$34,610,000
Takhzyro	$12,370,000	$12,250,000	$17,250,000

QALY: quality-adjusted life year.

*Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

Modified Societal Perspective

Indirect costs (including missed work, child care, and travel) for acute attacks (by severity) were obtained from Wilson et al.,[38] $959 for mild, $4,048 for moderate, and $6,656 for severe attacks. These were adjusted by the mean number of attacks per year (22.6) to produce a cost per attack. The cost of lost productivity was inflated to 2021 US dollars in the preliminary update phase.

Table C31. Cost of Lost Productivity

Variable	Original Value	Source	Preliminary Phase Updated Value	Source	Observational RWE Phase Updated Value	Source
Indirect cost of mild attack	$45	Wilson 2010[38]	$48	Wilson 2010[38] inflated to 2021 USD	Same as preliminary updated value	
Indirect cost of moderate attack	$191	Wilson 2010[38]	$203	Wilson 2010[38] inflated to 2021 USD	Same as preliminary updated value	
Indirect cost of severe attack	$311	Wilson 2010[38]	$331	Wilson 2010[38] inflated to 2021 USD	Same as preliminary updated value	

A modified societal perspective considering indirect costs associated with HAE attacks results in lower cost per QALY for all prophylaxis drugs, although all remain well $200,000 per QALY gained.

Table C32. Results for the Preliminary Phase Modified Societal Perspective for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Prophylaxis Drug Cost	Total Cost	Attacks	QALYs	Life Years
No prophylaxis	$0	$14,130,000	1,871	17.11	23.26
Haegarda	$12,490,000	$14,580,000	299	18.43	23.27
Cinryze	$12,890,000	$19,890,000	926	17.97	23.26
Takhzyro	$13,950,000	$15,680,000	230	18.44	23.27

QALY: quality-adjusted life year

Table C33. Incremental Cost-Effectiveness Ratios for the Preliminary Phase Modified Societal Perspective for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Cost per Attack Avoided	Cost per QALY Gained*	Cost per Life Year Gained*
Haegarda	$288	$342,000	$108,030,000
Cinryze	$6,092	$6,950,000	>$1,000,000,000
Takhzyro	$946	$1,170,000	$396,110,000

QALY: quality-adjusted life year

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

Note: Due to ratio properties of incremental cost-effectiveness ratios, results can become extreme with small denominators.

Table C34. Results for the Observational RWE Phase Modified Societal Perspective for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Prophylaxis Drug Cost	Total Cost	Attacks	QALYs	Life Years
No prophylaxis	$0	$6,860,000	926	18.00	23.30
Haegarda	$12,890,000	$13,960,000	148	18.53	23.31
Cinryze	$13,520,000	$16,920,000	458	18.33	23.30
Takhzyro	$12,660,000	$13,500,000	114	18.54	23.31

QALY: quality-adjusted life year

Table C35. Incremental Cost-Effectiveness Ratios for the Observational RWE Phase Modified Societal Perspective for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Cost per Attack Avoided	Cost per QALY Gained*	Cost per Life Year Gained*
Haegarda	$9,127	$13,300,000	>$1,000,000,000
Cinryze	$21,510	$29,960,000	>$1,000,000,000
Takhzyro	$8,180	$12,250,000	>$1,000,000,000

QALY: quality-adjusted life year

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million.

Note: Due to ratio properties of incremental cost-effectiveness ratios, results can become extreme with small denominators.

Generic Icatibant Scenario

A scenario was conducted assuming 100% use of generic icatibant rather than branded Firazyr for the treatment of acute HAE attacks, keeping the overall market basket of acute treatments constant.

Table C36. Cost of Generic Icatibant

Variable	Original Value	Source	Scenario Value	Source
Cost of generic icatibant (30 mg dose; scenario)	Not included	N/A	$2,796	WAC†

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

This scenario resulted in substantially lower cost of no prophylaxis owing to reduced cost of acute treatment. This translates into reduced cost-offsets from avoiding acute attacks with prophylactic treatment and higher incremental cost per QALY ratios.

Table C37. Results for the Preliminary Phase Generic Icatibant Scenario for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Prophylaxis Drug Cost	Total Cost	Attacks	QALYs	Life Years
No prophylaxis	$0	$11,109,116	1,871	17.11	23.26
Haegarda	$12,490,000	$14,089,693	299	18.43	23.27
Cinryze	$12,890,000	$18,390,310	926	17.94	23.26
Takhzyro	$13,950,000	$15,290,281	230	18.44	23.27

QALY: quality-adjusted life year

Table C38. Incremental Cost-Effectiveness Ratios for the Preliminary Phase Generic Icatibant Scenario for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Cost per Attack Avoided	Cost per QALY Gained*	Cost per Life Year Gained*
Haegarda	$1,985	$2,370,000	>$1,000,000,000
Cinryze	$7,788	$8,880,000	>$1,000,000,000
Takhzyro	$2,641	$3,260,000	>$1,000,000,000

QALY: quality-adjusted life year

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million. Note: Due to ratio properties of incremental cost-effectiveness ratios, results can become extreme with small denominators.

Table C39. Results for the Observational RWE Phase Generic Icatibant Scenario for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Prophylaxis Drug Cost	Total Cost	Attacks	QALYs	Life Years
No prophylaxis	$0	$3,760,000	926	18.00	23.30
Haegarda	$12,890,000	$13,460,000	148	18.33	23.30
Cinryze	$13,520,000	$15,380,000	458	18.33	23.30
Takhzyro	$12,660,000	$13,120,000	114	18.54	23.31

QALY: quality-adjusted life year

Table C40. Incremental Cost-Effectiveness Ratios for the Observational RWE Phase Generic Icatibant Scenario for HAE Prophylaxis Compared to no Prophylaxis

Treatment	Cost per Attack Avoided	Cost per QALY Gained*	Cost per Life Year Gained*
Haegarda	$12,472	$18,180,000	>$1,000,000,000
Cinryze	$24,851	$34,610,000	>$1,000,000,000
Takhzyro	$11,521	$17,250,000	>$1,000,000,000

QALY: quality-adjusted life year

* Results rounded to the nearest $1,000; Results rounded to the nearest $10,000 when over $1 million. Note: Due to ratio properties of incremental cost-effectiveness ratios, results can become extreme with small denominators.

C6. Threshold Analyses

Preliminary Phase Threshold Analyses

As the most influential model parameter, relatively small changes (but treatment-specific ranges) in the baseline monthly attack rate resulted in incremental cost per QALY results at or below thresholds of $50,000 to $200,000 per QALY (Table C41).

Table C41. Preliminary Phase Threshold Analysis on Baseline Attack Rate

	Attack Rate to Achieve $50,000 per QALY	Attack Rate to Achieve $100,000 per QALY	Attack Rate to Achieve $150,000 per QALY	Attack Rate to Achieve $200,000 per QALY
Haegarda	3.98	3.96	3.94	3.92
Cinryze	6.53	6.50	6.46	6.43
Takhzyro	4.31	4.29	4.26	4.24

QALY: quality-adjusted life year

Table C42. Preliminary Phase QALY-Based Threshold Analysis Results

	WAC per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY	Discount from List Price to Reach Threshold Prices
Haegarda	$1,994	$1,907	$1,917	$1,928	$1,938	2.8% to 4.4%
Cinryze	$2,842	$1,577	$1,587	$1,596	$1,605	43.5% to 44.5%
Takhzyro	$23,414	$20,656	$20,768	$20,879	$20,991	10.3% to 11.8%

QALY: quality-adjusted life year

Observational RWE Phase Threshold Analyses

Larger changes in the baseline monthly attack rate were needed to yield results at or below thresholds of $50,000 to $200,000 per QALY (Table C43) in the RWE Observational Phase updates than in the preliminary updates.

Table C43. Observational RWE Phase Threshold Analysis on Baseline Attack Rate

	Attack Rate to Achieve $50,000 per QALY	Attack Rate to Achieve $100,000 per QALY	Attack Rate to Achieve $150,000 per QALY	Attack Rate to Achieve $200,000 per QALY
Haegarda	4.17	4.15	4.13	4.11
Cinryze	6.75	6.72	6.70	6.67
Takhzyro	3.95	3.94	3.92	3.90

QALY: quality-adjusted life year

Table C44. Observational RWE Phase Cost-Effectiveness Health Benefit Price Benchmarks for Haegarda, Cinryze, and Takhzyro

	WAC per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY	Discount from List Price to Reach Threshold Prices
Haegarda	$1,994	$889	$892	$897	$901	55.4% to 54.8%
Cinryze	$2,842	$689	$691	$696	$699	75.8% to 75.4%
Takhzyro	$23,414	$11,051	$11,101	$11,151	$11,201	52.8% to 52.2%

QALY: quality-adjusted life year

C7. Model Validation

The model structure and assumptions were previously validated as part of the initial cost-effectiveness evaluation. Observational RWE estimates of baseline HAE attack rates and severity were similar to the expected distribution of attack severity based on published patient surveys and were deemed clinically valid upon review by an expert clinician who has experience treating patients with HAE. Findings of the preliminary phase update were largely consistent with the original 2018 model. Findings of the RWE update were consistent with the expected direction of resulting incremental cost-effectiveness ratios with the RWE inputs of lower baseline attack rate and a larger proportion of HAE attacks treated at home with on-demand treatment versus office, ED, or hospital-administered treatment. Prior cost-effectiveness evaluations have been published for acute treatment of HAE attacks; however, no other published cost-effectiveness models were identified that would allow for comparison of external validity against other models of HAE prophylaxis.

Prior Economic Models

Prior cost-effectiveness evaluations have been published for acute treatment of HAE attacks; however, no other published cost-effectiveness models were identified of HAE prophylaxis.