Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value

Modeling Analysis Plan

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Institute for Clinical and Economic Review

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1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of valoctocogene roxaparvovec and emicizumab as prophylactic therapy for patients with hemophilia A without inhibitors to Factor VIII. Refer to the Research Protocol for details on the systematic review of the clinical evidence on this topic.

Our approach is based on accomplishing two primary aims, using Markov models. The first will be to estimate the cost effectiveness of valoctocogene roxaparvovec compared to emicizumab and to prophylaxis with Factor VIII preparations in adult patients with severe hemophilia A without inhibitors to Factor VIII. The analysis for this first primary aim will follow the ICER ultra-rare disease framework and include a health care sector perspective (i.e., focus on direct medical care costs only) and a societal perspective as a joint base case, each using a lifetime time horizon. As valoctocogene roxaparvovec is a one-time gene therapy for hemophilia A, this analysis will also be conducted using ICER's High-Impact Single and Short-Term Therapies (SST) framework. The second primary aim will be to assess the cost effectiveness of emicizumab relative to prophylaxis with Factor VIII preparations for new patients with hemophilia A without inhibitors to Factor VIII who are eligible for prophylactic treatment. The base case for the second analysis, following ICER's standard framework, will use a health care sector perspective and a lifetime time horizon, with productivity and other indirect costs considered in a scenario analysis, as data allow. The models will be developed in Excel 2016.

2. Methods: Long-Term Cost Effectiveness

We will develop a *de novo* decision analytic model for patients with hemophilia A without inhibitors to Factor VIII (hereafter referred to as without inhibitors), informed by key clinical trials and prior relevant economic models. The model will be used in the evaluation of valoctocogene roxaparvovec in adult patients with severe hemophilia A without inhibitors, where there will be a dual base-case analysis following ICER's ultra-rare disease framework, and in the evaluation of emicizumab in patients with hemophilia A without inhibitors eligible for Factor VIII prophylaxis, where the base case will take a health care sector perspective. In each case, costs and outcomes will be discounted at 3% per year.

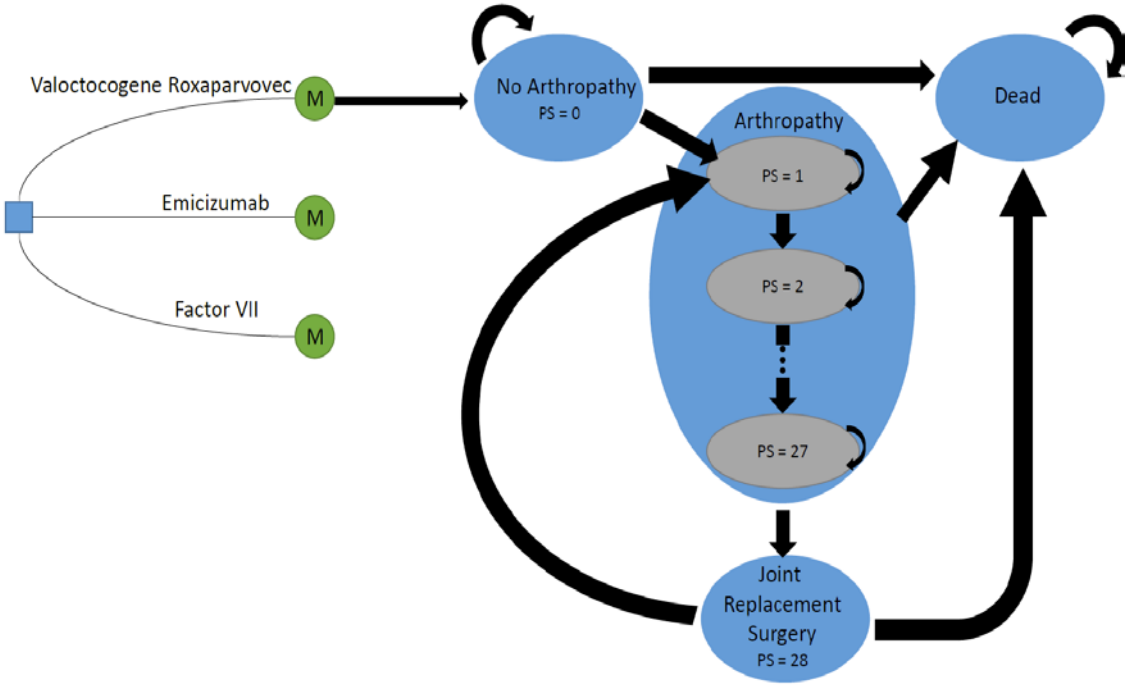
The first version of the model will focus on an intention-to-treat analysis, with a hypothetical cohort of adult patients with severe hemophilia A without inhibitors being treated with valoctocogene roxaparvovec, emicizumab, or Factor VIII prophylaxis. The second version of the model will focus on an intention-to-treat analysis, with a hypothetical cohort of patients with hemophilia A without inhibitors eligible for prophylaxis for Factor VIII being treated with emicizumab or Factor VIII. The cycle length in the models will be 6 months, based on the literature related to bleed rates and

subsequent long-term development of joint damage from target joint bleeds as tracked by Pettersson scores. The models will also use a lifetime time horizon for the base case.

2.1 Overview and Model Structure

Given the importance of acute bleeds, as well as the long-term joint damage caused by target joint bleeds that lead to arthropathy and the potential need for joint replacement surgery, the model will be structured using tunnel states corresponding to Pettersson scores (PS) that range from 0-28. Upon reaching a PS of 28, the model will assume patients have joint replacement surgery and return to a PS of 1. Transitions through the PS states in the models are based on the expected frequency of joint bleeds associated with the treatments and subsequent expected increases in the PS.[1] Patients will also have age-varying mortality rates that are not related to PS. Patients with a PS of 0 will be viewed as having "no joints with arthropathy," patients with a PS of 1-27 will be viewed as having "at least one joint with arthropathy," and patients with a PS of 28 will be viewed as "requiring surgery." Hence, while incorporating the tunnel states based on progression through PS, the model may be viewed as having four general health states: no arthropathy, arthropathy, joint replacement surgery, and death. In each cycle, the expected number of bleeds across treatments will be modeled along with related costs and impacts on patient utilities (Figure 2.1). Patients remain in the model until they die. All patients can transition to death from all causes from any of the alive health states.

Figure 2.1. Model Schematic



M: Markov node, PS: Pettersson score

Costs and utilities will be assigned in each cycle based on bleeds as well as on the level of arthropathy in the particular health states.

2.2 Key Model Choices and Assumptions

Below is a list of key model choices:

- Bleed rates determine transition rates across PS, costs, and utilities in the model.
- Relative bleed rates for emicizumab compared to Factor VIII are derived from an ICER network meta-analysis (NMA) of available trials, and are applied to bleeding rates seen in the HAVEN 3 trial to get the absolute rates used in the models.
- Bleed rates for valoctocogene roxaparvovec are derived from available data on factor levels seen in patients on that treatment and literature-based estimates of bleed rates across factor levels.
- Proportions of all bleeds relative to treated bleeds in the HAVEN 3 trial along with proportions of bleeds that are joint bleeds in the POTTER trial are used to estimate total joint bleeds from data on treated bleeds.
- The model structure is based around PS. This allows for longer-term cycles while still accounting for bleeds each year as well as the development of arthropathy and the possibility of requiring surgery.
- The model uses 6-month cycles. This was the longest standard cycle that allowed for reasonable transition rates between PS counts each cycle, given the expected bleeding rates possible in the model.
- Survival is weighted by health state utilities derived from the published literature.[2-6] The model includes separate utilities for different types of bleed events, and decreasing baseline utility tied to increasing arthropathy as defined by the PS.
- The model includes all direct treatment costs associated with each individual regimen, including drug acquisition costs and non-pharmacy costs (including all medical expenses except for drugs/clotting factor).
- All costs prior to 2019 were adjusted for inflation following methods outlined in the ICER reference case so that all cost inputs and outputs in the model reflect 2019 US dollars.[7,8]

Our model includes several key assumptions, stated below.

Table 2.1. Key Model Assumptions

Assumption	Rationale
Total bleeds relative to treated bleeds are modeled based on the emicizumab arm of the HAVEN 3 trial.[9] Joint bleeds were assumed to be the same percentage of all bleeds (for each comparator) in base case analyses as seen in the POTTER trial (76.26%)[10]	Treated bleeds are most commonly measured, but total joint bleeds have been shown to impact the PS.[10,11] The POTTER trial offered the only published account of all bleeds and all joint bleeds associated with hemophilia A. There is no clinical reason to believe that the proportion of bleeds that are joint bleeds, or what proportion of all bleeds would be treated, would vary by treatment.
Annual bleed rates are equivalent regardless of the degree of arthropathy.	Data on the relative occurrence of bleed events pre- and post-arthropathy are limited. Increasing bleed rates due to arthropathy are explored in a scenario analysis.
Pettersson scores (representing joint arthropathy development) increase as a function of joint bleeds (treated and/or untreated) over time at different rates for patients over and under the age of 25.	Pettersson scores have most recently been reported to increase by one point for every 36.52 joint bleeds (treated and/or untreated) in patients under 25 and by one for every 6.52 joint bleeds for patients over 25.[11]
All patients were assumed to be male, and patient weight and background mortality was based on US male population averages.	Hemophilia is an X-linked recessive disease primarily affecting males. Females with hemophilia A typically have less severe disease. We assume that hemophilia will not substantially impact weight or mortality.
The utilities associated with a bleed are applied for two days. After two days we assume the bleed state utility is an average of the no bleed and bleed values for the remainder of a week to reflect that the impact of the bleed on utility lingers after the bleeding stops.	The duration of a bleed is estimated to be two days. However, the impact of a bleed likely lingers beyond bleed duration and treatment time. The number of days per week for bleed utilities is varied in a scenario analysis.
Cost per treated bleed event is the same for all comparators.	We have not seen evidence to support different on-demand treatment costs for patients on different forms of prophylaxis.

2.3 Populations

The population of focus for the economic evaluation of valoctocogene roxaparvovec are adult males (age 18 and over) with severe hemophilia A without inhibitors who require prophylaxis. The population of focus for the economic evaluation of emicizumab are male patients with hemophilia A without inhibitors who require prophylaxis (assumed to start at age 1).

In the base case analysis for valoctocogene roxaparvovec, model 1, patients will enter the model at the age of 18 and will start in the average PS for that age, based on average Petterson scores of 18 year olds reported in the literature.[1] In the base-case analysis for emicizumab, model 2, patients will enter the model at age 1 year with a PS of 0.

2.4 Interventions

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

- valoctocogene roxaparvovec (Roctavian™, BioMarin Pharmaceutical)
- emicizumab-kxwh (Hemlibra®, Genentech)

Comparators

In the first analysis, the interventions will be compared with each other. In addition, each analysis will include the comparator of Factor VIII prophylaxis itself modeled using a mix of half life and extended half life regimens each with a representative drug for costing.

2.5 Input Parameters

Clinical Inputs

Bleed Rates

Relative rates of treated bleeds and treated joint bleeds from an ICER NMA involving emicizumab and Factor VIII treatments combined with the absolute rates of treated bleeds and treated joint bleeds in the HAVEN 3 trial for emicizumab will be used to determine rates of treated bleeds and treated joint bleeds. In addition, the ratio of all bleeds to treated bleeds seen in the HAVEN 3 trial, and the ratio of all bleeds that were joint bleeds in the POTTER trial, were used to estimate total joint bleeds from treated bleeds for emicizumab and Factor VIII.[9,10]

Treated bleed rates for valoctocogene roxaparvovec were modeled based on available evidence of factor levels in patients on the drug and a recent analysis of bleed rates across factor levels by Tiede et al.[12] To estimate treated bleed rates, average Factor VIII levels for the high dose patients reported by BioMarin were combined with estimated rates of treated bleeds by factor level and patient age in Tiede et al. [12,13] Declines across time in average patient factor levels were projected forward, based on the most recent available data. The projections used the percent decline in year 4 relative to year 3 to project year 5, and then the projected year 5 compared to year 4 was used to project year 6 and this was repeated. Bleed rates seen in Tiede et al. by ranges of Factor VIII levels was used to get projected bleed rates for each year.[12] Once the projected Factor VIII levels were projected to be below 1%, the maximum values in the Tiede study were carried forward.

Scenario analyses were also run using best (no decline after year 4) and worse (linear decline equal to the absolute decline from year 3 to 4 carried forward) case estimates of projected trends in factor level decline.

From the estimates of the number of treated bleeds for valoctogene roxaparvovec it was assumed that the proportion of treated bleeds that are treated joint bleeds and the proportion of total joint bleeds relative to treated bleeds would be the same for valoctogene roxaparvovec as seen for emicizumab in the HAVEN 3 trial.

Transition Probabilities

Transition probabilities between the PS-based health states were based on expected annual joint bleed rates and a literature-based assumption that on average 36.52 joint bleeds result in an increase of the PS by one for patients under 25 and 6.52 joint bleeds result in a one-point PS increase in patients aged 25 years or more.[11] Hence, the annual number of joint bleeds divided by 36.52 and subsequently by 6.52 as patients reach 25 years old can be thought of as an annual transition rate to the next highest PS. Consequently, half the annual bleed rate divided by 36.52 and then 6.52 corresponds to the transition rate using 6-month time cycles. Bleeding rates in the HAVEN 3 trial were only reported for those at or above the age of 12. For the child model, bleed rates from HAVEN 3 are proportionally lowered based on the observed bleed rates for those aged 12 and older versus those under age 12 in the HAVEN 1 trial. When the child reaches 12 years old, bleed rates from the HAVEN 3 trial are used. Following surgery, all patients (minus those expected to die of all causes) are assumed to return to the arthropathy health state with a PS of 1.

The transition rates corresponding to the bleed rates of the drugs are shown in Table 2.2 and are based on numbers described above related to bleed rates and PS by age in the POTTER trial. The rates will change across time for valoctocogene roxaparvovec based on the projections of factor levels described above; projections for the first two years are shown below.

Table 2.2. Transition Probabilities Across Petterson Scores Based on Bleed Rates

Drug	Age < 12	12 ≤ Age < 25	Age ≥ 25
Factor VIII	0.011	0.023	0.122
Emicizimuab	0.006	0.017	0.092
Valoctocogene Roxaparvovec Year 1	0.001	0.004	0.011
Valoctocogene Roxaparvovec Year 2	0.002	0.016	0.043

Discontinuation

The models do not include discontinuation due to lack of available data on discontinuation rates, and it is presumed that patients discontinuing one treatment would most likely switch to one of the other treatments.

Mortality

Age-specific all-cause mortality will be sourced from the CDC life tables for males which are representative of the male population in the US.[14] Hemophilia A is not associated with increased mortality in patients without inhibitors on prophylactic treatment.

Serious Adverse Events

Serious adverse event data reported in the HAVEN trials for emicizumab, particularly in HAVEN 3, were not clearly associated with the drug. Serious adverse events (SAEs) in data available for Factor VIII inhibitors were few and mainly bleed-related. For valoctocogene roxaparvovec, only minor liver inflammation has been reported, which was not deemed to rise to the level of an SAE. Consequently, the models here do not include SAEs.

Heterogeneity and Subgroups

There are insufficient data to derive potential subgroups that may have differential response to therapy.

Health State Utilities

Health state utilities were derived from published literature sources and will be applied to the relevant health states. Baseline utility was taken from results of EQ-5D utilities based on responses from hemophilia patients broken out by age and degree of arthropathy, found in Ohara et al. (Table 2.3)[15] All of the disutilities associated with bleeds and with surgery used in the model were measured in patients with hemophilia A using the EQ-5D.[2,5,15] We used the same health state utility values across treatments evaluated in the model. Utility in the surgery state was modelled using one month of having a time-tradeoff utility found in a general hip replacement pre-surgery patient group reported in the literature in 1993 (0.32), and 5 months with utility corresponding to a PS of 1-27 and the age of the patient getting surgery in the model.[5,16]

Table 2.3. Health State Utilities

Age	Pettersson 0	Pettersson 1-27	Surgery	Source
0-30	0.94	0.82	0.72	O'Hara 2018; Ballal 2011
31-40	0.84	0.74	0.65	O'Hara 2018; Ballal 2011
41-50	0.86	0.69	0.61	O'Hara 2018; Ballal 2011
51-60	0.83	0.63	0.56	O'Hara 2018; Ballal 2011
61-100	0.73	0.54	0.48	O'Hara 2018; Ballal 2011

The utility of surgery is based on one month of a utility of 0.32, and 5 months at a utility corresponding to a Pettersson score of 1-27.

Disutilities by bleed type were estimated based on differences in utilities reported during bleeds versus when having no bleeds, measured in patients with hemophilia A with inhibitors.[2,3] As stated

above, bleed-associated disutilities for treated target joint bleeds and treated non-target joint bleeds were applied in full for two days, followed by an average of "No Bleed" and "Bleed" utilities for five days (Table 2.4).[2] In reality, bleed duration will vary depending on severity of the bleed, time to treatment, and other variables including location, so we have varied this assumption in a scenario analysis.

Table 2.4. Bleed Related Disutilities

Bleed Disutilties	Value/Bleed/Cycle	Source
Bleed Not Into A Target Joint	-0.004	Neufeld 2012
Target Joint Bleed	-0.007	Mazza 2016

These are based on a -0.16 and -0.28 disutilty per day for treated bleed and treated joint bleed, respectively.

Drug Utilization

Drug utilization for Factor VIII will be based on a market basket approach using rates of different types of Factor VIII treatments seen in the HAVEN 3 trial, representative treatments of each type, and typical doses for those products. Specifically, Advate® is used to represent standard half-life treatment, used by 86% of the patients, and Eloctate® is used to represent extended half-life treatment, used by 12% of patients.[9] While 2% of patients used a mix of those two treatment types, we simplify this and assume 87% of patients use standard half life and 13% use extended half life in the model. To estimate utilization during bleeds, given input from clinical experts that most patients treat bleeds with the same drug they are using for prophylaxis, the same market basket will be used but with doses for each drug relevant to treating bleeds

Utilization of emicizumab will be assumed to be the same as seen in HAVEN 3.[9] Utilization for valoctocogene roxaparvovec will be the highest dose seen in the available trials, as that dose was associated with the largest treatment effects across time.

Use of Factor VIII prophylaxis will be modeled based on the median doses of Advate and Eloctate seen in HAVEN 3, which are also consistent with their corresponding drug labels.[9,17,18] Dosing of these drugs varies by weight. Patient weight by age will be modeled based on average weight by age for males in the US. Factor VIII prophylaxis with Advate assumes a dose of 60 IU/kg every week and 78 IU/kg every week for eloctate. For emicizumab, 3 mg/kg every week for the first month and then 1.5 mg/kg every week after the first month was used.[9] A lifetime treatment duration is assumed in the model.

For treated bleeds and treated joint bleeds, Factor VIII use was assumed to be 50.4 IU/Kg per bleed.

Table 2.5. Treatment Regimen Recommended Dosage

Generic name	Drug A	Drug B	Drug C	Drug C
Brand name	Hemlibra®	Roctavian™	Advate®	Eloctate®
Generic name	Emicizumab	Valoctocogene roxaparvovec	Antihemophilic Factor (recombinant)	Antihemophilic Factor (recombinant), Fc fusion protein
Manufacturer	Genentech	BioMarin	Baxter	Biogen
Route of administration	subcutaneous	IV	IV	IV
Dosing	3mg/kg every week for the first month and then 3 mg/kg every 2 weeks after	$6x10^{13}$ vg/kg	60 IU/kg every week	78 IU/kg every week

All costs used in the model will be updated to 2019 dollars.

Drug Costs

As valocotocogene roxaparvovec has not yet been approved, no WAC or net price estimates were available at the time of this analysis. We therefore conducted the base-case analysis using a placeholder price of $2,500,000, based on statements from the manufacturer indicating consideration of prices of around $2 million to $3 million per therapy[19]. In the absence of data on usual discounts for gene therapy, we assumed no discounting and used this placeholder for the net price of this treatment. For the other drugs in this analysis, we derived net prices from average sales prices (ASP) to calculate treatment-related health care costs, as we did not have other data on net prices that included discounts/rebates for these agents[20]. Based on the regimen dosage specified in Table 2.6 and available formulations for each drug, the model will utilize the lowest-cost combination of vials for each regimen.

Table 2.6. Drug Costs

Drug	WAC per Dose	Discount from WAC*	Net Price per Dose**	Net Price per Year***
Valoctocogene roxaparvovec (Roctavian™)	$2,500,000	--	$2,500,000	$2,500,000
Emicizumab** (Hemlibra®)**	$100.19/mg	4.7%	$95.45/mg	$530,590
Antihemophilic Factor (recombinant) (Advate®)	$1.69/IU	18.6%	$1.37/IU	$305,783
Antihemophilic Factor (recombinant), Fc fusion protein (Eloctate®)	$2.23/IU	3.2%	$2.16/IU	$623,771

*Calculated from WAC and ASP
**Net price from July 2020 ASP Pricing File, available at: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files, accessed June 30, 2020.
***Assume weight is 71kg for the average 18-year-old male
****Maintanenace dose

Treatment Cost Per Bleed

Based on the market basket seen in trials (87% standard half life, and 13% extended half life) at a dose of 54 IU/kg per bleed and using the costs described above in table 2.6 the treatment related costs of a bleed are $5,286.90 for a 71 kg male.

Non-Drug Costs

Health State Costs

Non-pharmacological costs from Shrestha et al. were used to inform the direct non-pharmacy related medical costs associated with treated bleeds and treated joint bleeds. The model purposely uses per-bleed costs here to focus on cost reductions associated with reductions in bleeds reductions. Some fixed costs, for example those associated with diagnosis of hemophilia A, are ignored in the model knowing that they would likely be the same across treatments and would not affect incremental cost ratios. Estimates of these costs were available for three age groups: < 18, 18 to 45, and > 45 years old. Shrestha et al. examined mostly patients not on prophylactic treatment, and the costs per bleed generally were not statistically significantly different for those on prophylaxis. However, the study found statistically significantly lower costs for patients under the age of 18 on prophylaxis and the estimated reduction was included for those patients in the model.[21]

Table 2.7 Non-Drug Costs per Bleed by Age

Age (years)	Cost	Source
≤ 18	$765.48	Shrestha 2017
18-45	$4,604,32	Shrestha 2017
> 45	$6,858.24	Shrestha 2017

Added Cost of Arthropathy

In addition to the per-bleed costs, published findings of increased utilization associated with arthropathy were incorporated into the model. Specifically, reported differences in annual use of outpatient physician visits, outpatient nurse visits, as well as joint-related tests including X-ray and magnetic resonance imaging were used along with CMS physician fee schedule costs for 2018, inflated to 2019.[21,22]

Table 2.8. Utilization Related Cost Differences of Arthropathy versus No Arthropathy

	Annual Cost	Source
No Arthropathy	$354.20 per cycle based on office visits and joint related tests	O'Hara 2018 and CMS Fees
Arthropathy	$618.28 per cycle based on office visits and joint related tests	O'Hara 2018 and CMS Fees
Surgery	Arthropathy plus $44,717.17*	Earnshaw 2015

*The cost of surgery was derived from Earnshaw et al., which reported a surgery cost of $44,717.17 when inflated to 2019 dollars.[24]

Societal Costs

Costs associated with lost time from work for patients and caregivers were estimated based on a burden of illness analysis by Zhou et al.[25] The costs were inflated from 2011 to 2019 by using the total compensation per hour for civilian workers from the Bureau of Labor Statistics. The calculated cost per treated bleed was $1,162.28.

2.6 Model Outcomes

Model outcomes will include the total number of bleeds avoided, total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYG), and total costs for each intervention over a lifetime time horizon. The model outcomes will also include total number of additional bleeds prevented as well. Costs, LYs, QALYs, and evLYG will also be reported by the health state to understand the contribution of different costs elements. Total costs, LY's, QALYs, and evLYG will be reported as discounted values, using a discount rate of 3% per annum. (Undiscounted results will be presented in an Appendix.)

2.7 Model Analysis

Cost effectiveness will be estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing valoctocogene roxaparvovec to emicizumab and to prophylaxis with Factor VIII preparations, as well as comparing emicizumab to prophylaxis with Factor VIII preparations. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Productivity impacts and other indirect costs (as data permit) will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. Additionally, we will present a cost per additional bleeds prevented.

Sensitivity Analyses

For each of the two primary analyses described above, we will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 10,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and per evLYG).

Scenario Analyses

Currently planned scenario analyses include:

- Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.
- Doubling the bleed rates for patients with arthropathy across all treatments.
- Including societal costs for emicizumab versus Factor VIII prophylaxis (model 2)

As valoctocogene roxaparvovec falls under ICER's SST framework, we will consider conducting further scenario analyses that include:

1. 50/50 shared savings in which 50% of lifetime health care cost offsets from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment

2. Cost offset cap in which health care cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment

3. A) Optimistic and B) conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the base case

4. Threshold analysis for duration of effect in patients receiving short-term benefit that would be needed to achieve cost-effectiveness thresholds

5. Outcome-based payment arrangements for the intervention under review if relevant information is available

Model Validation

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

3. Methods: Potential Budget Impact

3.1 Overview

ICER will use results from the cost-effectiveness model to estimate the potential total budgetary impact of valoctocogene roxaparvovec treatment for adults with hemophilia A without inhibitors to Factor VIII who would be appropriate for routine prophylaxis with Factor VIII. We will use the estimated placeholder price and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for valoctocogene roxaparvovec in our estimates of budget impact. Emicizumab will not be included in this potential budget impact analysis due to its established presence on the market.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

3.2 Methods

We will use results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs will be undiscounted and estimated over a five-year time horizon.

This potential budget impact analysis will include the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used the total number of hemophilia A patients receiving care at hemophilia treatment centers that are part of the US Hemophilia Treatment Center Network (USHTCN), which was reported as 19,192 in 2019.[26] Based on data published in a report on 2018 survey results by the World Federation of Hemophilia (WFH), an estimated 55% of all US hemophilia A patients are over 18 years of age, or approximately 10,550 adults with hemophilia A.[27] Valoctocogene roxaparvovec is intended for the treatment of adults with severe hemophilia A, and according to the WHF report, approximately 45% of patients with hemophilia A in high-income countries have severe disease. We excluded the approximately 6.6% of hemophilia A patients reported by the WHF to have inhibitors. Finally, we excluded patients who were positive for AAV5 antibodies, which we assumed would be 21% of patients based on a study of seroprevalence in an adult hemophilia A cohort in the United Kingdom.[28] Applying these proportions to the estimated US hemophilia A population results in an estimate of approximately 3,530 eligible patients aged 18

years and older. Among these eligible patients, we will assume a 20% uptake each year over five years, or 706 patients per year.

We will evaluate whether the new treatment would take market share from one or more existing treatments and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we will assume that valoctocogene roxaparvovec will likely draw patients both from those currently treated with emicizumab and those currently treated with Factor VIII prophylaxis. The analysis will use clinical expert opinion to estimate the percentage of patients converted from each existing treatment to valoctocogene roxaparvovec treatment within the eligible population.

3.3 Analyses

The analysis will indicate when the potential budget impact threshold is reached at each combination of price and percent uptake among eligible patients at five years. The goal is to estimate the net cost per patient treated with new interventions so that decision-makers can use their own assumptions about uptake and pricing to determine estimates of potential budget impact. Results of the analysis will be presented as cumulative per-patient potential budget impact for each year over the five-year time horizon, with results being presented graphically for each intervention, and numerical data presented in tabular format in an appendix. The graph will show the average potential budget impact for a single patient over various time horizons from one to five years, and the estimated average net cost of treating a patient with the intervention relative to comparator(s) over the five years of the potential budget impact analysis.

If the potential budget impact threshold is reached, a figure will be presented showing the approximate proportion of eligible patients that could be treated in a given year without crossing the threshold at each price, indicating when the potential budget impact threshold is reached at each combination of price and percent uptake among eligible patients at 5 years. If the potential budget impact threshold is not reached, a table for each treatment and population of interest will present the annual potential budgetary impact of treating the entire eligible populations across all prices (placeholder price and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY), and the percent of the potential budget impact threshold that this represents.

Access and Affordability

In the final evidence report, ICER will include an “affordability and access alert” if discussion among clinical experts at the public meeting of ICER’s independent appraisal committees suggests that full, “clinically optimal” utilization at estimated net pricing (or at the $150,000 per QALY threshold price if estimated net price is not available) would exceed the ICER annual potential budget impact threshold without active intervention by insurers and others to manage access to the treatment.

References

1. Fischer K, van Hout BA, van der Bom JG, Grobbee DE, van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. *Acta radiologica (Stockholm, Sweden : 1987).* 2002;43(5):528-532.
2. Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value in Health.* 2012;15(6):916-925.
3. Mazza G, O'Hara J, Carroll L, Camp C, Hoxer CS, Wilkinson L. The Impact of Haemophilia Complications on Health-Related Quality of Life for Adults with Severe Haemophilia. *Value in Health.* 2016;19(7):A593.
4. Fischer K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. *Haemophilia.* 2016;22(6):833-840.
5. Ballal RD, Botteman MF, Foley I, Stephens JM, Wilke CT, Joshi AV. Economic evaluation of major knee surgery with recombinant activated factor VII in hemophilia patients with high titer inhibitors and advanced knee arthropathy: exploratory results via literature-based modeling. *Current medical research and opinion.* 2008;24(3):753-768.
6. Naraine V, Risebrough N, Oh P, et al. Health-related quality-of-life treatments for severe haemophilia: utility measurements using the Standard Gamble technique. *Haemophilia.* 2002;8(2):112-120.
7. Agency for Healthcare Research and Quality. Using Appropriate Price Indices for Analyses of Health Care Expenditures or Income Across Multiple Years. 2019.
8. Bureau of Economic Analysis. National Data: National Income and Product Accounts. 2020.
9. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. *The New England journal of medicine.* 2018;379(9):811-822.
10. Tagliaferri A, Feola G, Molinari AC, et al. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost.* 2015;114(1):35-45.
11. Coppola A, D'Ausilio A, Aiello A, et al. Cost-effectiveness analysis of late prophylaxis vs. on-demand treatment for severe haemophilia A in Italy. *Haemophilia.* 2017;23(3):422-429.
12. Tiede A, Abdul Karim F, Jimenez-Yuste V, et al. Factor VIII activity and bleeding risk during prophylaxis for severe hemophilia A: a population pharmacokinetic model. *Haematologica.* 2020.
13. Pasi KJ, Fuchs H. First-In-Human Four-year Follow-Up Study of Durable Therapeutic Efficacy and Safety : AAV Gene Therapy with Valoctocogene roxaparvovec for Severe Hemophilia A. In: BioMarin; 2020.
14. Arias E, Xu, J., *United States Life Tables, 2017.*: Centers for Disease Control and Prevention, Division of Vital Statistics; June 24, 2019 2017.
15. O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health and quality of life outcomes.* 2018;16(1):84.
16. Laupacis A, Bourne R, Rorabeck C, et al. The effect of elective total hip replacement on health-related quality of life. *J Bone Joint Surg Am.* 1993;75(11):1619-1626.
17. Baxter Healthcare Corp. Advate (Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method) [package insert]. 2011.
18. Biogen Idec, Inc. Eloctate (Antihemophilic Factor (Recombinant), FcFusion Protein) [package insert]. U.S. Food and Drug Administration

website. https://www.fda.gov/media/88746/download. Revised September 2019. Accessed May 15, 2020.
19. Liu A. JPM: Watch out, Roche. BioMarin's gene therapy might bleed off the hemophilia A market. 2020.
20. Services CfMaM. 2020 ASP Drug Pricing Files. 2020.
21. Shrestha A, Eldar-Lissai A, Hou N, Lakdawalla DN, Batt K. Real-world resource use and costs of haemophilia A-related bleeding. *Haemophilia.* 2017;23(4):e267-e275.
22. O'Hara J, Walsh S, Camp C, et al. The relationship between target joints and direct resource use in severe haemophilia. *Health Econ Rev.* 2018;8(1):1.
23. Centers for Medicare and Medicaid Services. *Physician Fee Schedule Search.*
24. Earnshaw S, Graham C, McDade C, Spears J, Kessler C. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. *Haemophilia.* 2015;21(3):310-319.
25. Zhou ZY, Koerper MA, Johnson KA, et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. *Journal of medical economics.* 2015;18(6):457-465.
26. Prevention CfDCa. HTC Population Profile. 2020; https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2019-3/table-2-factor.html. Accessed July 1, 2020, 2020.
27. World Federation of Hemophilia. *Report on the Annual Global Survey 2018.* Montreal, Canada2019.
28. Stanford S, Pink R, Creagh D, et al. Adenovirus-associated antibodies in UK cohort of hemophilia patients: A seroprevalence study of the presence of adenovirus-associated virus vector-serotypes AAV5 and AAV8 neutralizing activity and antibodies in patients with hemophilia A. *Res Pract Thromb Haemost.* 2019;3(2):261-267.