Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value

Public Meeting — October 30, 2020

Meeting materials available at: https://icer-review.org/topic/hemophilia-a/

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Why are we here today?

As a person with severe hemophilia who has survived to celebrate my 76th birthday on October 10, 2020, I can reflect on the advances in treatment over the past seven decades…. I have confidence that my great-grandchildren, if they have hemophilia, will benefit from miraculous treatment advances and perhaps even a cure.

Donald Goldman, Person with Hemophilia

Why Are We Here Today?

- What happens the day these treatments are approved by the FDA?
- What happens to patients and others in the health care “system”?

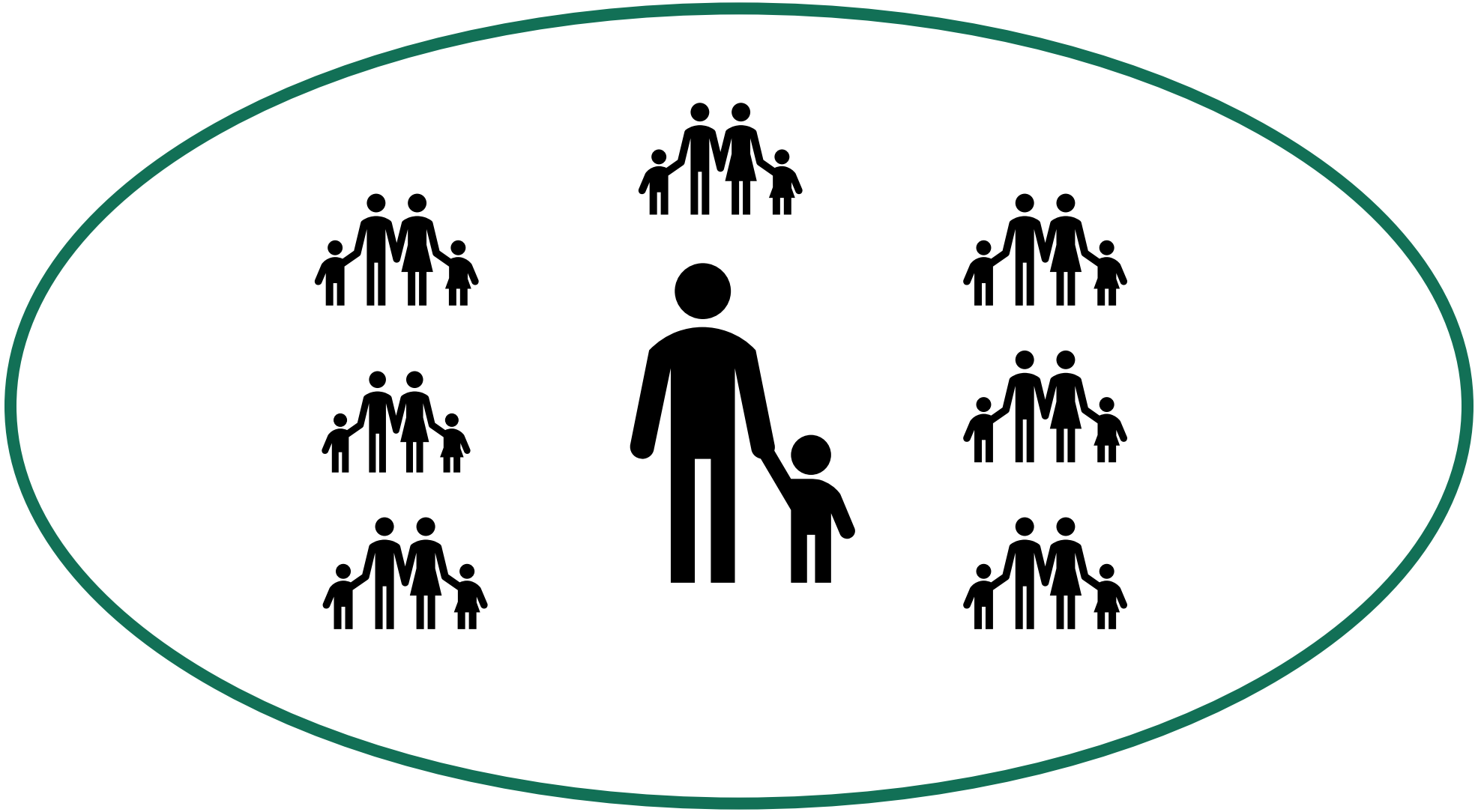
When There Isn’t Enough Money For Health Insurance

Gustavo Bendeck, Lubbock, Texas

The Whitmans, Bird City, Alaska

Luke Breen, Minneapolis, Minnesota

ICER

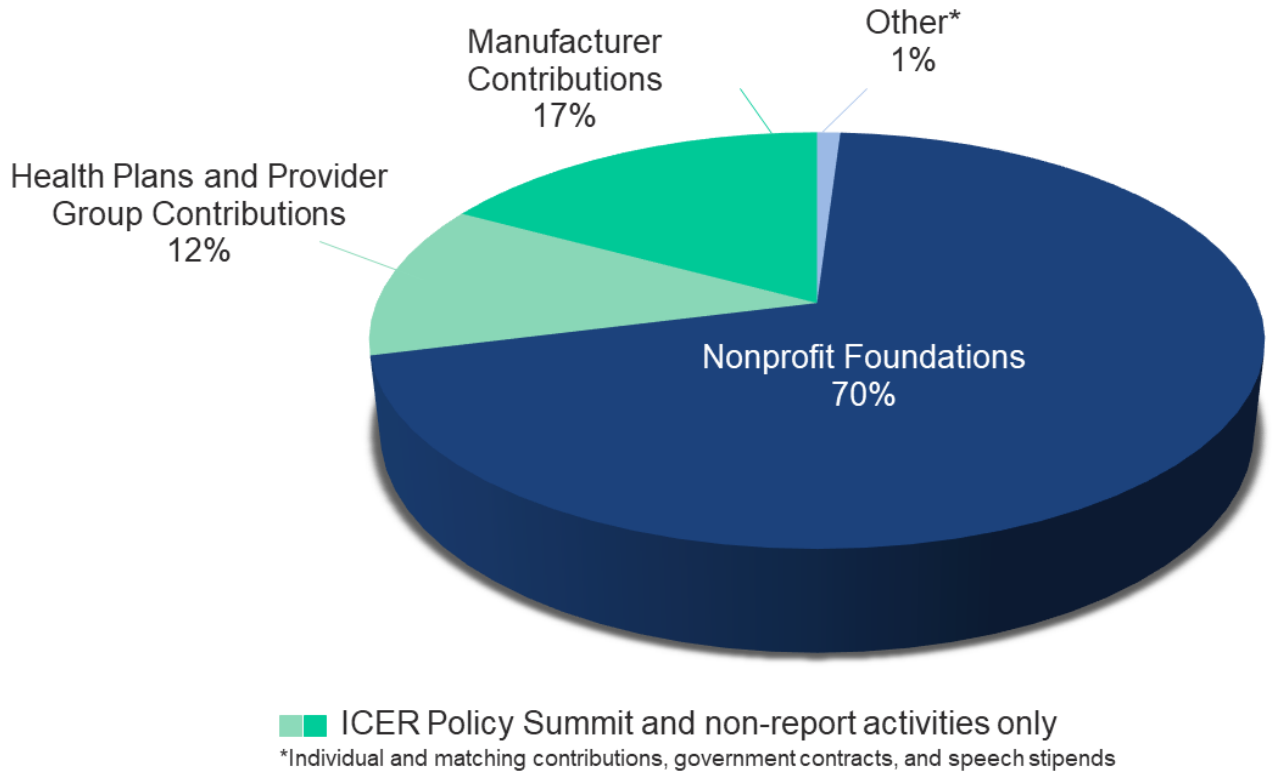


Organizational Overview

- The New England Comparative Effectiveness Public Advisory Council (CEPAC)
- The Institute for Clinical and Economic Review (ICER)

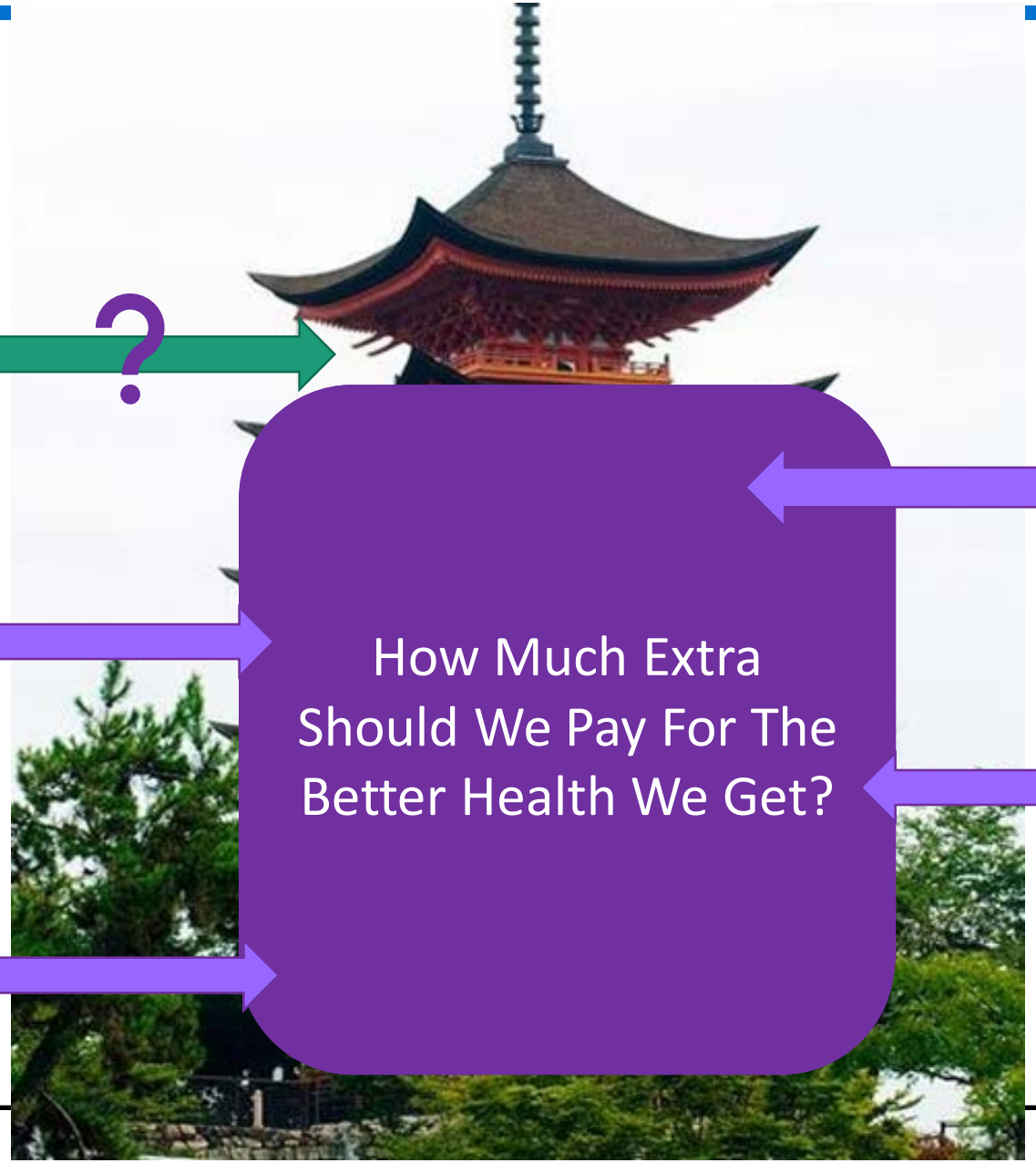
Sources of Funding, 2020

https://icer-review.org/about/support/



How Was the ICER Report Developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Illinois Chicago (UIC) cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
    - Steven Pipe, MD, Professor of Pediatrics and Pathology Pediatric Medical Director, Hemophilia and Coagulation Disorders Program Director, University of Michigan
    - Margaret V. Ragni, MD, MPH, Professor of Medicine and Clinical and Translational Science, Medical Director of Hemophilia Center of Western PA, University of Pittsburgh Medical Center
    - Mark W. Skinner, JD, President & CEO, Institute for Policy Advancement Ltd.
- How is the evidence report structured to support New England CEPAC voting and policy discussion?



Benefits Beyond Health and Special Social or Ethical Priorities

?

Health Benefits: Fewer Side Effects

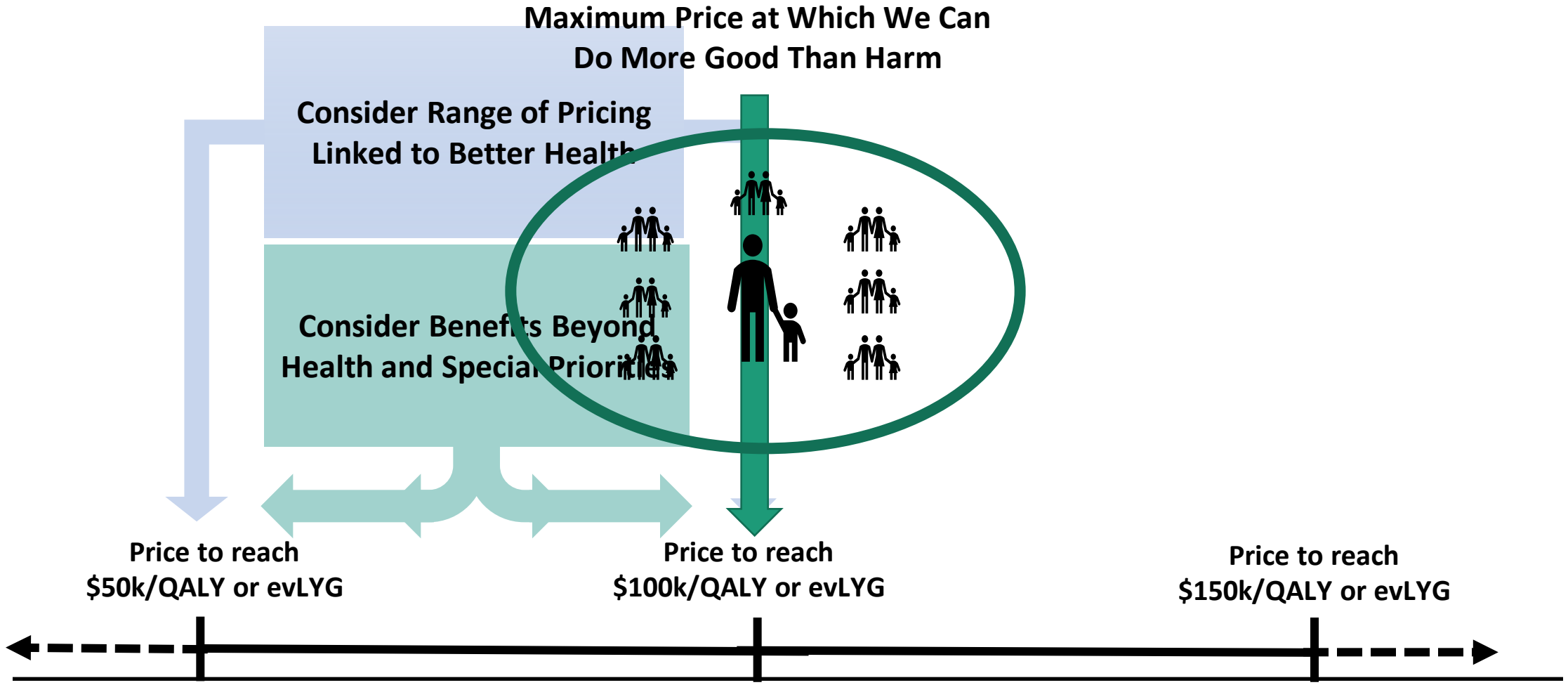
Health Benefits: Longer Life

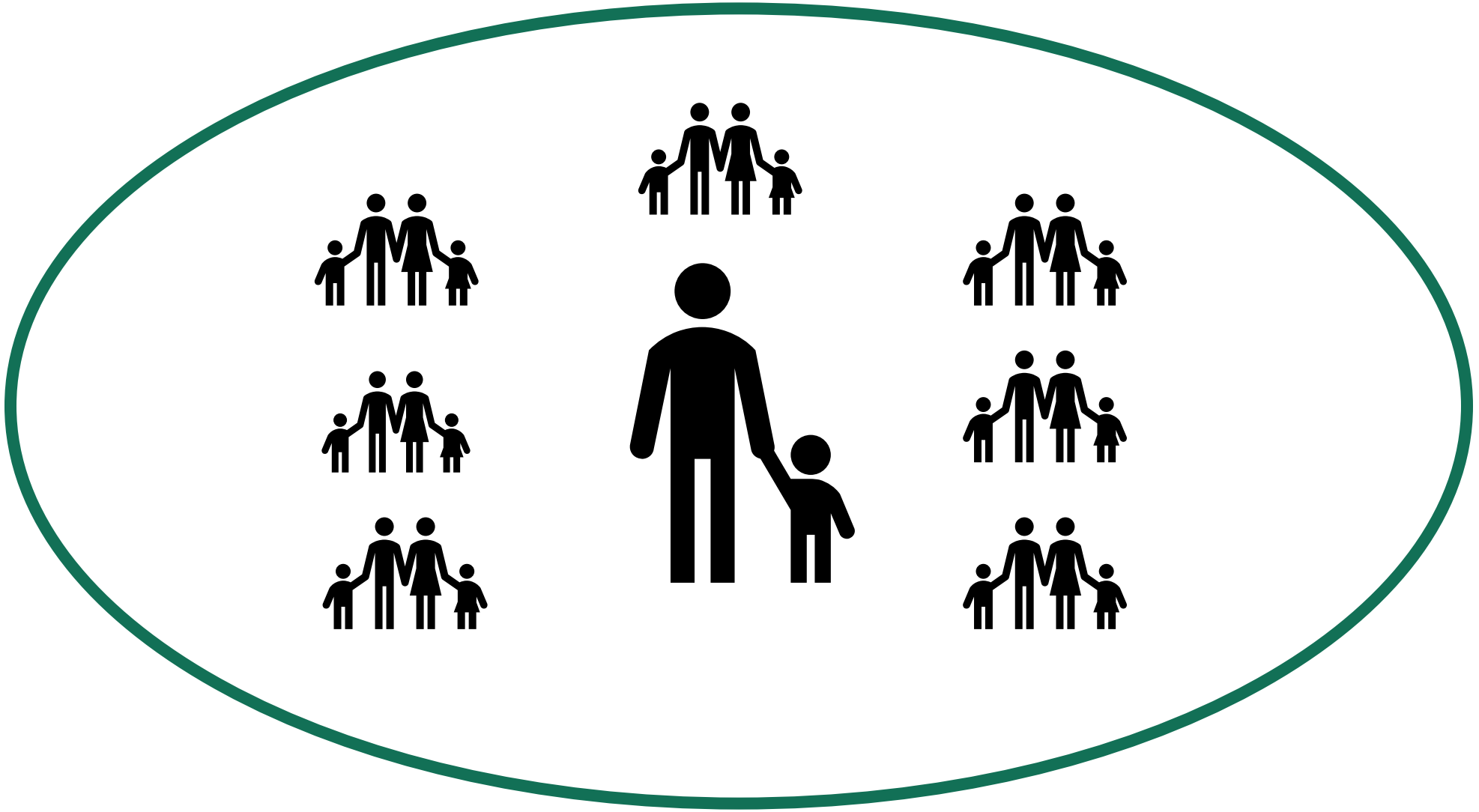
How Much Extra Should We Pay For The Better Health We Get?

Total Costs Including any Cost Savings from Better Health

Health Benefits: Improved Function

Cost Effectiveness as a Part of Pricing to Value





Agenda

Time	Activity
10:00 AM—10:20 AM	**Meeting Convened and Opening Remarks** Steven D. Pearson, MD, MSc, President, ICER
10:20 AM—10:40 AM	**Presentation of the Clinical Evidence** David Rind, MD, Chief Medical Officer, ICER
10:40 AM—11:10 AM	**Presentation of the Economic Model** Surrey Walton, PhD, University of Illinois at Chicago College of Pharmacy
11:10 AM—11:20 AM	**Break**
11:20 AM—12:00 PM	**Public Comments and Discussion**
12:00 PM—12:40 PM	**Lunch Break**
12:40 PM—1:20 PM	**New England CEPAC Vote on Clinical Effectiveness and Value**
1:20 PM -- 1:30 PM	**Break**
1:30 PM—2:30 PM	**Policy Roundtable**
2:30 PM—3:00 PM	**Reflections from New England CEPAC**
3:00 PM	**Meeting Adjourned**

Clinical and Patient Experts

Brian O'Mahony, Chief Executive, Irish Haemophilia Society, Patient Advocate

- *Brian O'Mahony has received fees for participation in advisory boards or educational activities from Bayer, BioMarin, Freeline, Roche and Uniqure.*

Mark Skinner, JD, President & CEO, Institute for Policy Advancement Ltd, Patient Advocate

- *Mr. Skinner has received fees and honoraria of more than $5,000 for educational presentations and advisory board participation from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, and the Blue Cross Blue Shield Association. Mr. Skinner's household has or held equity interests in the following companies in the health sector: Cryosport, CVS Health, Editas Medicine, Horizon discovery, Illumina, Intellia Therapeutics, Intuitive Surgical, Johnson & Johnson (Sold), Novartis, Regeneron (Sold) and Teladoc Health. These holdings are independently managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders. Mr. Skinner is a member of the ICER Governing Board; Board of Directors of the World Federation of Hemophilia USA, which receives product and monetary donations for a global humanitarian aid program; serves as a consultant for the US National Hemophilia Foundation, and is a member of the NHF Scientific Advisory Council. Mr. Skinner is a Principal investigator for the Patient-Reported Outcomes and Burdens and Experiences (PROBE) study, which has received fees and grant support from Bayer, BioMarin, CSL-Behring, Freeline Therapeutics, Novo Nordisk, F. Hoffman-La Roche, Sanofi, Sobi, Takeda, uniQure. The PROBE study is an independent, investigator-led research project led by patients and patient advocacy organizations. Mr. Skinner is a person with severe hemophilia A.*

Steven Pipe, MD, Pediatric Medical Director, Hemophilia and Coagulation Disorders Program, University of Michigan

- *Dr. Steven Pipe has received consulting fees from Apcintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure.*

Margaret Ragni, MD, MPH, Professor of Medicine and Clinical and Translational Medicine, University of Pittsburgh

- *Dr. Margaret Ragni receives research funding (through the University of Pittsburgh) for gene therapy trials with SPARK, a gene therapy trial with BioMarin, and past gene therapy trial funding with Sangamo.*

Evidence Review

David M. Rind, MD, MSc

Chief Medical Officer

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Key Collaborators

- Foluso Agboola, MBBS, MPH
- Serina Herron-Smith, BA
- Eric Borrelli, PharmD, MBA

Disclosures:

We have no conflicts of interest relevant to this report

Hemophilia A

- Deficiency in factor VIII
- Increased tendency to bleed
- X-linked recessive (1/5000 male births)
- Risk for life-threatening bleeding
- Bleeds into joints and muscles
- Joint bleeds lead to further bleeding and progressive joint damage

Prophylaxis

- Factor VIII for home treatment of bleeds became available in the 1970s
- Use of factor VIII infusions for prophylaxis became routine in severe hemophilia A by the early-to-mid 2000s
- Randomized trials demonstrated efficacy by the mid-to-late 2000s

Prophylaxis

- Burdensome
  - Factors are administered intravenously
  - Must be given frequently
  - Venous access can be difficult in young children
  - Elderly patients and those who develop arthropathy may find self-administration difficult
  - Adherence is a substantial problem

Potential Patient and Caregiver Restrictions

- Patient career
  - Bleeding risk
  - Near specialized care
  - Accessibility of factor
  - Flexible time
- Education
  - Near specialized care
  - Accessibility of factor
  - Flexible time
- Caregiver Career
  - Near specialized care
  - Flexible Time
- Location of Residence
  - Near specialized care
  - Accessibility of factor
- Recreation
  - Bleeding risk
  - Near specialized care
  - Accessibility of factor

Valoctocogene Roxaparvovec (Roctavian, BioMarin)

- “Valrox”
- AAV5 liver-directed gene therapy
- One-time administration to adults
- Complete Response Letter from FDA in August 2020

Emicizumab (Hemlibra®, Genentech)

- Bispecific antibody bridging aFIX and FX
- Subcutaneous injection every 1 to 4 weeks
- Used only for prophylaxis
- Approvals
  - Patients with inhibitors: 2017 (prior ICER review)
  - Patients without inhibitors: 2018

Scope of the Review

- **Population**: People with hemophilia A without inhibitors to factor VIII who would be appropriate for routine prophylaxis. For valoctocogene roxaparvovec, limited to adults.
- **Interventions:**
  - Gene therapy with valoctocogene roxaparvovec
  - Prophylaxis with emicizumab
- **Comparators:**
  - Prophylaxis with factor VIII
    - For valoctocogene roxaparvovec assessed benefit mainly by achieved factor levels
    - For emicizumab assessed benefit mainly by annualized bleed rates (ABRs)
  - Each other

Insights from Discussions with Patients

- Annualized bleeding rates do not adequately capture all aspects of the benefits, burdens, and harms of prophylaxis
- A curative therapy may be transformational in ways that even someone with hemophilia may not be able to understand before it happens
- Patients and patient groups have struggled to get insurance coverage for dosing regimens that maintain higher trough levels of factor VIII

Clinical Evidence

Valoctocogene Roxaparvovec

- Severity of Hemophilia
  - Severe: Factor VIII level < 1% of normal
  - Moderate: Factor VIII level 1% to 5% of normal
  - Mild: Factor VIII level 6% to 40% of normal
- Phase I/II open-label dose-finding trial (n = 15)
  - Primary endpoint of factor VIII activity ≥ 5 IU/dL
    - Achieved by 4 out of 5 patients who received $4x10^{13}$ vg/kg
    - Achieved by 7 out of 7 patients who received $6x10^{13}$ vg/kg

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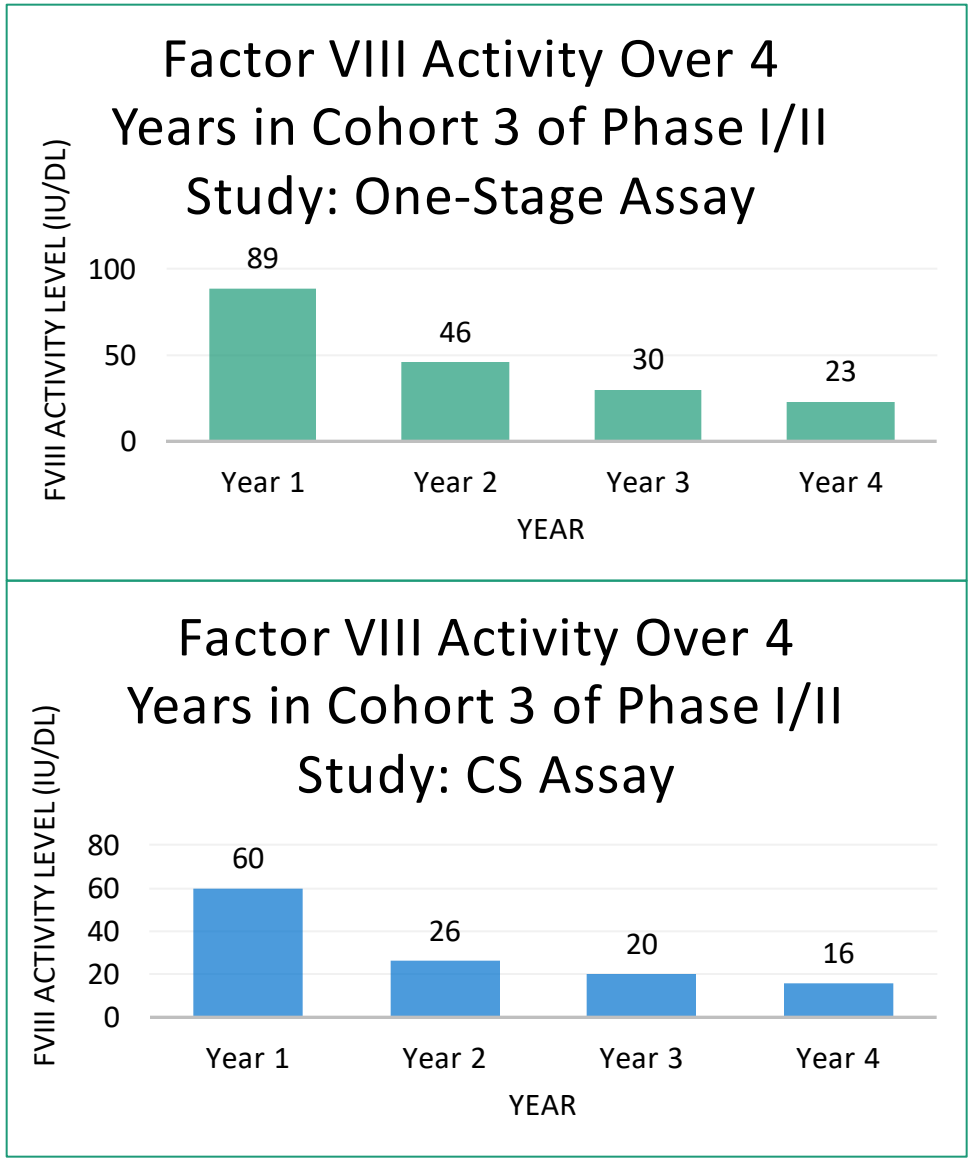

Year Four Severity (Chromogenic Assay)

- Non-hemophilic: 1
- Mild: 4
- Moderate: 1
- Severe: 1

Year Four Severity (One-Stage Assay)

- Non-hemophilic: 2
- Mild: 5

Other Information

- Mean ABR dropped from 16.3 to 0.8 after four years
- Years 2-4, 6 out of 7 patients had 0 bleeds (1/7 at baseline)
- Quality of life measures increased each year
- Most common adverse event was increase in liver enzymes
- All patients developed antibodies to AAV5
- Limited phase III data show only 7/16 achieved ≥40 IU/dL

Emicizumab

- HAVEN 3
  - Open label phase III RCT in patients without inhibitors
  - 89 patients not receiving prophylaxis: two dosing schedules of emicizumab versus no prophylaxis
  - (63 patients receiving prophylaxis, switched to emicizumab)
- SPINART
  - Open label RCT of factor VIII versus no prophylaxis in 84 patients
  - Standard half-life factor VIII dosed **25 IU/kg** three times weekly

NMA of Emicizumab vs. Factor VIII

Annualized Treated Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab	FVIII prophylaxis	On-demand FVIII
0.57 (0.22, 1.47)		
0.03 (0.02, 0.07)	0.06 (0.03, 0.11)	

Annualized Treated Joint Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab	FVIII prophylaxis	On-demand FVIII
0.53 (0.2, 1.39)		
0.03 (0.02, 0.07)	0.07 (0.03, 0.12)	

Other Information

- RWE on bleeds in 39 children switching from FVIII to emicizumab
  - ABR decreased to 0.2 from 1.1
  - Zero bleeds in six months: 94% vs. 73%
- HAVEN 3
  - Non-statistically significant improvements in quality of life vs. no prophylaxis
  - Fewer missed days of work vs. no prophylaxis
  - In before/after study, 98% preferred emicizumab to FVIII prophylaxis
- Most common harms with emicizumab were injection site reactions

Valrox Uncertainties and Controversies

- Very few patients studied and reported on
- Interim phase III data appear to show lower success rates
- Factor levels declining over time
- Target cell is hepatocytes; factor VIII normally made in endothelial cells

Emicizumab Uncertainties and Controversies

- Effects on inhibitor development likely but unknown
- Best RCT evidence is against doses of factor VIII lower than typically used today in US
- RCT evidence may overestimate adherence to a burdensome therapy like factor VIII

Potential Other Benefits and Contextual Considerations

- Valoctocogene Roxaparvovec
  - Antibodies to AAV5
  - Even if limited duration of benefit, could allow period of time “cured”
  - Decreased burden/time of administering prophylaxis
- Emicizumab
  - Less burdensome administration (including for caregivers) and better adherence
- Both
  - Past iatrogenic harms

Public Comments Received

- B+ rating for emicizumab unreasonably high
- Inhibitor development
- Valoctocogene roxaparvovec bleeding rates

Summary: Valoctocogene Roxaparvovec vs. Factor VIII

- Marked improvements in many patients for a period of years
- Antibodies to AAV5 perhaps limiting better future treatments
- Potential long-term harms such as liver disease

- **Promising but inconclusive (P/I)**

Summary: Emicizumab vs. Factor VIII

- Emicizumab is superior to lower doses of factor VIII used in SPINART
- Uncertainties versus current doses of factor VIII
- Less burdensome and likely better adherence
- Thrombotic complications not seen in this population

- **Comparable or better (C++)**

Summary: Valoctocogene Roxaparvovec vs. Emicizumab

- **Insufficient (I)**

Questions?

Cost-Effectiveness

Surrey M Walton, PhD

Professor, Department of Pharmacy Systems Outcomes and Research

University of Illinois Chicago (UIC) College of Pharmacy

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Key Review Team Members

Danny Quach, PharmD, PhD Student, Department of Pharmacy Systems Outcomes and Research

- University of Illinois Chicago

Disclosures:

Financial support was provided to the University of Illinois at Chicago from the Institute for Clinical and Economic Review.

The University of Illinois at Chicago researchers have no conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

Objectives

There were two primary objectives:

1) Estimate the life-time cost-effectiveness of valoctocogene roxaparvovec relative to prophylaxis with factor VIII in adult patients with severe hemophilia A and without inhibitors.

2) Estimate the life-time cost-effectiveness of emicizumab relative to prophylaxis with factor VIII in patients with hemophilia A suitable for factor VIII prophylaxis and without inhibitors.

Methods in Brief

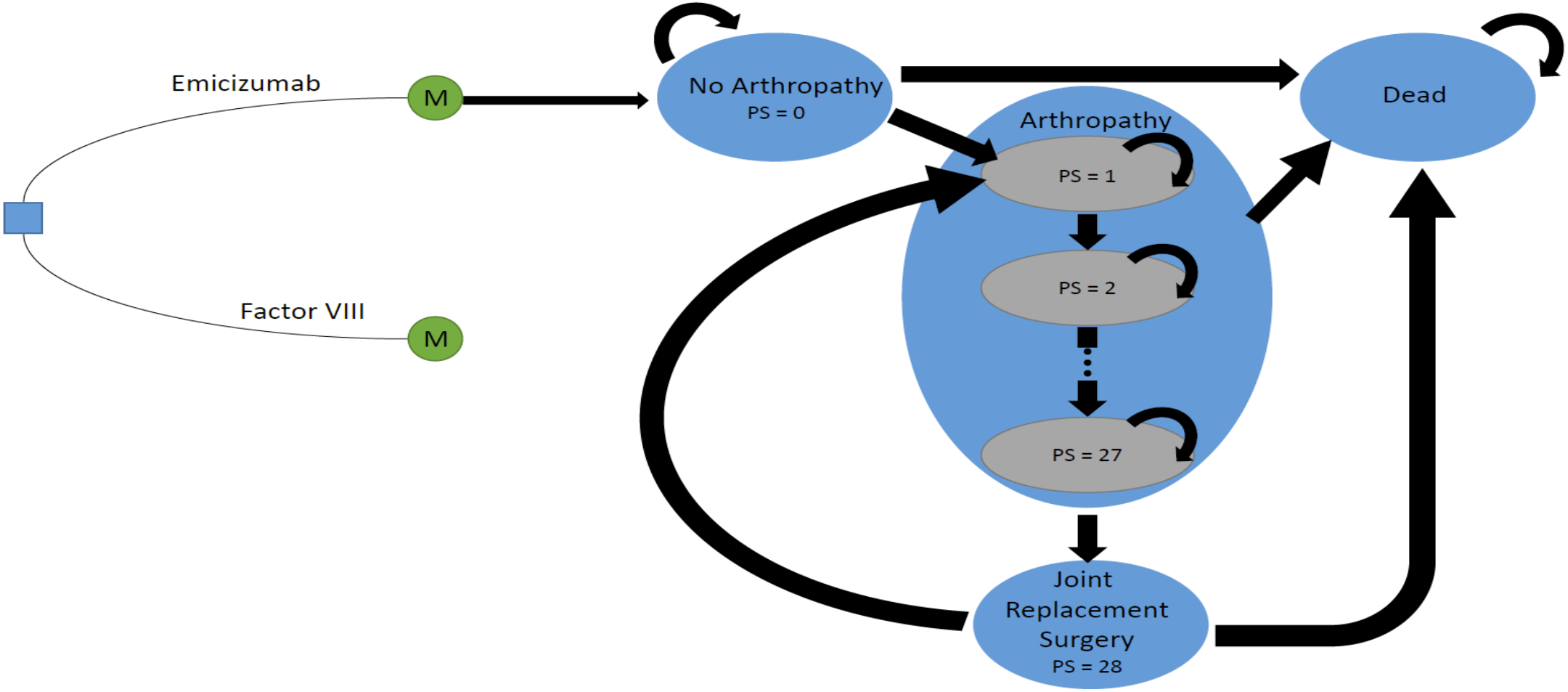
Methods Overview Model 1

- **Model**: Semi-Markov Model
- **Setting**: United States
- **ICER Frameworks:** Ultra rare and Single/Short-term Transformative Therapy;
- **Perspective**: Health Care Sector Perspective
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 6 Months
- **Primary Outcome**: Cost per quality-adjusted life year (QALY) gained, cost per life year (LY) gained, cost per treated bleed avoided

Methods Overview Model 2

- **Model**: Semi-Markov Model
- **Setting**: United States
- **ICER Framework:** Standard
- **Perspective**: Health Care Sector Perspective
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 6 Months
- **Primary Outcome**: Cost per quality-adjusted life year (QALY) gained, cost per life year (LY) gained, cost per treated bleed avoided

Model Schematic



Key Model Assumptions

- Model 1 bleed rates for valoctocogene roxaparvovec were based on projected factor levels and literature-based estimates of bleed rates across factor levels.
- In Model 1, at projected factor levels below 5%, 5% of patients are assumed to switch to emicizumab prophylaxis. At projected factor levels below 1%, all patients were assumed to switch to emicizumab.
- Bleed rates for emicizumab are taken from the Haven 3 trial.
- Bleed rates for factor VIII are from a recent published study by Malec et. al. examining bleed rates in US hemophilia treatment centers affiliated with the American Thrombosis & Hemostasis Network (ATHN).
    - We view the factor VIII rates as an evidence based lower bound for bleeds associated with current dosing.

Key Model Assumptions

- Proportions of bleed types relative to treated bleeds in the HAVEN 3 trial were used to estimate different types of bleeds relative to treated bleeds for factor VIII and valoctocogene roxaparvovec.
  - An average proportion of all bleeds that are joint bleeds in the HAVEN 3 and POTTER trials determined joint bleeds relative to total bleeds.
- Factor VIII costs are based on two representative treatments, Advate for standard half-life, and Eloctate for extended half-life, using doses and proportions of patients on those drugs consistent with patients treated with those treatments in US hemophilia treatment centers affiliated with ATHN.

Key Model Assumptions

- The utilities associated with a bleed are applied fully for two days and an average of the no bleed and bleed values for the remainder of a week.
- Cost per treated bleeds are the same for all comparators.
- Patient weights and mortality rates were based on US male population averages.
- There were no mortality effects for any treatment.

Starting Points and Transitions

- In Model 1 patients start with a PS of 13. In model 2 they start with a PS of 0.
- PS transition rates are consistent with a 1-point increase for every 36.52 bleeds for patients under 25 and for every 6.52 joint bleeds over the age of 25.
- At a PS score of 28, patients have surgery and return to a PS of 1.

Key Model Inputs: Bleed Rates

Drug	All Bleeds*	All Joint Bleeds*	Non-Target Joint Bleeds (Treated)	Target Joint Bleeds (Treated)
Factor VIII	2.60	1.72	0.60	0.70
Emicizumab	2.60	1.72	0.60	0.70
Valoctocogene Roxaparvovec Year 2	0.45	0.30	0.10	0.12
Valoctocogene Roxaparvovec Year 10	7.05	4.65	1.63	1.90
Valoctocogene Roxaparvovec Year 13	2.60	1.72	0.60	0.70

*Includes treated and untreated bleeds

Key Model Inputs: Health State Utilities

Age	Pettersson 0	Pettersson 1-27	Surgery	Source
0-30	0.94	0.82	0.72	O'Hara 2018; Laupacis 1993
31-40	0.84	0.74	0.65	O'Hara 2018; Laupacis 1993
41-50	0.86	0.69	0.61	O'Hara 2018; Laupacis 1993
51-60	0.83	0.63	0.56	O'Hara 2018; Laupacis 1993
61-100	0.73	0.54	0.48	O'Hara 2018; Laupacis 1993

Utilities are based on EQ-5D surveys completed by hemophilia patients in Europe. The surgery utility is a time trade off score from patients pre hip surgery. 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

Key Model Inputs: Utilities

Bleed Disutilities	Value/Bleed/Cycle	Source
Bleed Not Into A Target Joint	-0.002	Neufeld 2012
Target Joint Bleed	-0.003	Mazza 2016

These are based on a -0.16 and -0.28 disutility per day for treated bleed and treated joint bleed. EQ-5D based utilities by patients or caregivers.

Key Model Inputs: Drug Regimens

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	118.2 IU/kg every week	111.2 IU/kg every week

For Factor VIII, 71.18% take Advate and 28.82% take Eloctate. For all bleeds, the same basket and a 54 IU/kg dose of each drug was used. We recognize dosing regimens vary widely in practice.

Key Model Inputs: Treatment Costs

Drug	WAC per Dose	Discount from WAC	Add-On Discount	Net Price per Dose	Net Price per Year
Valoctocogene roxaparvovec (Roctavian™)	$2,500,000	--	0%	$2,500,000	Not applicable
Emicizumab (Hemlibra®)	$100.19/mg	4.7%	6%	$89.33/mg	$569,105
Antihemophilic Factor (recombinant) (Advate®)	$1.69/IU	18.6%	6%	$1.08/IU	$542,539
Antihemophilic Factor (recombinant), Fc fusion protein (Eloctate®)	$2.23/IU	3.2%	6%	$1.82/IU	$858,026

These all vary by weight and are shown for an 81.4 Kg patient. The average cost of Factor VIII is $633,462. The average treatment cost per bleed was $5,275 for an 81.4kg male.

Key Model Inputs: Non-Drug Costs per Bleed

Age (years)	Cost	Source
< 18	$765.48	Shrestha 2017
18-45	$4,604.32	Shrestha 2017
> 45	$6,858.24	Shrestha 2017

Additional societal costs per bleed were $1,162

Key Model Inputs: Other Costs

	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

Results

Base-Case Results Model 1

Treatment	Drug Cost	Total Cost	Infusions	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model 1– Health Sector Perspective)	$18,269,000	$18,722,000	3705.17	68.97	15.92	18.57	26.53	19.087
Valoctocogene Roxaparvovec (Model 1 – Health Sector Perspective)	$13,293,000	$13,693,000	31.11	43.70	15.28	17.83	26.53	19.091

QALYs: quality-adjusted life years

Base-Case Incremental Results Model 1

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Valoctocogene Roxaparvovec vs. Factor VIII (Model 1 – Health Sector Perspective)	-$4,988,000	0.004	Dominant

QALY: quality-adjusted life year

Base-Case Results Model 2

Treatment	Drug Cost	Total Cost	Infusions	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model 2 – Health Sector Perspective)	$14,821,000	$15,104,000	4058.67	38.60	12.64	13.76	29.14	24.141
Emicizumab (Model 2 – Health Sector Perspective)	$13,316,000	$13,598,000	26.41	38.60	12.64	13.76	29.14	24.141

QALYs: quality-adjusted life years

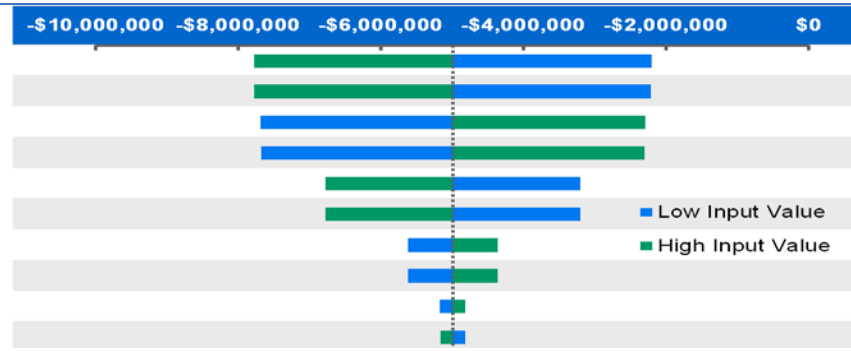
Base-Case Incremental Results Model 2

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Emicizumab vs Factor VIII (Model 2 – Health Sector Perspective)	-$1,505,000	0.000	Cost Saving

QALY: quality-adjusted life year

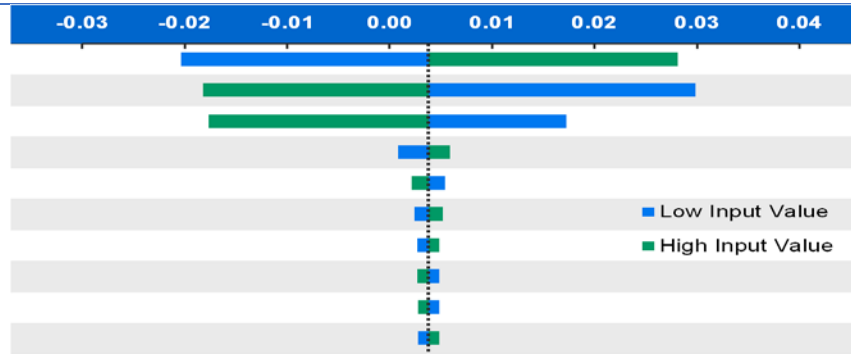
One Way Sensitivity Analyses - Model 1

Model 1 Health Sector - Valrox Incremental Costs



Parameter	Low Input Value	High Input Value
Advate (F8) Net Drug Cost	$0.86	$1.44
Advate (F8) Prophylaxis Drug Dosing	88.65	147.75
Emicizumab Net Drug Cost	$71.27	$118.79
Emicizumab (Month 2+) Prophylaxis Drug Dosing	1.13	1.88
Eloctate (F8) Net Drug Cost	$1.45	$2.42
Eloctate (F8) Prophylaxis Drug Dosing	83.40	139.00
Valactogene Net Drug Cost	$1,875,000.00	$3,125,000.00
Valactogene Prophylaxis Drug Dosing	0.75	1.25
Advate (F8) Furnishing Discount (%)	4.50%	7.50%
Emicizumab Furnishing Discount (%)	0.05	0.08

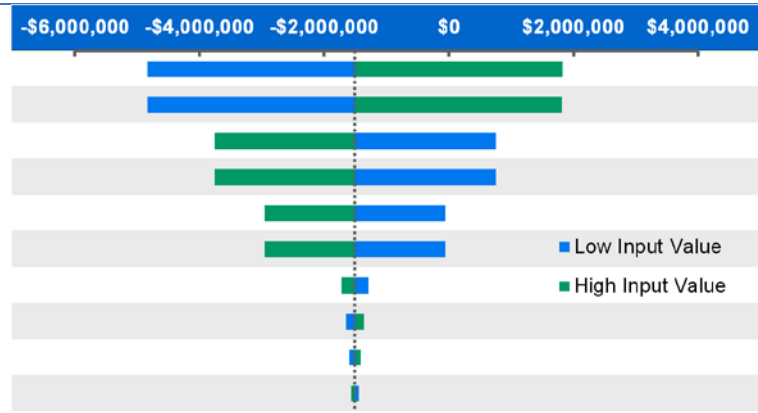
Model 1 - Valrox Incremental QALYs



Parameter	Low Input Value	High Input Value
Factor VIII Total Treated Bleeds	0.98	1.63
Emicizimuab Total Treated Bleeds	0.98	1.63
Valacocogene Treated Joint Bleed RR	0.09	0.30
Average Number of Blood Days	1.00	7.00
Pettersson 13-21 Utilities (Age > 60)	0.41	0.68
Pettersson 22-28 Utilities (Age > 60)	0.41	0.68
Pettersson 13-21 Utilities (30 < Age ≤ 40)	0.56	0.93
Pettersson 22-28 Utilities (30 < Age ≤ 40)	0.56	0.93
Pettersson 13-21 Utilities (50 < Age ≤ 60)	0.47	0.79
Pettersson 22-28 Utilities (50 < Age ≤ 60)	0.47	0.79

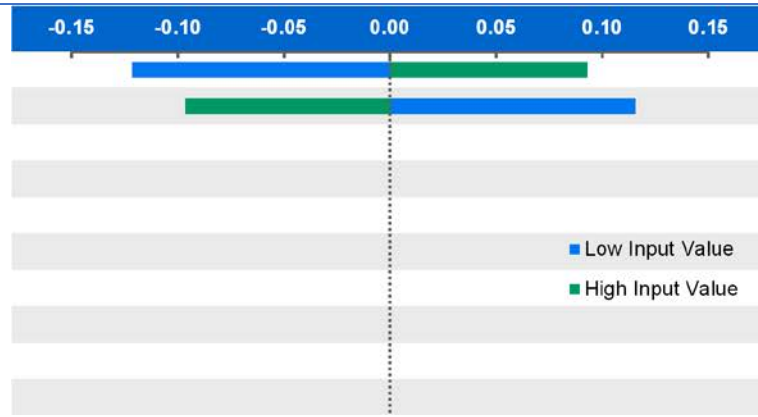
One Way Sensitivity Analyses - Model 2

Model version 2 - Emicizumab Incremental Costs



Parameter	Low Input Value	High Input Value
Emicizumab Net Drug Cost	$71.27	$118.79
Emicizumab (Month 2+) Prophylaxis Drug Dosing	1.13	1.88
Advate (F8) Net Drug Cost	$0.86	$1.44
Advate (F8) Prophylaxis Drug Dosing	88.65	147.75
Eloctate (F8) Net Drug Cost	$1.45	$2.42
Eloctate (F8) Prophylaxis Drug Dosing	83.40	139.00
Emicizumab Furnishing Discount (%)	4.50%	7.50%
Advate (F8) Furnishing Discount (%)	4.50%	7.50%
Eloctate (F8) Furnishing Discount (%)	0.05	0.08
Factor VIII Total Treated Bleeds	97.50%	162.50%

Model version 2 - Emicizumab Incremental QALYs



Parameter	Low Input Value	High Input Value
Factor VIII Total Treated Bleeds	0.98	1.63
Emicizimuab Total Treated Bleeds	0.98	1.63

Probabilistic Sensitivity Analysis Model 1

	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	Cost Effective at $250,000 per QALY
Valoctocogene Roxaparvovec (Model 1 – Health Sector Perspective)	93.92%	93.93%	93.93%	93.93%	93.93%

Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Probabilistic Sensitivity Analysis Model 2

	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	Cost Effective at $250,000 per QALY
Emicizumab (Model 2)	69.43%	69.43%	69.42%	69.46%	60.47%

QALY: quality-adjusted life year

Scenario Analyses

- Using higher bleed durations, higher bleed rates, an older starting age in model 1, surgery return to PS score of 13, and societal perspectives had very little impact on the results.
- In the SST scenarios for model 1, the conservative and optimistic duration scenarios as well as a proposed payment scenario all resulted in valoctocogene roxaparvovec being dominant.

Limited Savings SST Scenario Analyses Model 1

Scenario	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Half Savings During Treatment	Valoctocogene Roxaparvovec	-$666,000	0.004	Dominant
Cap Savings at $150,000/Year During Treatment	Valoctocogene Roxaparvovec	$923,000	0.004	$230,750,000/QALY

*The incremental costs were the same in the societal and health sector scenarios only after rounding to the nearest $1000.

NMA Scenario Analyses Model 1

Treatment (Perspective)	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Valoctocogene Roxaparvovec (Health Sector Perspective)	$452,000	0.076	$5,949,000/QALY gained

Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

NMA Scenario Analysis Model 2

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Emicizumab	$2,948,000	0.284	$10,393,000/QALY gained

Limitations

- Both models are based on limited data particularly for valoctocogene roxaparvovec .
- The models do not include adherence.
- Dosing for Factor VIII was from US hemophilia centers while those for emicizumab and valoctocogene roxaparvovec were from clinical trials.
- We also did not incorporate inhibitor development into model 2 as we received conflicting clinical opinion about which regimen would lead to more inhibitor development and it has already been shown that emicizumab is a dominant treatment for patients with inhibitors.

Limitations

- The relationship between joint bleeds and surgery is imperfect and the model assumes one joint requiring surgery at a time. This may undercount surgeries overall. To help address this, we examined the impact of varying some of the model assumptions around surgery and the impact was small.
- Utility scores for bleeds came from patients with inhibitors and these may be different in patients without inhibitors.
- We are using a placeholder price for valoctocogene roxaparvovec.
- We use Advate and Eloctate as representative treatments and average doses from ATHN data. There are numerous other factor VIII products on the market and a wide variance of treatment regimens.
    - The results here would not directly apply to those products and as shown in the sensitivity and scenario analyses variation in dosing can have major implications on the projected cost effectiveness of factor VIII.

Comments Received

- Lots of comments that dosing should not be based on one trial for factor VIII which prompted changing the base case from being based on the NMA to being based on doses in the ATHN data set.
- Several other comments on dosing as well as use of other factor VIII products.
  - We recognize the variance in treatment and that dosing is a KEY variable.
- Using a pharmacokinetic based model around dosing.
  - Theoretically this should mimic the average dose we used but could impact the variance.
- Accounting for treatment burden of factor VIII in the model.
  - We did not find high quality inputs for this, but we do report the number of infusions.

Conclusions

- With representative doses and a data driven upper bound on efficacy for factor VIII, and using a placeholder price of $2.5 million, valoctocogene roxaparvovec was found to be a dominant treatment for adult patients with hemophilia A without inhibitors.
- With representative doses and a data driven upper bound on efficacy for factor VIII, emicizumab was found to be a highly cost saving treatment with equal efficacy to factor VIII.
- These results depend heavily on the high costs of factor VIII products.

Questions?

Break

Meeting will resume at 11:31am ET

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Manufacturer Public Comment and Discussion

Richard Ko, MD, MHS, MS
Head of Rare Blood Disorders, US Medical Affairs, Genentech, Inc.

Conflicts of Interest:

- *Dr. Richard Ko is a full-time employee of Genentech, Inc.*

00 : 05 : 00

Bob G. Schultz, PharmD, MS, Senior Manager – Outcome Research
Takeda Pharmaceuticals, Inc.

Conflicts of Interest:

Snooze Options: 30 Seconds | 1 Minute | 5 Minutes | 10 Minutes

- *Dr. Bob Shultz is a full-time employee of Takeda Pharmaceuticals, Inc.*

00 : 00 : 00

Parth Vashi, PharmD, Assistant Director, Research Strategy US Data Generation & Observational Studies, Bayer

Conflicts of Interest:

- *Dr. Parth Vashi is a full-time employee of Bayer.*

00 : 05 : 00

Wing Yen Wong, MD, Group Vice President, Global Medical Affairs, BioMarin Pharmaceutical Inc

Conflicts of Interest:

- *Dr. Wing Yen Wong is a full-time employee of BioMarin.*

Snooze Options: 30 Seconds | 1 Minute | 5 Minutes | 10 Minutes

00 : 00 : 00

Public Comment and Discussion

Len Valentino, MD, President & Chief Executive Officer, National Hemophilia Foundation

Conflicts of Interest:

- *The National Hemophilia Foundation is a 501c3 organization that receives program and educational grant funding from manufacturers of hemophilia products to support their mission.*

Snooze Options: 30 Seconds | 1 Minute | 5 Minutes | 10 Minutes

00 : 00 : 00

Sonji Wilkes, Senior Director, Policy, Advocacy & Government Education, Hemophilia Federation of America

Conflicts of Interest:

- *Hemophilia Federation of America receives manufacturer support, consulting fees and honoraria from Takeda, Genentech, Bayer, CSL Behring, Novo Nordisk, Sanofi Genzyme, HEMA Biologics, Kedrion BioPharma, Pfizer, Aptevo, BioMarin, Grifols, Octapharma, Spark Therapeutics, UniQure, Siaglon Therapeutics, PCORI.*

00 : 05 : 00

George Stone, Patient Advocate

Conflicts of Interest:

- *No financial conflicts to disclose.*

Snooze Options: 30 Seconds | 1 Minute | 5 Minutes | 10 Minutes

00 : 00 : 00

Ryan Hallock, LPN, Patient Advocate

Conflicts of Interest:

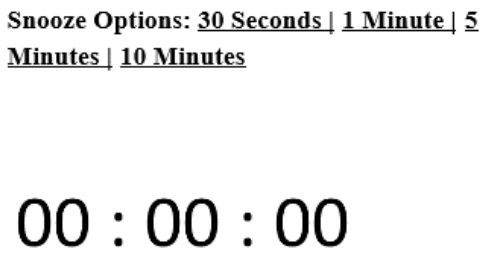
- *Ryan Hallock is a Board Member for the Mississippi Hemophilia Foundation.*

00 : 05 : 00

Jennifer Sleboda, Patient Advocate

Conflicts of Interest:

- *Jennifer Sleboda is a Board Member of the Hemophilia Association of the Capital Area, which receives funding from pharmaceutical and home care companies.*



Lunch

Meeting will resume at 1pm ET

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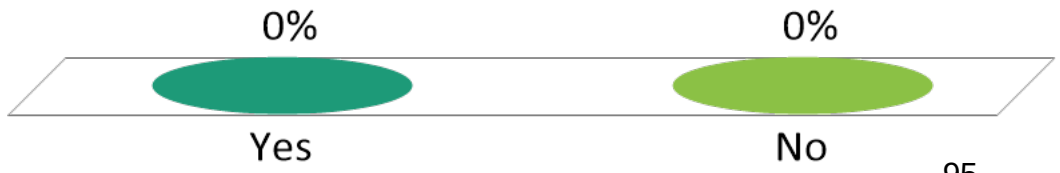
Voting Questions

1. For patients with hemophilia A without inhibitors to factor VIII, is the evidence adequate to demonstrate that the net health benefit of emicizumab (Hemlibra, Genentech) is superior to that provided by prophylaxis with factor VIII?

A. Yes

B. No



2. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

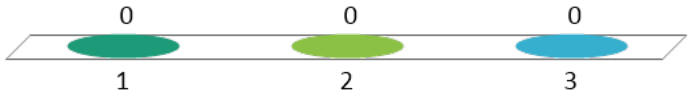
2a. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.



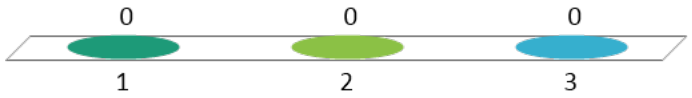
2b. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.



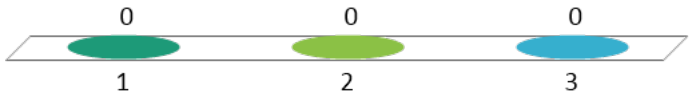
2c. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.



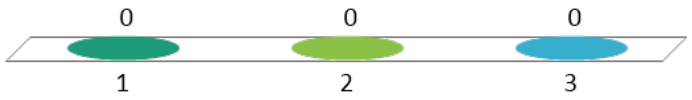
2d. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.



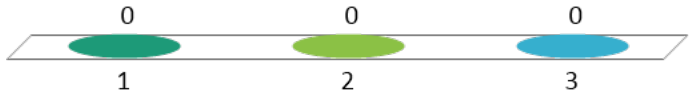
2e. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.



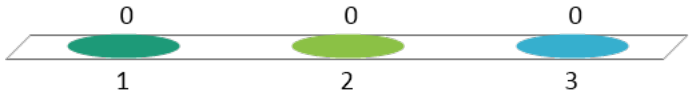
2f. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.



2g. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.

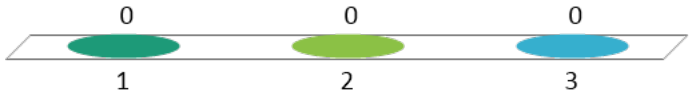
2h. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.



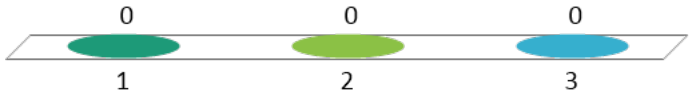
2i. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.



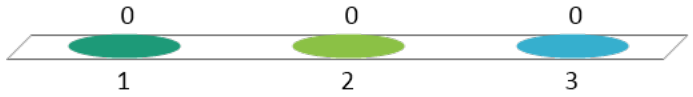
2j. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.



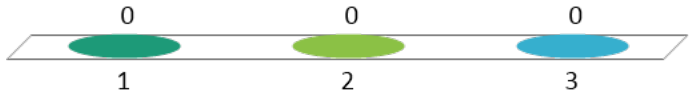
2k. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to emicizumab.

A. 1

B. 2

C. 3

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Other		Other



Break

Meeting will resume at 1:50pm ET

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Policy Roundtable

Policy Roundtable

Policy Roundtable Participant	Conflict of Interest
Leslie Fish, RPh, PharmD, Vice President of Clinical Pharmacy, IDP Analytics	No financial conflicts to disclose.
Richard Ko, MD, MHS, MS, Head of Rare Blood Disorders, US Medical Affairs, Genentech, Inc.	Dr. Richard Ko is a full-time employee of Genentech, Inc.
Brian O'Mahony, Chief Executive, Irish Haemophilia Society, Patient Advocate	Brian O'Mahony has received fees for participation in advisory boards or educational activities from Bayer, BioMarin, Freeline, Roche and Uniqure.
Steven Pipe, MD, Pediatric Medical Director, Hemophilia and Coagulation Disorders Program, University of Michigan	Dr. Steven Pipe has received consulting fees from Apcintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure.
Margaret Ragni, MD, MPH, Professor of Medicine and Clinical and Translational Medicine, University of Pittsburgh	Dr. Margaret Ragni receives research funding (through the University of Pittsburgh) for gene therapy trials with SPARK, a gene therapy trial with BioMarin, and past gene therapy trial funding with Sangamo.
Mark Skinner, JD, President & CEO, Institute for Policy Advancement Ltd, Patient Advocate	*
Wing Yen Wong, MD, Group Vice President, Global Medical Affairs, BioMarin Pharmaceutical Inc	Dr. Wing Yen Wong is a full-time employee of BioMarin Pharmaceuticals.
John Watkins, PharmD, MPH, BCPS Formulary Manager, Premera Blue Cross	Dr. John Watkins is a full-time employee of Premera Blue Cross.
Todd Williamson, PhD, MSc, Vice President, Data Generation & Observational Studies, Bayer	Dr. Todd Williamson is a full-time employee of Bayer Pharmaceuticals.

*Please refer to Clinical and Patient Expert slide for conflicts of interest.

New England CEPAC Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around November 20, 2020
    - Includes description of New England votes, deliberation, policy roundtable discussion
- Materials available at: https://icer-review.org/topic/hemophilia-a/

Adjourn

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