
Gene Therapy for Hemophilia B and Hemophilia A: Effectiveness and Value

Public Meeting — November 18, 2022

Meeting materials available at:

<https://icer.org/assessment/hemophilia-a-and-b-2022/#timeline>



Patient Experts

- **Brian O'Mahony, FACSLM.** Chief Executive, Irish Hemophilia Society
 - *Mr. O'Mahony has received fees and honoraria of more than \$5,000 from Bayer Healthcare and BioMarin.*
- **Mark Skinner, JD.** President & CEO, Institute for Policy Advancement Ltd.
 - *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, Novo Nordisk 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, Illumina, Intellia Therapeutics, Novartis, and Regeneron. 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.*

Clinical Experts

- **Miguel Escobar, MD.** Director of the Clinical Research Center and Professor of Medicine and Pediatrics at McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth).
 - *Dr. Escobar has received honoraria for participating in advisory boards and/or consultation for NovoNordisk, CSL Behring, Genentech, Biomarin, Sanofi, Takeda, Pfizer, NHF, Bayer, Hemabiologics/LFB, UniQure, Magellan. The University of Texas also received funds for participating in research sponsored by UniQure, NovoNordisk, Takeda, Bayer, ATHN, Sanofi.*
- **Margaret V. Ragni, MD, MPH.** Professor of Medicine and Clinical Translational Research, University of Pittsburgh. Director, Hemophilia Center of Western PA.
 - *Dr. Ragni is a member of BioMarin Advisory Board; Consultant, Advisory Board member and Symposium Speaker for Takeda. She also receives research funding (received by the university) from Biomarin and SPARK.*



Why are we here today?

One would think that once you are treated prophylactically you are able to avoid future setbacks. Wrong! Not in the life of a person with hemophilia. There are still times when you need to drop everything to head to the emergency room (ER) to seek treatment. Living in a rural area where hemophilia is uncommon and there is a lack of knowledge of bleeding disorders makes seeking care difficult. Therefore, when we need to head to the ER, we call not only the Hemophilia Treatment Center but also the pediatrician and the ER to give them our estimated arrival time.....

Ashley, mother of Jackson (person with hemophilia B)

<https://www.cdc.gov/ncbddd/hemophilia/stories/ashley.html>

Why Are We Here Today?

- What happens the day these treatments receive FDA approval?
- Questions about:
 - Evidence – what are the risks and benefits?
 - How do new treatments fit into the evolving landscape?
 - What are reasonable prices and costs to patients, the health system, and the government?
 - What lessons are being learned to guide our actions in the future?

The Impact on Rising Health Care Costs for Everyone



<https://khn.org/news/article/diagnosis-debt-investigation-100-million-americans-hidden-medical-debt/>

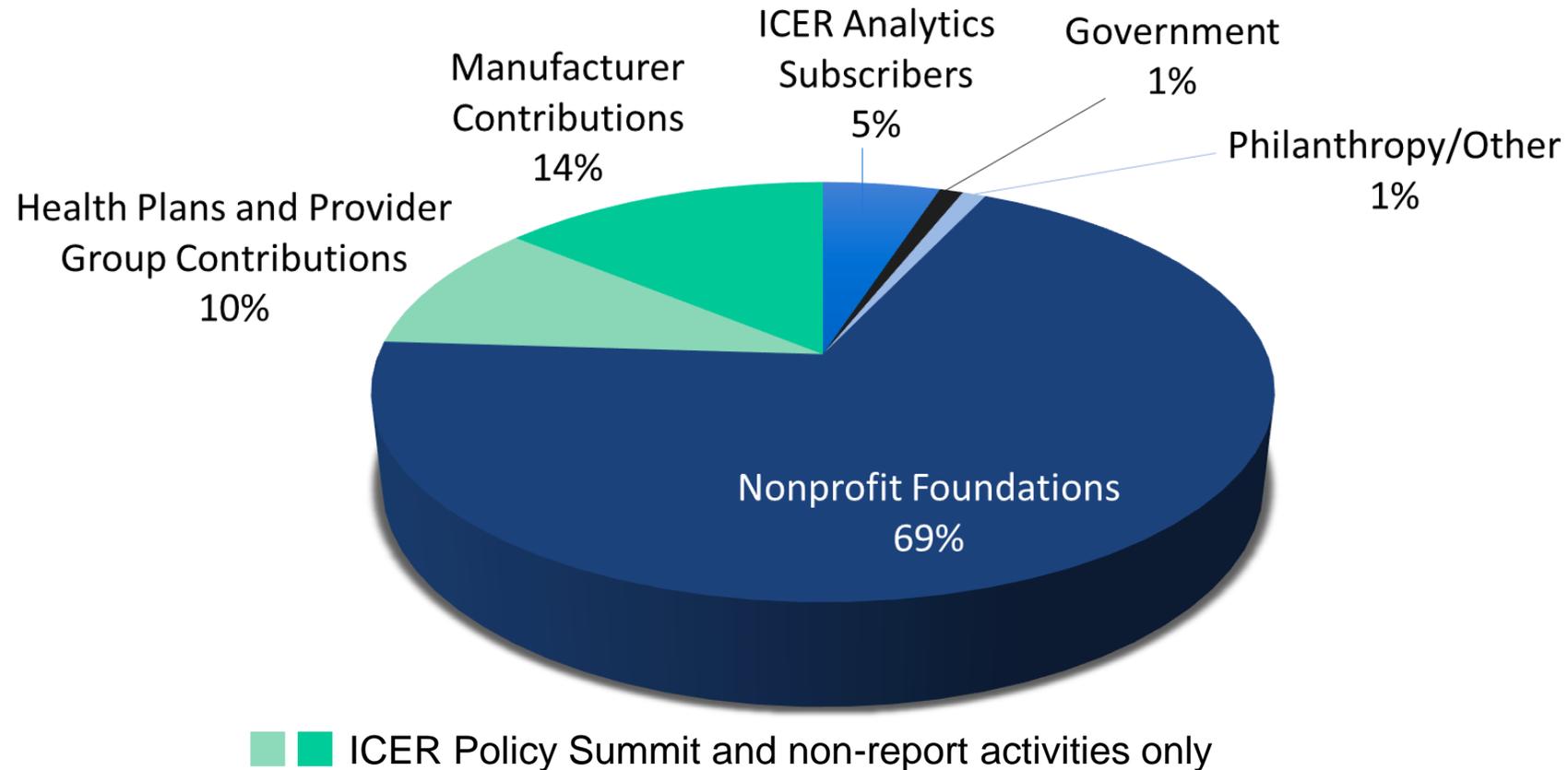


Organizational Overview

- California Technology Assessment Forum (CTAF)
- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2022

<https://icer.org/who-we-are/independent-funding/>



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 cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
 - **Steven W. Pipe, MD**, Professor of Pediatrics and Pathology, Michigan Medicine, University of Michigan
 - **Margaret V. Ragni, MD, MPH**, Professor of Medicine and Clinical Translational Research, University of Pittsburgh; Director, Hemophilia Center of Western PA
 - **Mark Skinner, JD**, President & CEO, Institute for Policy Advancement Ltd.
- How is the evidence report structured to support CTAF voting and policy discussion?

Value Assessment Framework: Long-Term Value for Money

Special Social/Ethical Priorities

Benefits Beyond “Health”

Total Cost Overall
Including Cost Offsets

Health Benefits:
Return of Function, Fewer Side Effects

Health Benefits:
Longer Life

Agenda (PT)

9:00	Meeting Convened and Opening Remarks
9:20	Presentation of the Clinical Evidence
10:00	Presentation of the Economic Model
10:40	Public Comments and Discussion
11:15	Lunch Break
11:50	CTAF Deliberation and Voting on Clinical Effectiveness and Value
12:50	Break
1:00	Policy Roundtable
2:30	Reflections from CTAF
3:00	Meeting Adjourned

Presentation of the Clinical Evidence

Jeffrey A. Tice, MD

Professor of Medicine

School of Medicine, University of California, San Francisco



Key Collaborators

- **Shahariar Mohammed Fahim**, Research Lead, ICER
- **Belen Herce-Hagiwara**, Research Assistant, ICER
- **Janet Chu, MD, MPH, MAS**, Assistant Professor of Medicine, UCSF

Disclosures:

We have no conflicts of interest relevant to this report

Hemophilia

- Deficiency in factor IX (Hemophilia B)
- Deficiency in factor VIII (Hemophilia A)
- X-linked recessive (male predominance)
- Increased tendency to bleed
 - Life-threatening
 - Joints leading to progressive damage and disability

Prophylaxis with Factor Replacement

- Burdensome
 - IV administration
 - Frequent
 - Venous access can be difficult in young children
 - Elderly patients can find self-administration challenging
 - Adherence is a substantial problem

Patient and Caregiver Restrictions

- Burdens

- Bleeding risk
- Access to specialized care
- Factor accessibility
- Time limitations

- Impacts

- Patient career
- Patient education
- Patient recreation
- Patient residence
- Caregiver carerer

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 adequately high factor levels

Hemophilia B

Etranacogene Dezaparvovec (CSL Behring)

- “EtranaDez”
- AAV5 liver-directed gene therapy for hemophilia B
- One-time administration to adults
- Priority review from FDA

Scope of Review: Hemophilia B

- **Population:** Adults with hemophilia B without inhibitors to factor IX who would be appropriate for routine prophylaxis with factor IX
- **Intervention:**
 - Etranacogene dezaparvovec ‘EtranaDez’ gene therapy
- **Comparator:**
 - Prophylaxis with factor IX

Key Clinical Trials: Hemophilia B

Study	Group	N	F/U Months	Age, Years	Primary outcome
HOPE B	Etranacogene Dezaparvovec	54	24	41.5	Annualized bleeding rate at 12 months

Inclusion: Age \geq 18 years, moderate to severe disease on prophylaxis

Exclusion: Factor IX inhibitor

HOPE B Trial Etranacogene Dezaparvovec Reduction in Annualized Bleeding Rates*

Bleed Type	Relative Risk Reduction
Treated Joint Bleeds	80%
Treated Bleeds	77%
All Bleeds	64%

* Months 7-18 after treatment

HOPE B Trial Etranacogene Dezaparvovec Factor IX Levels over Time

	Month		
	6	12	18
Factor IX Activity (IU/dL) <i>Mean (range)</i>	39 (8-97)	41 (6-113)	37 (4-123)

Long-term results from Phase 2 Trial: N=3

- Factor IX levels
 - 50 IU/dL at 30 months (n=3)
 - 36.9 IU/dL at 36 months (n=2)
- No resumption of Factor IX prophylaxis

HOPE B Trial Etranacogene Dezaparvovec

Harms

- Liver enzyme elevation
 - 17% treated with corticosteroids for a mean of 79 days
- Headaches, flu-like illness, infusion reactions
- 1 death urosepsis: assessed as unrelated to treatment
- 1 hepatocellular carcinoma: unrelated to treatment

Etranacogene Dezaparvovec

Uncertainties and Controversies

- Single arm design: selection bias
- Very few patients treated to date
- Follow-up relatively short when anticipating lifelong benefits
- Long term harms possible
 - Oncogenesis from insertional mutagenesis
 - Liver injury

Public Comments Received

- There is sufficient certainty from the etranacogene dezaparvovec data to warrant a B or an A rating

Summary: Etranacogene Dezaparvovec vs. Factor IX

- Marked improvements in most patients
 - Marked reduction in burdens of treatment
 - Significant uncertainties due to study design, small n, short FU
 - Antibodies to AAV5 perhaps limiting better future treatments
 - Potential long-term harms including oncogenesis
-
- **Moderate certainty of a small or substantial net health benefit (B+)**

Hemophilia A

Valoctocogene Roxaparvovec (Roctavian, BioMarin)

- “Valrox”
- AAV5 liver-directed gene therapy for hemophilia A
- One-time administration to adults
- PDUFA date March 31, 2023

Scope of Review: Hemophilia A

- **Population:** Adults with hemophilia A without inhibitors to factor VIII who would be appropriate for routine prophylaxis with factor VIII
- **Intervention:**
 - Valoctocogene roxaparvovec ‘Valrox’ gene therapy
- **Comparators:**
 - Prophylaxis with emicizumab
 - Prophylaxis with factor VIII

Key Clinical Trials: Hemophilia A

Study	Group	N	F/U Months	Age, Years	Primary outcome
GENEr8-1	Valoctocogene roxaparvovec	134	24	31.7	<ol style="list-style-type: none">1. Factor VIII level at 12 months2. Annualized bleeding rate at 12 months

Inclusion: Age \geq 18 years, on prophylaxis

Exclusion: Factor VIII inhibitor

GENEr-8 Trial: Valoctocogene Roxaparvovec Reduction in Annualized Bleeding Rates*

Bleed Type	Relative Risk Reduction
Treated Joint Bleeds	84%
Treated Bleeds	84%
All Bleeds	NR

* Weeks 5-60 after treatment

GENEr-8 Trial: Valoctocogene Roxaparvovec Factor VIII Levels over Time

	Month	
	12	24
Factor VIII Activity (IU/dL) <i>Mean (interquartile range)</i>	42.2 (11-55)	24.2 (6-29)

Long-term results from Phase 2 Trial: N = 7

- Factor VIII levels
 - From 64 IU/dL at year 1 to 9.8 IU/dL at year 6
- No resumption of Factor VIII prophylaxis through 6 years

GENEr-8 Trial: Valoctocogene Roxaparvovec Harms

- Liver enzyme elevation
 - 79% treated with corticosteroids for a mean of 230 days
- Headaches, nausea, arthralgias, fatigue
- 1 acinar cell carcinoma: assessed as unrelated to treatment
- 1 acute leukemia: unrelated on initial analysis

HAVEN 3 Trial, Group D: Emicizumab Reduction in Annualized Bleeding Rates*

Bleed Type	Relative Risk Reduction
Treated Joint Bleeds	NR
Treated Bleeds	68%
All Bleeds	63%

*Weeks 1-24

Valoctocogene Roxaparvovec

Uncertainties and Controversies

- Single arm design: selection bias
- Very few patients treated to date
- Follow-up relatively short when anticipating lifelong benefits
- Factor levels declining over time
- Target cell is hepatocytes; factor VIII normally made in endothelial cells
- Long term harms possible
 - Oncogenesis from insertional mutagenesis
 - Liver injury

Public Comments Received

- Data on the number of patients treated with valoctocogene roxaparvovec who return to factor VIII prophylaxis were reported at a recent conference
- Steroid use following therapy with valoctocogene roxaparvovec will be lower in the real world

Summary: Valoctocogene Roxaparovec vs. Emicizumab

- No head-to-head comparisons
- Different inclusion / exclusion criteria
- Similar reductions in bleeding events
- Different adverse events and burdens of treatment

- **Low certainty of evidence: Insufficient (I)**

Summary: Valoctocogene Roxaparvovec vs. Factor VIII

- Marked improvements in many patients for a period of years
- Decline in Factor VIII levels over time raise concerns about the durability of treatment
- Marked reduction in burdens of treatment
- Significant uncertainties due to study design, small n, short FU
- Antibodies to AAV5 perhaps limiting better future treatments
- Potential long-term harms including liver disease and oncogenesis

- **Moderate certainty of a comparable, small, or substantial health benefit (C++)**

Potential Other Benefits / Contextual Considerations

Potential Other Benefits and Contextual Considerations for Gene Therapy for Hemophilia

- With current therapy (prophylaxis), the short-term risk for disability or death is low
- Normal life expectancy, but significant disability from progressive joint disease
- Greater freedom to achieve goals (education, family, work, recreation)
- Relief of caregiver burden
- Reduced complexity of care after 1st year: no longer needing IV therapy

Questions?

Presentation of the Economic Model

Surrey Walton, PhD

Professor

Department of Pharmacy Systems, Outcomes and Policy, College of Pharmacy,
University of Illinois Chicago



Key Review Team Members

- **Ashton Moradi**, Health Economist, ICER
- **Jyotirmoy Sarker**, PhD student, University of Illinois Chicago

Disclosures:

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

The University of Illinois 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.

Objective

This project involves two separate objectives as follows:

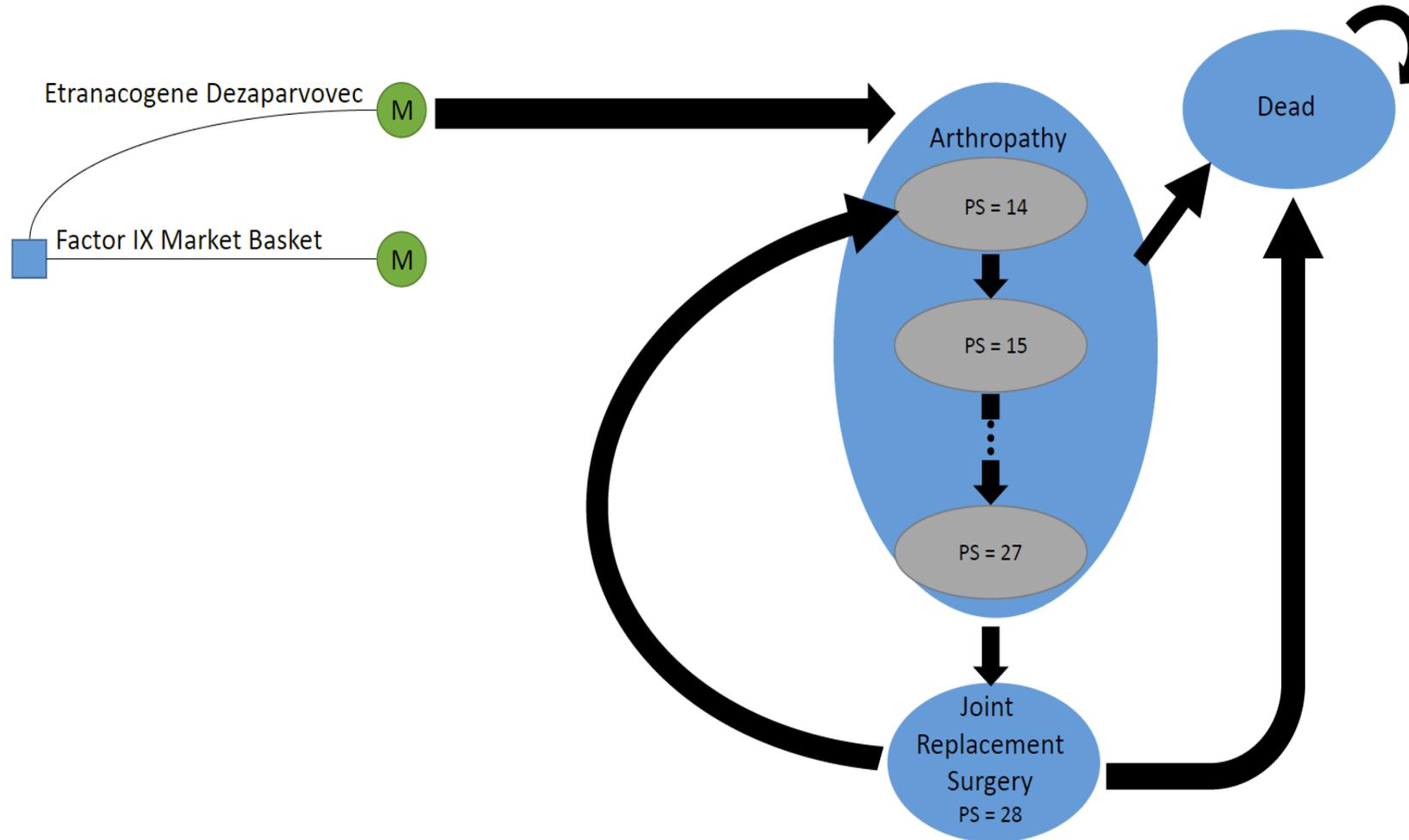
1. Evaluate the lifetime cost effectiveness of using etranacogene dezaparvovec (etranadez) relative to treatment with factor IX
2. Evaluate the lifetime cost effectiveness of using valoctocogene roxaparvovec (valrox) relative to treatment with emicizumab (emi)

Methods in Brief

Methods Overview

- **ICER Frameworks:** Ultra rare and Single/Short-term Transformative Therapy
- **Model:** Semi-Markov Model
- **Setting:** United States
- **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 equal value life year (evLY) gained; Cost per bleed averted

Model Schematic



Key Assumptions in Both Models

- Estimates of specific types of bleeds relative to all bleeds are based on proportions in the HAVEN 3 and POTTER trials
- Gene therapy patients return to prophylaxis when efficacy of the gene therapy is projected to end
- No mortality effects of the treatments

Key Assumptions Specific to Hemophilia B Model

- Bleed rates for etranacogene dezaparvovec and factor IX are taken from the HOPE trial
- Available evidence on factor IX levels across time are used to consider the impact of declining efficacy across time for etranadez. This involves using adjusted (0.43) estimates of bleeds relative to factor VIII in Hemophilia A patients (Uijl 2011; Soucie 2018)
- Projected factor IX activity levels below 5 (IU dl⁻¹) are assumed to lead to 5% of etranacogene dezaparvovec patients initiating factor IX and at levels below 1 all patients are assumed to initiate factor IX

Key Assumptions Specific to Hemophilia A Model

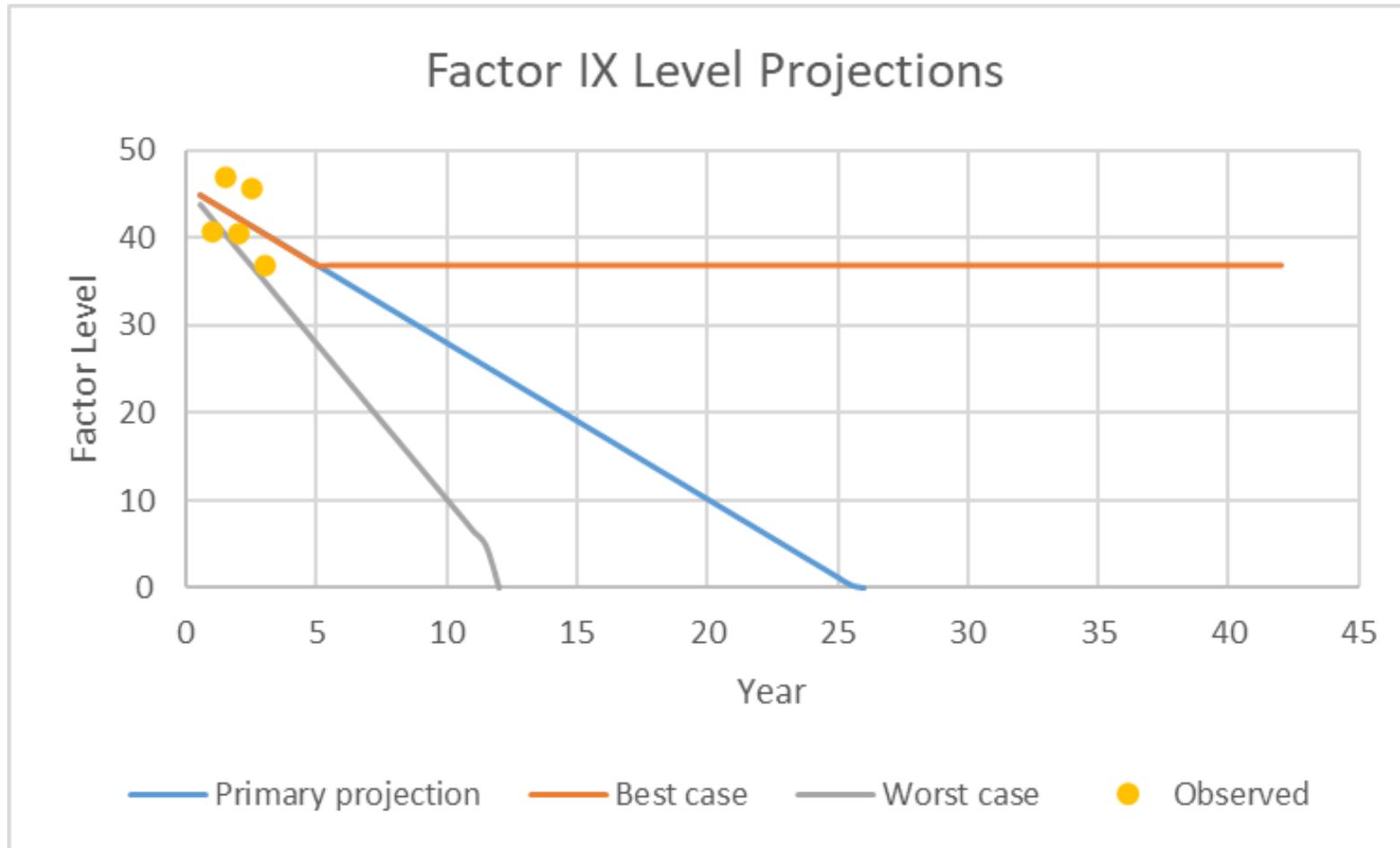
- Bleed rates across time for valoctocogene roxaparvovec in the hemophilia A model are derived from GENER8-v1 data and then projected on factor levels (Uijl 2011)
- 2% of (assumed high bleed rate) patients fail each year in the first four years and receive a payment rebate approximately equal to a pro-rated maximum of four years of prophylaxis treatment costs
- At projected factor activity levels below 5 (IU/dL), 5% of valoctocogene roxaparvovec patients are assumed to initiate emicizumab. At projected factor activity levels below 1, all valoctocogene roxaparvovec patients are assumed to initiate emicizumab.
- Bleed rates are taken from the HAVEN 3 group D trial for emicizumab.

Initial Bleed Rates for Hemophilia B

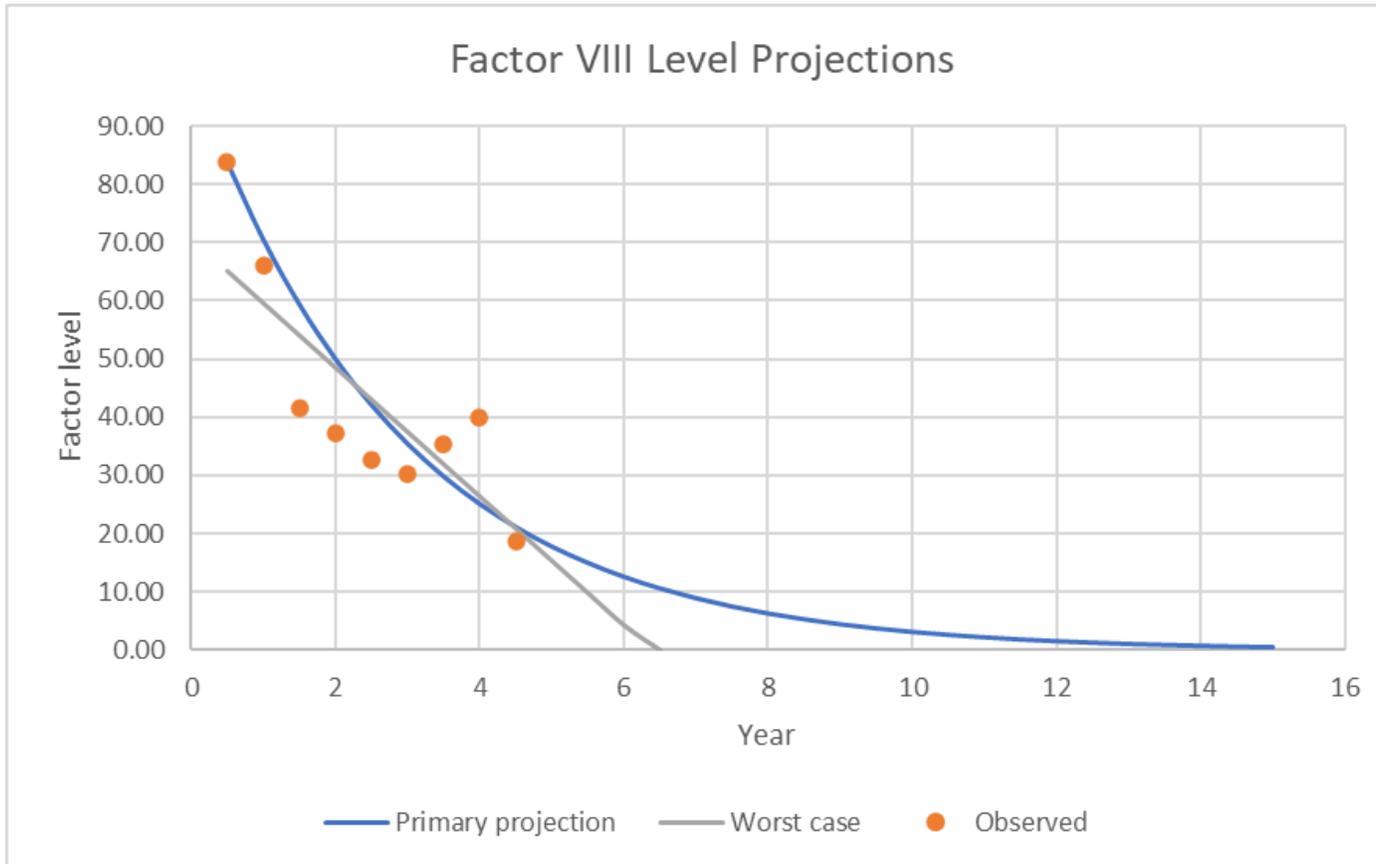
Drug	All Bleeds	All Joint Bleeds
Etranacogene Dezaparvovec	1.51	0.51
Factor IX	4.19	2.35

Rates are from the HOPE trial

Projected Factor IX Levels Across Cycles for Model 1



Projected Factor VIII Levels Across Cycles for Model 2



Optimistic case mirrors primary projection's factor levels but with lower bleed rates at low factor levels

Projecting Bleed Rates from Factor VIII Levels

Factor VIII	All Bleeds	Joint Bleeds
11-40*	0.451	0.297
9	1.936	1.277
7	2.311	1.525
1-3	7.280	4.805

*For Hemophilia B, rates were adjusted by 0.43 (Soucie 2018). Rates are used in both models when they were higher than the available estimates for early cycles.

Some Selected Bleed rates in Hemophilia A

Drug	All Bleeds	All Joint Bleeds
Emicizumab	3.00	1.98
Valoctocogene Roxaparvovec, Year 2	0.49	0.33
Valoctocogene Roxaparvovec, Year 10	7.28	4.82
Valoctocogene Roxaparvovec, Year 20	3.00	1.98

Health State Utilities

Age	Pettersson Score (PS) 14-27	Surgery*	Source
18-30	0.94	0.72	O'Hara 2018; Laupacis 1993
31-40	0.84	0.65	O'Hara 2018; Laupacis 1993
41-50	0.86	0.61	O'Hara 2018; Laupacis 1993
51-60	0.83	0.56	O'Hara 2018; Laupacis 1993
61 and over	0.73	0.48	O'Hara 2018; Laupacis 1993

*The utility of surgery is based on one month of utility at 0.32 and 5 months of utility in Pettersson Score 14-27.

Bleed Type	Disutility per Cycle*	Source
Treated Bleed Not Into a Target Joint	-0.002	Neufeld 2012
Treated Target Joint Bleed	-0.003	Mazza 2016

*Based on -0.16 and -0.28 disutility per day (2 days full, 5 half per bleed) for a treated bleed and treated joint bleed, respectively.

Treatment Costs for Hemophilia B

Drug	Net Price per Dose	Discount Relative to Net	Net Price per Year
Etranacogene Dezaparvovec	\$4,000,000	N/A	\$4,000,000
Factor IX	\$10,903*	N/A	\$688,941

The price for etranadez is a manufacturer provided placeholder cost

*Based on ASP/IU with no discount for a patient weighing 81.4 kg and most common dose.

Treatment Costs Hemophilia A

Drug	Price per Dose	Discount per Dose	Net Price per Year
Valoctogogene Roxaparvovec	\$2,500,000*	N/A	\$2,500,000
Emicizumab	\$25,706**	12%‡	\$639,543†

*The price for valoctocogene roxaparvovec is a placeholder cost based on industry projections

**The price for emicizumab is based on a patient weighing 81.4 kg; emicizumab price per dose corresponds to WAC

† Assumes 3 mg/kg every 7 days for month 1; 3mg/kg every 14 days for month 2+

‡ Based on most recent [U.S. Department of Veterans Affairs Federal Supply Schedule Service](#) rate, as SSR rebate data did not exist for emicizumab

Per Bleed Costs

Age (Years)	Non-Drug Cost	Source
18-45	\$4,832.33	Shrestha 2017
>45	\$7,197.87	Shrestha 2017

Per Bleed Drug Cost for Hemophilia B: \$10,903

Per Bleed Drug Cost for Hemophilia A: \$7,253 (81.4 kg patient)

Societal Perspective Per Bleed Additional Costs: \$1,235.30 (Zhou 2015)

Per Cycle Costs Arthropathy and Surgery

State	Cost	Source
Arthropathy (PS 14-27)	\$648.90 per cycle based on office visits and joint related tests	O'Hara 2018; CMS
Surgery	Above plus \$46,931.65	Earnshaw 2015

Results

Full Cost Offset Results: Model 1

Conventional Cost Effectiveness for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Etranacogene Dezaparvovec	\$9,000,000*	\$9,954,000*	182	17.96	27.13	17.96
Factor IX	\$14,029,000	\$15,797,000	247	17.32	27.13	17.32

*At a manufacturer-provided placeholder price of \$4,000,000
QALYs: quality-adjusted life years, evLYs: equal value of life years

Full Cost Offset Results: Model 2

Conventional Cost Effectiveness for Valoctocogene roxaparvovec Compared to Emicizumab

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene roxaparvovec	\$13,635,000*	\$14,077,000*	171	17.57	27.13	17.57
Emicizumab	\$17,492,000	\$18,084,000	177	17.47	27.13	17.47

*Using a placeholder price of \$2,500,000; interpret cost findings with caution
QALYs: quality-adjusted life years, evLYs: equal value of life years

Sensitivity and Scenario Analyses

- Conducted one-way and probabilistic sensitivity analyses
- In the conventional sensitivity analyses, none of the conclusions changed in either model
 - This was also true across most of the scenario analyses, including doubling the bleeding rates, having all patients switch at a factor level of 5, optimistic and pessimistic duration models, and having patients start and return to a Pettersson score of 20.

Durability Thresholds

- In the full cost offset model, we varied time until 100% switch cycle by cycle.
 - In model 1, at a placeholder price of \$4,000,000, etranacogene dezaparovec becomes cost saving at 8.5 years.
 - In model 2, at a placeholder price of \$2,500,000, valoctocogene roxaparovec becomes cost saving after 4 years.

\$150,000 Cost-Offset Cap Analysis

- Comparators not high-value care and cost > \$300,000 per year
 - ICER suggests cost-offset cap of \$150,000 per year most policy relevant

Gene Therapy	Gene Therapy Cost	Cost Offsets for \$150k Cap (Full Cost Offsets)	Incremental Costs for \$150k Cap (Full Cost Offsets)	Incremental QALYs	Cost per QALY for \$150k Cap
Etranacogene dezaparvovec	*\$4 Million	-\$2.9 Million (-\$9.8 Million)	\$1,140,000 (cost saving)	0.64	\$1.8 Million / QALY
Valoctocogene roxaparvovec	*\$2.5 Million	-\$1.97 Million (-\$6.5 Million)	\$530,000 (cost saving)	0.10	\$5.3 Million / QALY

*At a manufacturer provided placeholder price of \$4,000,000 and assumed placeholder price of \$2,500,000 respectively
 QALYs: quality-adjusted life years

Health Benefit Price Benchmarks (HBPBs)

Annual Price Benchmarks for Etranacogene Dezaparvovec

Intervention	Annual Price at \$100,000 Threshold	Annual Price at \$150,000 Threshold
\$150,000 Annual Cap Analysis	\$2,926,000	\$2,958,000

Health Benefit Price Benchmarks (HBPBs)

Annual Price Benchmarks for Valoctocogene Roxaparvovec

Intervention	Annual Price at \$100,000 Threshold	Annual Price at \$150,000 Threshold
\$150,000 Annual Cap Analysis	\$1,956,000	\$1,961,000

Comments Received

- Projected bleed rates are too high and switching rates too low at low projected factor levels.
- The Hemophilia A model should include factor VIII as a comparator
- There is not enough uncertainty projected in durability of the gene therapies.
- The models do not adequately project heterogeneity in patient responses.

Uncertainties and Controversies

- There was limited data on the efficacy and duration of the gene therapies across time
- The relationship between joint bleeds and surgery is imperfect and the model assumes one joint surgery at a time likely undercounting surgeries
- Many of the utility scores in the models come from patients with hemophilia
- The bleed data for both arms in model 1 come from trial data which may differ from rates in actual practice
- The bleed comparisons in model 2 are based on indirect comparisons across patient populations and settings
- Finally, we have placeholder prices for valoctocogene roxaparvovec and for etranacogene dezaparvovec

Conclusions

- There are very large lifetime costs associated with both the treatments and comparators in both models
- The gene therapies are projected to have large cost savings and small QALY gains in the conventional full cost-offset analysis
- In the capped cost-savings analysis of \$150,000 per year and assuming the placeholder prices, the gene therapies do not achieve common cost-effectiveness benchmarks

Questions?



Public Comment and Discussion

Manufacturer Public Comments

Speaker	Title	Affiliation
Debbie Benson-Kennedy, MD	Vice President, Medical Affairs	CSL Behring
Wing Yen Wong, MD	Special Advisor, Worldwide Research & Development (WWRD)	BioMarin Pharmaceutical, Inc.
Richard Ko, MD, MHS, MS	Executive Medical Director	Genentech

Debbie Bensen-Kennedy, MD

Vice President Medical Affairs, CSL Behring

Conflicts of Interest:

- *Dr. Bensen-Kennedy is the employee of a healthcare company, CSL Behring*
- *Dr. Bensen-Kennedy has equity interests in employee stock in excess of \$10,000.*

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Wing Yen Wong, MD

Special Advisor, Worldwide Research & Development, BioMarin

Conflicts of Interest:

- *Dr. Wong has received salary from BioMarin Pharmaceutical Inc. in excess of \$5,000*
- *Dr. Wong has had equity interests such as individual stocks, stock options or other ownership interests in BioMarin in excess of \$10,000.*
- *Dr. Wong has had status or position as an officer, board member, trustee, owner, or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies.*
- *Dr. Wong has been a patent holder for Vonvendi, Baxter Healthcare*

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Richard Ko, MD, MHS, MS

Executive Medical Director, Genentech

Conflicts of Interest:

- *Dr. Ko is an employee of a health care company, Genentech. Dr. Ko received salary in excess of \$5,000 from Genentech.*
- *Dr. Ko has had equity interests in stock options in Roche in excess of \$10,000.*

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Patient Public Comments

Speaker
Jim Rippy , Person with hemophilia A, Arkansas, USA
Will Hubbert, BA , Person with hemophilia A, Virginia, USA
Nathan Schaefer, MSW (joint comment from Hemophilia Federation of America & National Hemophilia Foundation)

Will Hubbert, BA

Conflicts of Interest:

- Mr. Hubbert is participating in ICER's public meeting in his personal capacity as a person with a bleeding disorder. He has had status or position as an officer, board member, trustee, owner, or employee of a health care organization, the National Psoriasis Foundation, which receives more than 25% of its funding from health care companies. A full list of NPF's sponsors can be found here:
<https://www.psoriasis.org/npf-partnerships/>*

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Nathan Schaefer, MSW, National Hemophilia Foundation & Hemophilia Federation of America

Conflicts of Interest:

- *The Hemophilia Federation of America (HFA) has received consulting fees or honoraria from various health care companies. A full list of sponsors can be found here: <https://www.hemophiliafed.org/our-sponsors/>*
- *The National Hemophilia Foundation (NHF) has no relevant conflicts to disclose.*

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Lunch

Meeting will resume at 11:50 am PST





Voting Questions



Clinical Evidence Questions

Patient Population for question 1: Adults ≥ 18 years of age with hemophilia B without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

1. Is the evidence adequate to demonstrate that the net health benefit of etranacogene dezaparvovec is superior to that provided by prophylaxis with Factor IX?

A. Yes

B. No



Patient Population for questions 2 – 3a: Adults ≥ 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

2. Is the evidence adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior to that provided by prophylaxis with Factor VIII?

A. Yes

B. No



Patient Population for questions 2 – 3a: Adults \geq 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

3. Is the evidence adequate to distinguish the net health benefit between valoctocogene roxaparvovec and prophylaxis with emicizumab?

A. Yes

B. No



Patient Population for questions 2 – 3a: Adults ≥ 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

3a. If the answer to question 3 is yes, is the evidence adequate to demonstrate that the net health benefit of valoctogene roxaparvovec is superior to that provided by emicizumab?

A. Yes

B. No



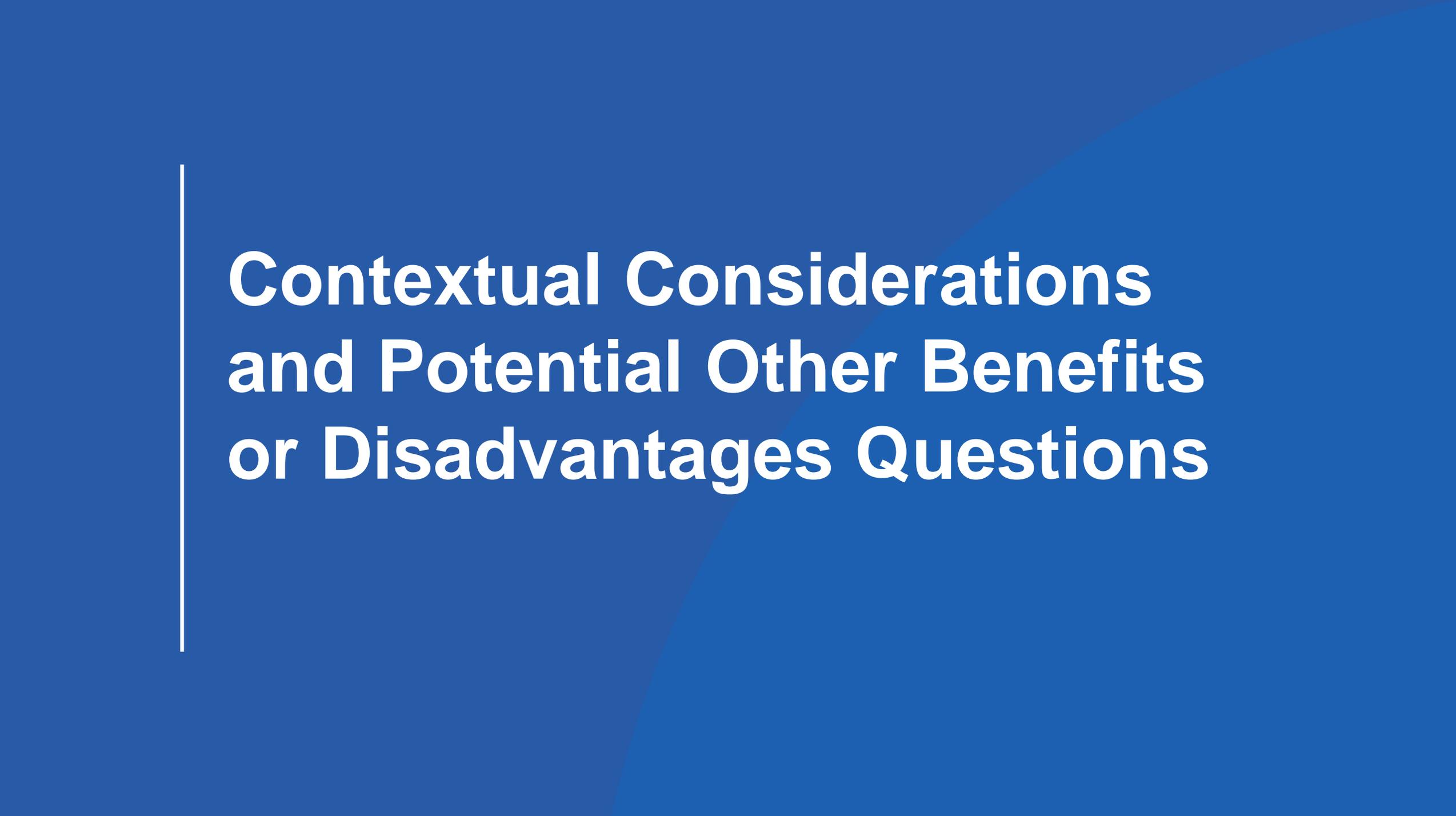
Patient Population for questions 2 – 3a: Adults ≥ 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

3b. If the answer to 3a is no, is the evidence adequate to demonstrate that the net health benefit of emicizumab is superior to that provided by valoctocogene roxaparvovec?

A. Yes

B. No



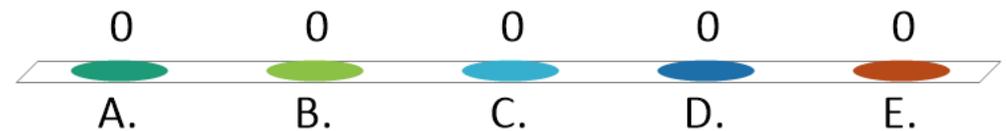


Contextual Considerations and Potential Other Benefits or Disadvantages Questions

When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for hemophilia A, on the basis of the following contextual considerations:

4. Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability

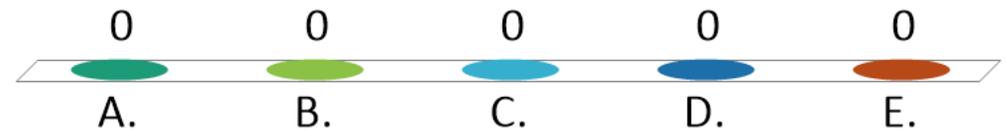
- A. Very low priority
- B. Low priority
- C. Average priority
- D. High priority
- E. Very high priority



When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for hemophilia A, on the basis of the following contextual considerations:

5. Magnitude of the lifetime impact on individual patients of the condition being treated

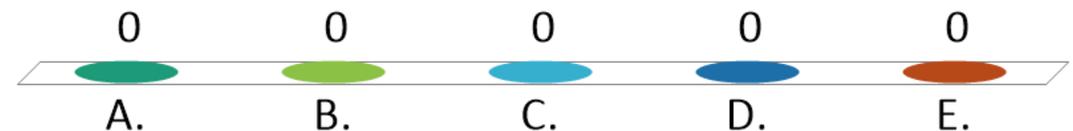
- A. Very low priority
- B. Low priority
- C. Average priority
- D. High priority
- E. Very high priority



When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for hemophilia B, on the basis of the following contextual considerations:

6. Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability

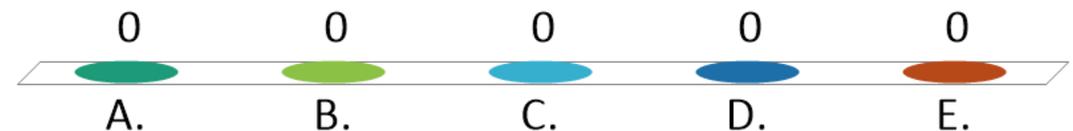
- A. Very low priority
- B. Low priority
- C. Average priority
- D. High priority
- E. Very high priority



When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for hemophilia B, on the basis of the following contextual considerations:

7. Magnitude of the lifetime impact on individual patients of the condition being treated

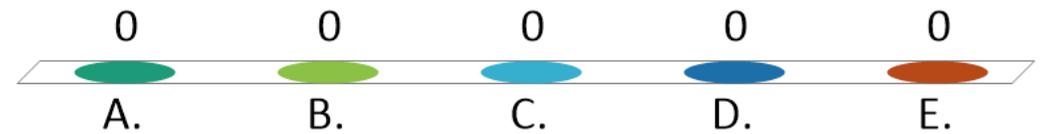
- A. Very low priority
- B. Low priority
- C. Average priority
- D. High priority
- E. Very high priority



What are the relative effects of etranacogene dezaparvovec versus prophylaxis with Factor IX on the following outcomes that inform judgment of the overall long-term value for money of etranacogene dezaparvovec?

8. Patients' ability to achieve major life goals related to education, work, or family life

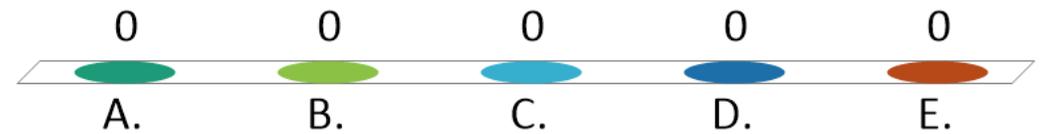
- A. Major negative effect
- B. Minor negative effect
- C. No difference
- D. Minor positive effect
- E. Major positive effect



What are the relative effects of etranacogene dezaparvovec versus prophylaxis with Factor IX on the following outcomes that inform judgment of the overall long-term value for money of etranacogene dezaparvovec?

9. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

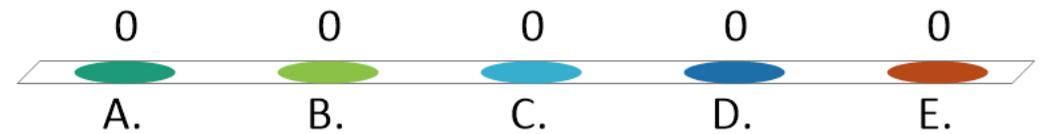
- A. Major negative effect
- B. Minor negative effect
- C. No difference
- D. Minor positive effect
- E. Major positive effect



What are the relative effects of etranacogene dezaparvovec versus prophylaxis with Factor IX on the following outcomes that inform judgment of the overall long-term value for money of etranacogene dezaparvovec?

10. Patients' ability to manage and sustain treatment given the complexity of regimen

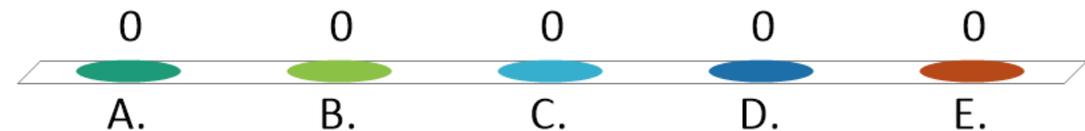
- A. Major negative effect
- B. Minor negative effect
- C. No difference
- D. Minor positive effect
- E. Major positive effect



What are the relative effects of valoctocogene roxaparvovec versus prophylaxis with emicizumab on the following outcomes that inform judgment of the overall long-term value for money of valoctocogene roxaparvovec?

11. Patients' ability to achieve major life goals related to education, work, or family life

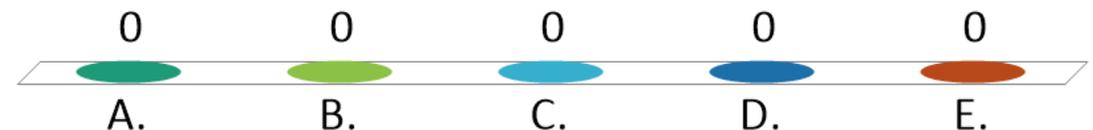
- A. Major negative effect
- B. Minor negative effect
- C. No difference
- D. Minor positive effect
- E. Major positive effect



What are the relative effects of valoctocogene roxaparvovec versus prophylaxis with emicizumab on the following outcomes that inform judgment of the overall long-term value for money of valoctocogene roxaparvovec?

12. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

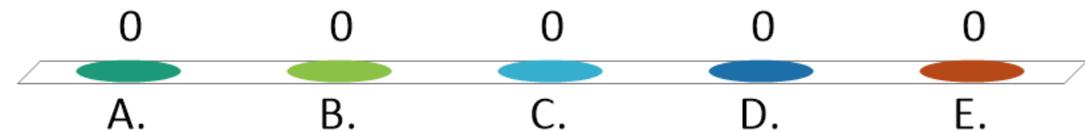
- A. Major negative effect
- B. Minor negative effect
- C. No difference
- D. Minor positive effect
- E. Major positive effect



What are the relative effects of valoctocogene roxaparvovec versus prophylaxis with emicizumab on the following outcomes that inform judgment of the overall long-term value for money of valoctocogene roxaparvovec?

13. Patients' ability to manage and sustain treatment given the complexity of regimen

- A. Major negative effect
- B. Minor negative effect
- C. No difference
- D. Minor positive effect
- E. Major positive effect



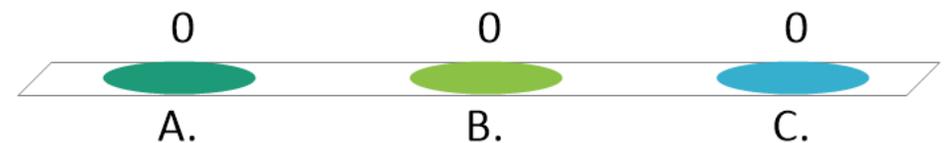


Long-Term Value for Money Questions

14. Given the available evidence on comparative effectiveness, incremental cost effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with etranacogene dezaparovec versus prophylaxis with Factor IX?*

- A. Low long-term value for money at current pricing
- B. Intermediate long-term value for money at current pricing
- C. High long-term value for money at current pricing

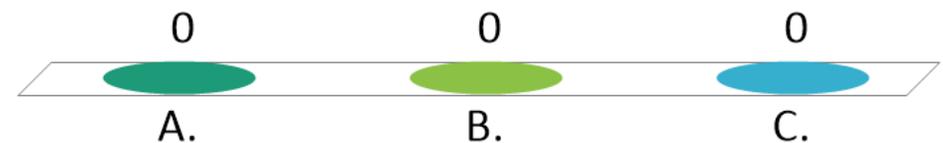
*We will take this vote based on the placeholder price provided by the manufacturer.



15. Given the available evidence on comparative effectiveness, incremental cost effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with valoctocogene roxaparvovec versus prophylaxis with emicizumab?⁺

- A. Low long-term value for money at current pricing
- B. Intermediate long-term value for money at current pricing
- C. High long-term value for money at current pricing

⁺This vote will only be taken if a price becomes available for valoctocogene roxaparvovec.



Break

Meeting will resume at 1 pm PST



Policy Roundtable

Participant	Conflict of Interest
Debbie Benson-Kennedy, MD , VP Medical Affairs, CSL Behring	Dr. Bensen-Kennedy is a full-time employee of CSL Behring.
Chuck Bucklar, BS , SVP Commercial Operations, BioMarin	Mr. Bucklar is a full-time employee of BioMarin.
Miguel A. Escobar, MD , Professor of Medicine and Pediatrics, McGovern Medical School	Dr. Escobar has received honoraria from NovoNordisk, CSL Behring, Genentech, Biomarin, Sanofi, Takeda, Pfizer, NHF, Bayer, Hemabiologics/LFB, UniQure, Magellan.
Leslie Fish, PharmD , IPD Analytics	Dr. Fish is a full-time employee of IPD Analytics.
Brian O'Mahony, FACSLM , Chief Executive, Irish Hemophilia Society	Mr. O'Mahony has received consulting fees or honoraria from Bayer Healthcare and BioMarin.
Margaret Ragni, MD, MPH , Professor of Medicine and Clinical and Translational Science, University of Pittsburgh Medical Center	Dr. Ragni is a member of BioMarin Advisory Board; Consultant, Advisory Board member and Symposium Speaker for Takeda. Her university also receives funding from Biomarin and SPARK.
Michael Sherman, MD, MBA, MS , Executive VP and Chief Medical Officer, Point32Health	Dr. Sherman is a full-time employee of Point32Health.
Mark Skinner, JD , President & CEO, Institute for Policy Advancement Ltd.	Mr. Skinner has received honoraria from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, Novo Nordisk and the Blue Cross Blue Shield Association.

CTAF Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around December 19, 2022
 - Includes description of CTAF votes, deliberation, policy roundtable discussion
- Materials available at: <https://icer.org/assessment/hemophilia-a-and-b-2022/#overview>

Adjourn



References