Relationship between transgene-produced FVIII and bleeding rates 2 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1

Johnny Mahlangu,[1] *Hervé Chambost,*[2] *Sheng-Chieh Chou,*[3] *Amy Dunn,*[4] *Annette von Drygalski,*[5] *Radoslaw Kaczmarek,*[6,7] *Gili Kenet,*[8] *Michael Laffan,*[9] *Andrew D Leavitt,*[10] *Bella Madan,*[11] *Jane Mason,*[12,13] *Johannes Oldenburg,*[14] *Margareth C Ozelo,*[15] *Flora Peyvandi,*[16,17] *Doris V Quon,*[18] *Mark T Reding,*[19] *Susan Shapiro,*[20–22] *Hua Yu,*[23] *Tara M Robinson,*[23] *Steven W Pipe*[24]

[1]Hemophilia Comprehensive Care Center, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand and NHLS, Johannesburg, South Africa; [2]AP-HM, Department of Pediatric Hematology Oncology, Children Hospital La Timone & Aix Marseille University, INSERM, INRA, C2VN, Marseille, France; [3]Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Nationwide Children's Hospital Division of Hematology, Oncology and Bone Marrow Transplant and The Ohio State University College of Medicine, Columbus, OH, USA; [5]Department of Medicine, University of California San Diego, San Diego, CA, USA; [6]Department of Pediatrics, Indiana University School of Medicine, IUPUI-Wells Center for Pediatric Research, Indianapolis, IN, USA; [7]Laboratory of Glycobiology, Hirszfeld Institute of Immunology and Experimental Therapy, Wroclaw, Poland; [8]The National Hemophilia Center, and Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Tel Aviv University, Tel Aviv, Israel; [9]Centre for Haematology, Imperial College London, London, UK; [10]University of California San Francisco, San Francisco, CA, USA; [11]Guy's & St. Thomas' NHS Foundation Trust, London, UK; [12]Queensland Haemophilia Centre, Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [13]University of Queensland, Brisbane, QLD, Australia; [14]Institute of Experimental Haematology and Transfusion Medicine and Center for Rare Diseases, University Hospital Bonn, Bonn, Germany; [15]Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, SP, Brazil; [16]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa, Milan, Italy; [17]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy; [18]Orthopaedic Hemophilia Treatment Center, Los Angeles, CA, USA; [19]Center for Bleeding and Clotting Disorders, University of Minnesota, Minneapolis, MN, USA; [20]Oxford University Hospitals National Health Service Foundation Trust, Oxford, UK; [21]Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [22]Oxford National Institute for Health Research Biomedical Research Centre, Oxford, UK; [23]BioMarin Pharmaceutical Inc., Novato, CA, USA; [24]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA

Disclosures for JOHNNY MAHLANGU

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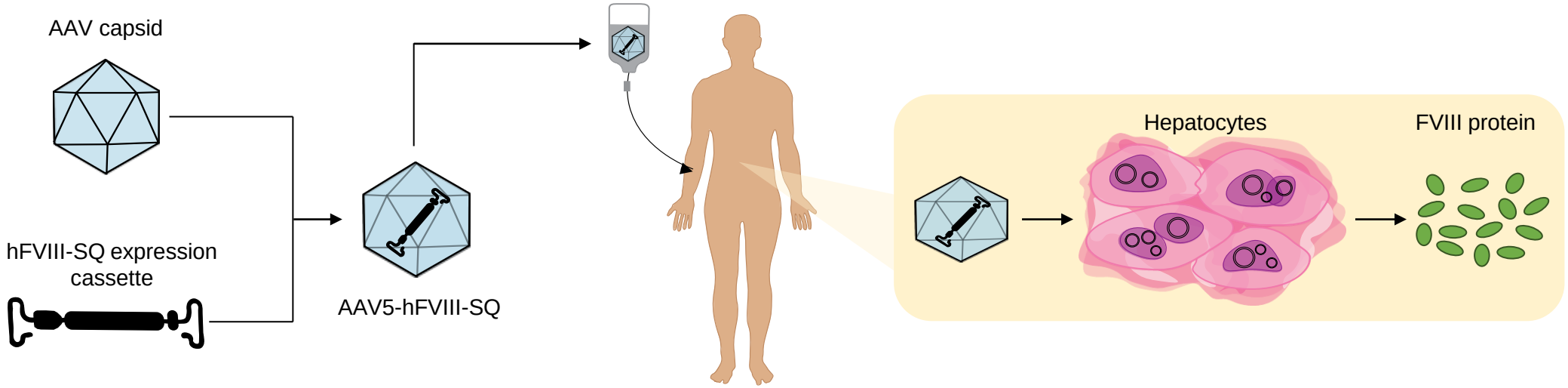
Research Support/P.I.	**BioMarin Pharmaceutical, Inc., CSL Behring, Novo Nordisk, SOBI, F. Hoffman-La Roche Ltd, and uniQure**
Employee	**No relevant conflicts of interest to declare**
Consultant	**CSL Behring, Catalyst BioSciences, Novo Nordisk, F. Hoffman-La Roche Ltd, Spark Therapeutics, and Takeda**
Major Stockholder	**No relevant conflicts of interest to declare**
Speakers Bureau	**No relevant conflicts of interest to declare**
Honoraria	**No relevant conflicts of interest to declare**
Scientific Advisory Board	**No relevant conflicts of interest to declare**

Evaluating safety and efficacy for 2 years following treatment with valoctocogene roxaparvovec

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence to hepatocytes using a recombinant AAV5 vector, enabling endogenous FVIII production in people with severe hemophilia A[1–4]
- In the global, open-label, Phase 3 trial GENEr8-1, participants achieved FVIII activity providing improved protection from bleeding compared with prophylaxis for 52 weeks[4,5]
- Findings from the ongoing Phase 3 trial are presented, focusing on the relationship between transgene-produced FVIII and bleeding events after 2 years of follow-up



AAV, adeno-associated virus; AAV5, AAV serotype 5; hFVIII-SQ, human FVIII SQ-variant; FVIII, factor VIII

1. Rangarajan S, et al. *N Engl J Med*. 2017;377(26):2519–30; 2. Pasi KJ, et al. *N Engl J Med.* 2020;382(1):29–40; 3. Pasi KJ, et al. *Haemophilia.* 2021;27(6):947–56; 4. Ozelo M, et al. *N Engl J Med.* 2022;386(11):1013–25; 5. Mahlangu J, et al. 15th Annual Congress of EAHAD. February 2–4, 2022

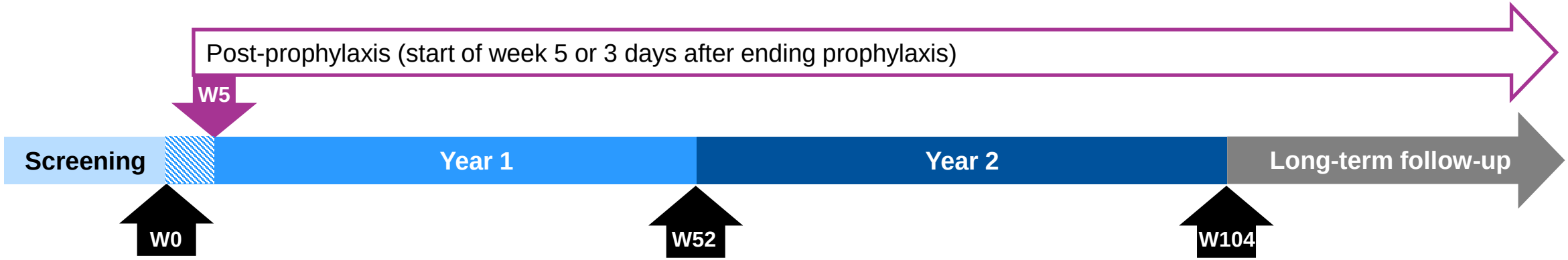
Phase 3 GENEr8-1 study design

Eligible participants (directly enrolled or rolling over from the noninterventional study BMN 270-902)

- Adult men with severe hemophilia A (FVIII ≤1 IU/dL)
- Previously receiving FVIII prophylaxis
- No history of FVIII inhibitors or anti-AAV5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

Definitions

- **All bleeds[a] –** every bleed, regardless of treatment
- **Treated bleeds[b]** – bleeds followed by FVIII treatment
- **Traumatic bleeds** – bleeds with an identifiable cause
- **Spontaneous bleeds** – bleeds with no obvious cause
- **Problem joints** – joints with chronic pain, chronic synovitis, arthropathy, limited motion, or recurrent bleeding

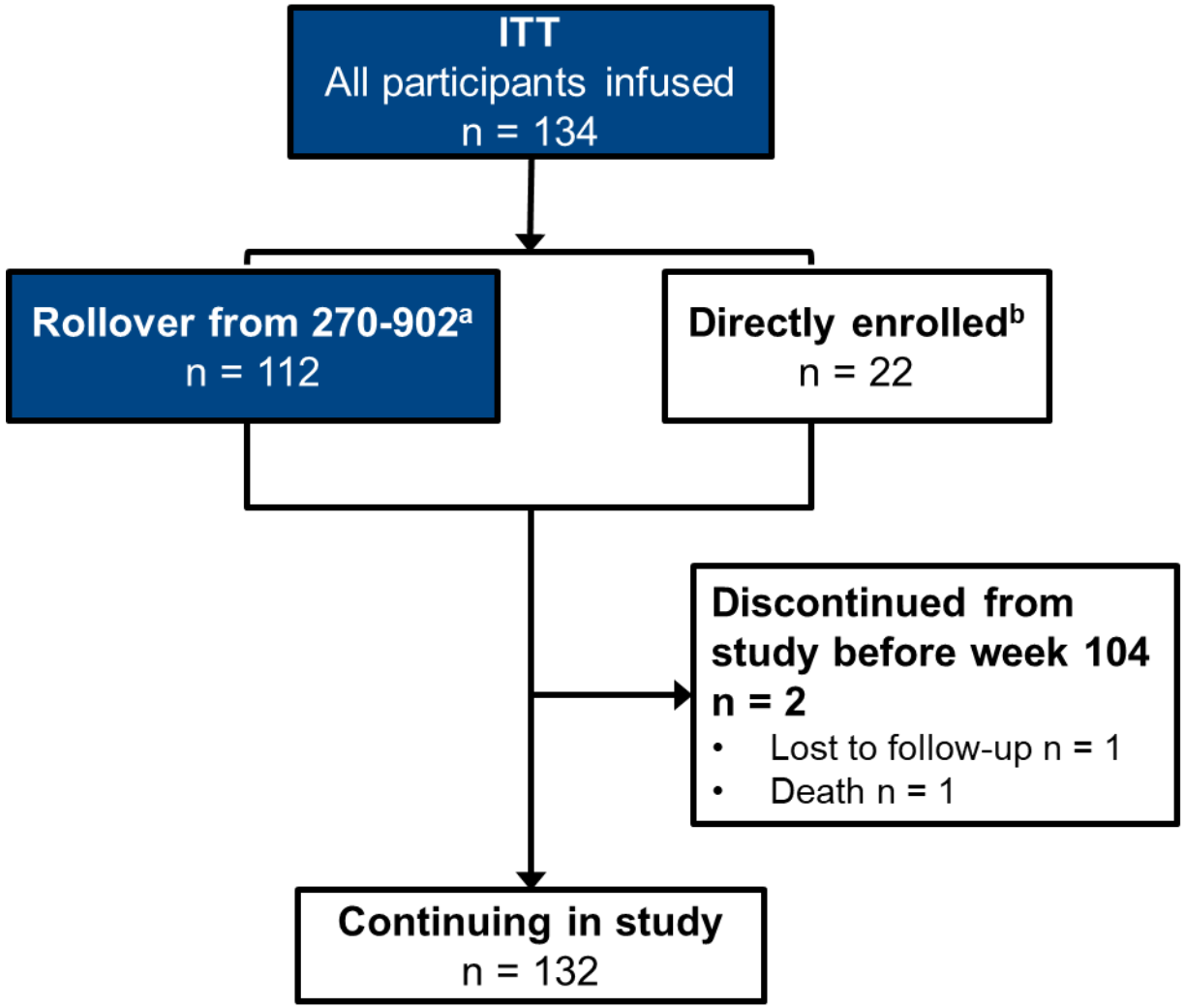


$6x10^{13}$ vg/kg valoctocogene roxaparvovec infusion

[a]Bleeds were self-reported by participants without adjudication, and surgery/procedure-related bleeds were excluded; [b]Annualized rate of treated bleeds was the primary efficacy endpoint. Surgery/procedure-related bleeds were excluded

AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; W, week

Participant disposition and baseline demographics



Baseline Characteristics	Rollover Population n = 112	ITT n = 134
Age, years, mean ± SD	31.8 ± 10.6	31.7 ± 10.3
Race, n (%)		
White	78 (69.9)	96 (71.6)
Asian	17 (15.2)	19 (14.2)
Black or African American	14 (12.5)	15 (11.2)
Hawaiian or Pacific Islander	1 (0.9)	1 (0.7)
Not provided	2 (1.8)	3 (2.2)
Hispanic or Latino ethnicity, n (%)	5 (4.5)	7 (5.2)
BMI, kg/m², mean ± SD	25.2 ± 4.7	25.3 ± 4.6
Medical history, n (%)		
Hepatitis B	17 (15.2)	20 (14.9)
Hepatitis C	33 (29.5)	41 (30.6)
HIV	0	2 (1.5)
Number of problem joints,[c] n (%)		
0	82 (73.2)	97 (72.4)
1	13 (11.6)	17 (12.7)
2	9 (8.0)	9 (6.7)
3	6 (5.4)	8 (6.0)
>3	2 (1.8)	3 (2.2)

[a]Includes the participant who died during week 96; [b]Includes the participant lost to follow-up at week 66; [c]Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding
BMI, body mass index; HIV, human immunodeficiency virus; ITT, intent-to-treat; SD, standard deviation

Safety profile of valoctocogene roxaparvovec remains consistent in year 2 with year 1 findings

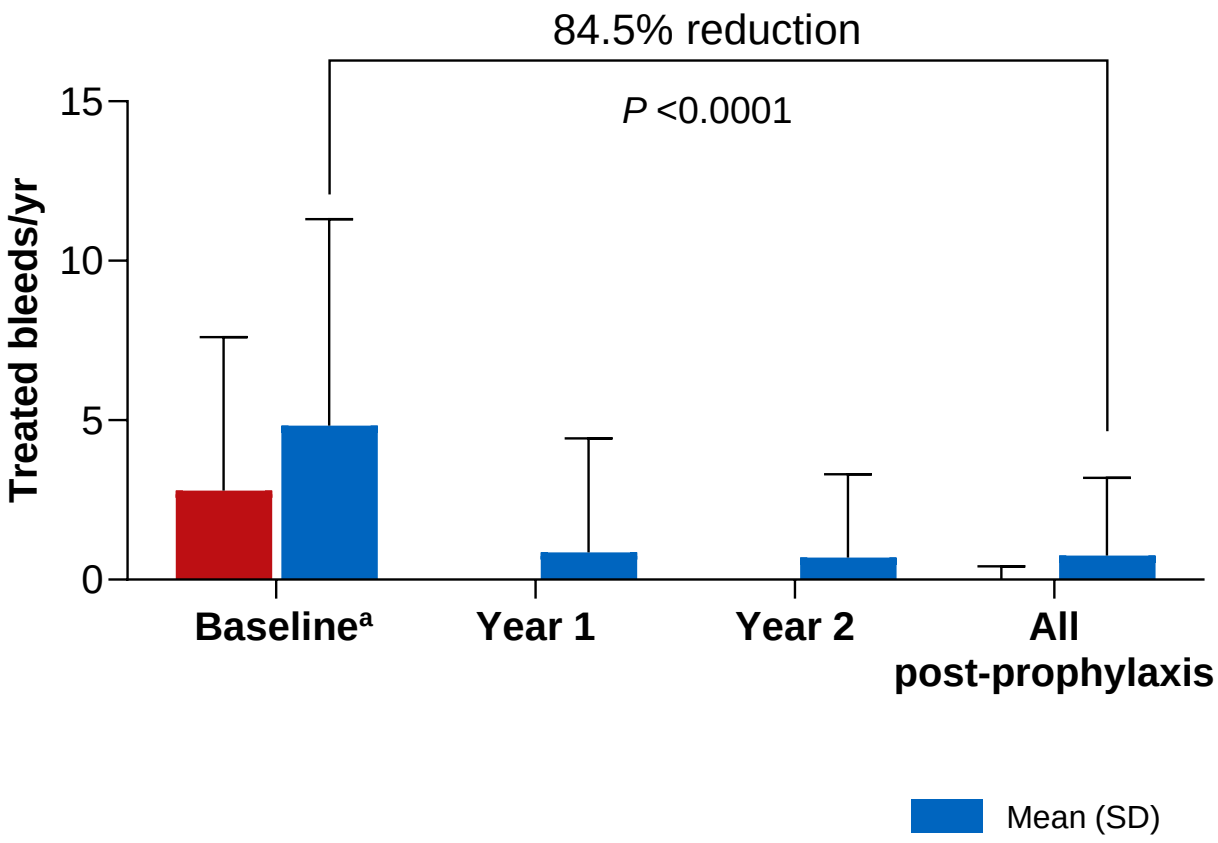
- Most common AE remains ALT elevation[a] (89%)
  - Others include headache (41%), arthralgia (40%), nausea (38%), AST elevation (35%), and fatigue (30%)
- Overall, 83% received immunosuppressants for ALT elevation
  - By week 52, 53% were not using immunosuppressants
  - By week 104, 99% were not using immunosuppressants
- Overall, 60% experienced corticosteroid-related AEs
- New events occurring in year 2
  - One treatment-related Grade 3 AE: ALT elevation at week 70
  - Four SAEs unrelated to treatment:
    - Apnea, anaphylactic reaction, suicide, coronary artery disease
    - All unrelated to transgene infusion

[a]AEs of ALT elevation were initially defined as ≥1.5x ULN, then amended to include elevations >ULN when ALT >2x baseline, then amended again to include elevations >ULN or ≥1.5x baseline

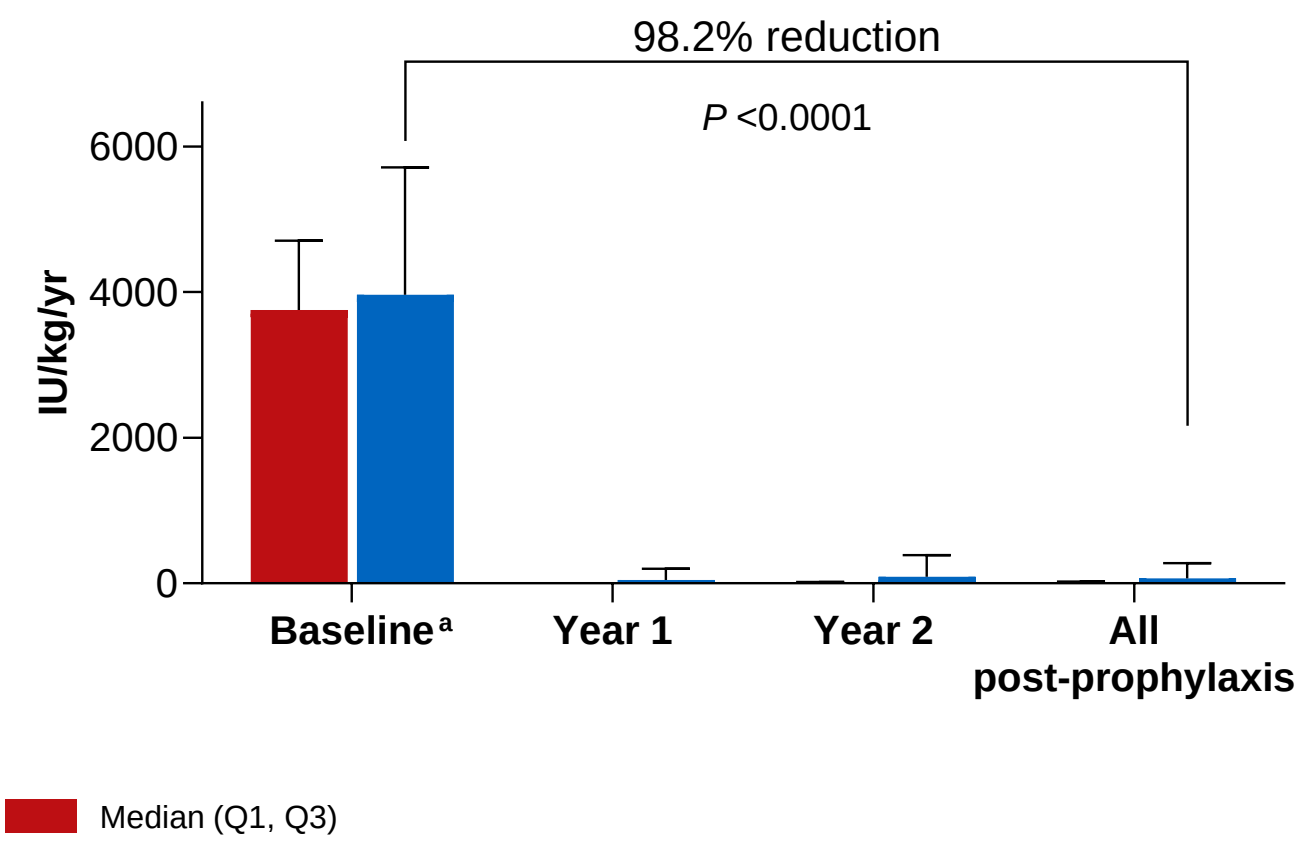
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious AE; ULN, upper limit of normal

Significant reduction in annualized rate of treated bleeds and FVIII utilization compared to baseline in rollover population (n = 112)

Annualized treated bleeding rate

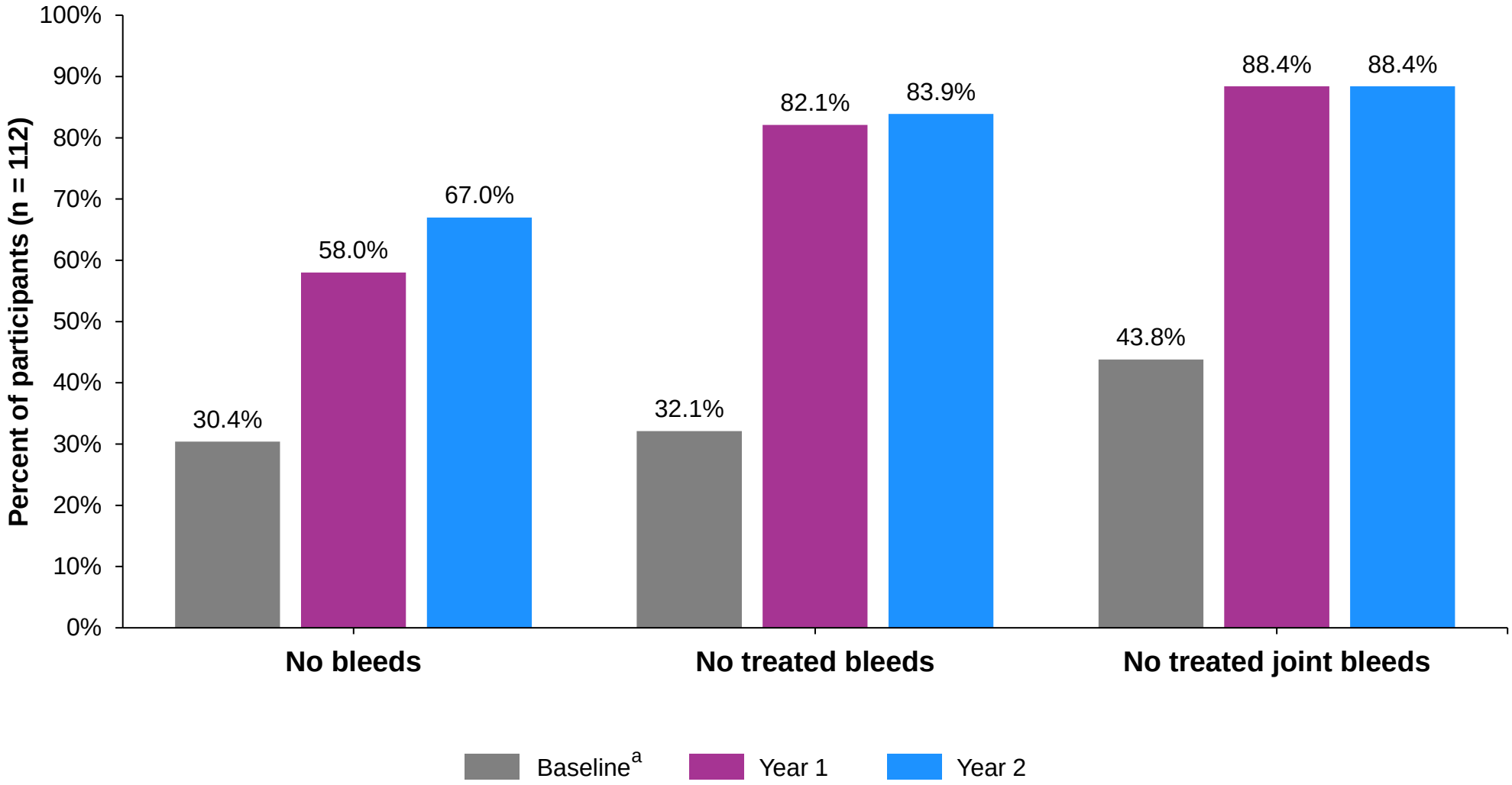


Annualized FVIII utilization



[a]Baseline values were from the 6-month prospective data collection period in the noninterventional study BMN 270-902
FVIII, factor VIII; Q1, first quartile; Q3, third quartile; SD, standard deviation; yr, year

Most participants in rollover population remained bleed free for up to 2 years



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Predicting treated joint bleeds from FVIII activity

- Phenotypic categorizations are based on observational studies of individuals with a variety of mutations in the gene *F8* and therefore, different protein products
  - Spontaneous bleeding requiring prophylaxis occurs when FVIII is low

Hemophilia A phenotype[1]	FVIII (IU/dL)
Severe	<1
Moderate	1–5
Mild	6–40

- FVIII produced after gene therapy with valoctocogene roxaparvovec contains the natural sequence of B-domain–deleted replacement FVIII, but is produced in the liver, not endothelial cells
- To guide management of individuals over the range of observable FVIII levels post-gene transfer, it is useful to understand the relationship of transgene-produced FVIII and bleeding outcomes

FVIII, factor VIII

1. Srivastava A, et al. *Haemophilia*. 2020;26(Suppl 6):1–158

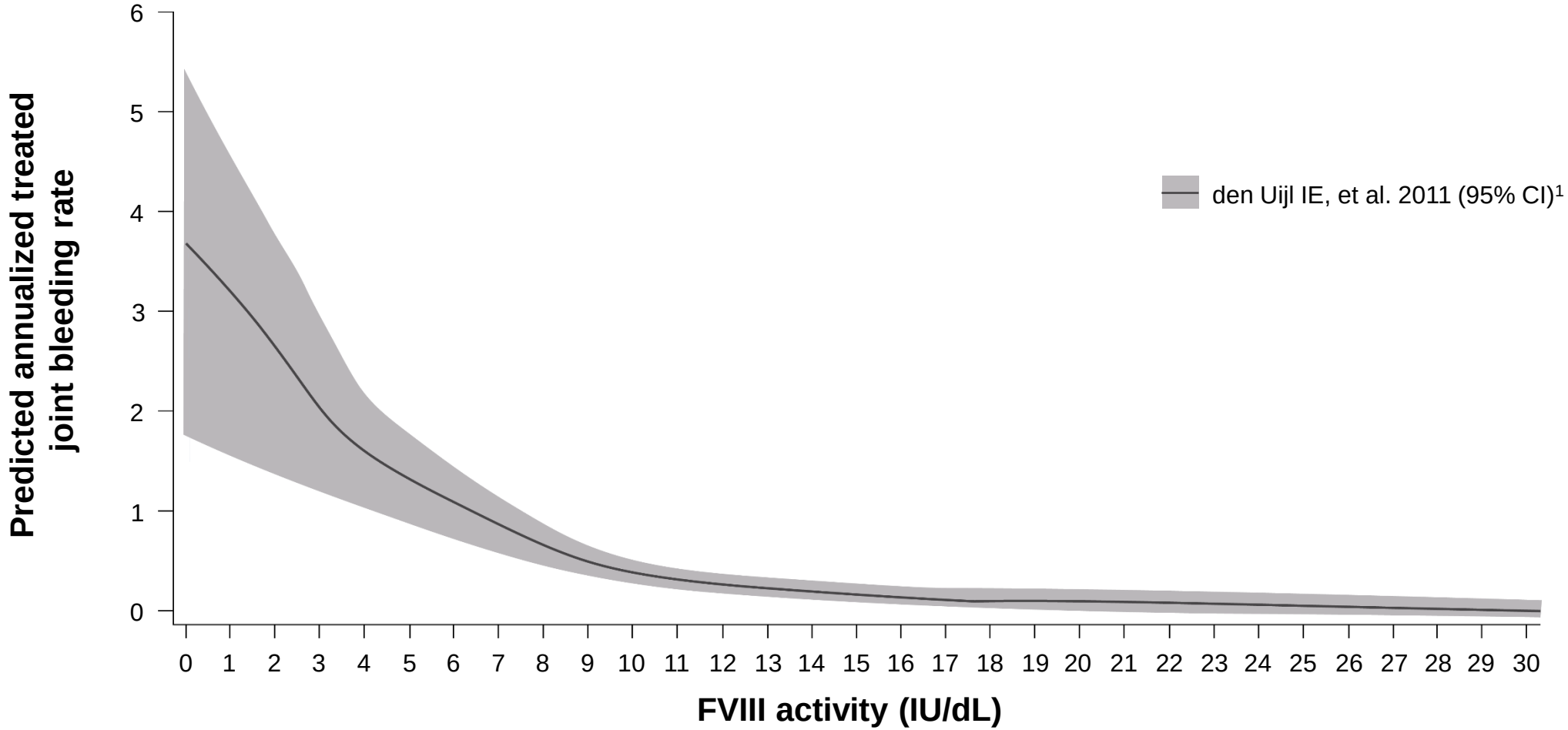
Predicting treated joint bleeds from FVIII activity

- Follow-up was divided into 4- or 6-week intervals for all 134 participants
  - Count of treated joint bleeds
  - Median FVIII activity (CSA and OSA)
- Relationship between count of joint bleeds and matched median FVIII activity was modeled using negative binomial regression
- Results were compared to the estimate of treated joint bleeding rates and self-reported FVIII activity in 433 individuals with mild and moderate hemophilia A[1]

CSA, chromogenic substrate assay; FVIII, factor VIII; OSA, one-stage assay

1. den Uijl IE, et al. *Haemophilia.* 2011;17:41–4

Estimates of treated joint bleeding rates per transgene-derived FVIII activity align with epidemiological data in people with hemophilia A



CI, confidence interval; FVIII, factor VIII

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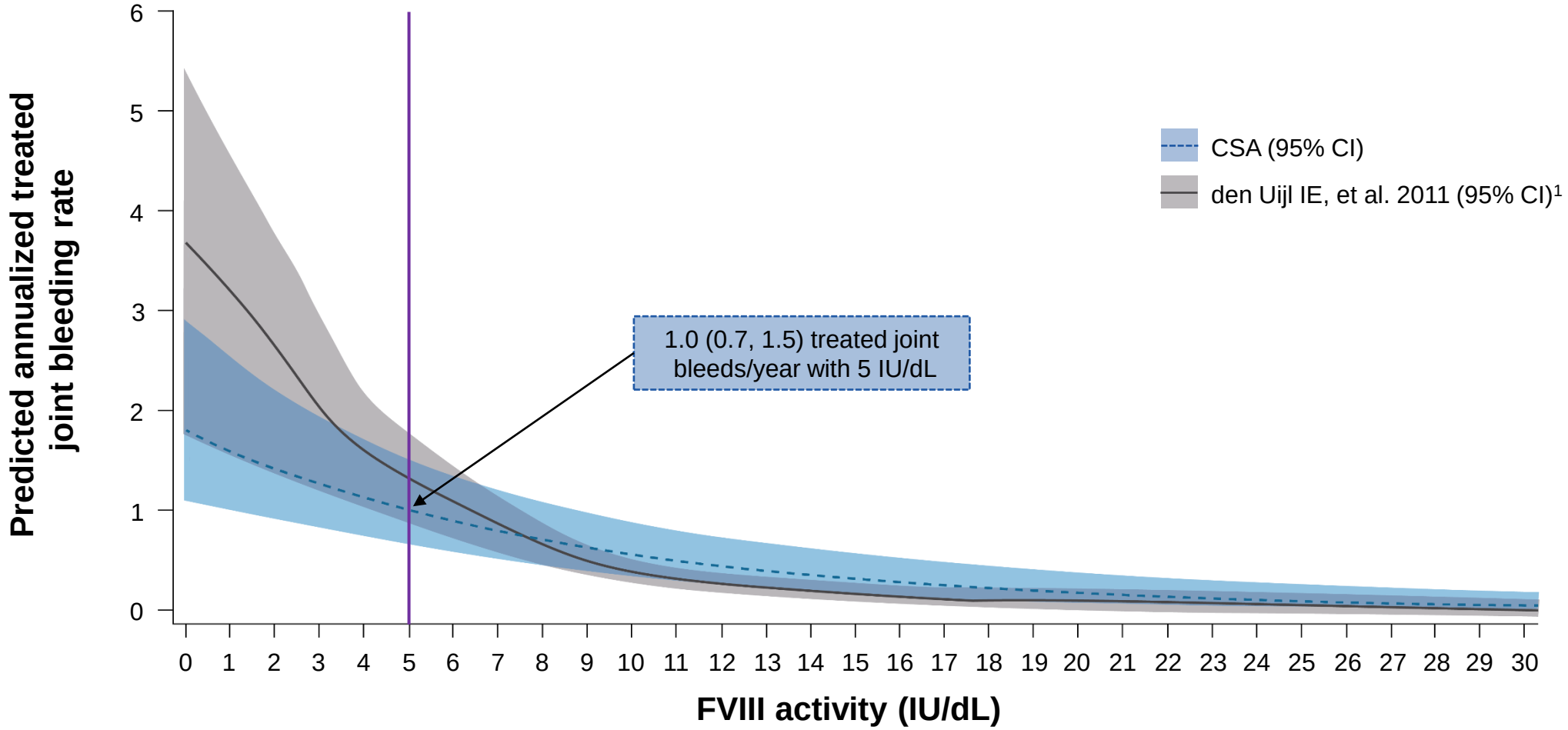

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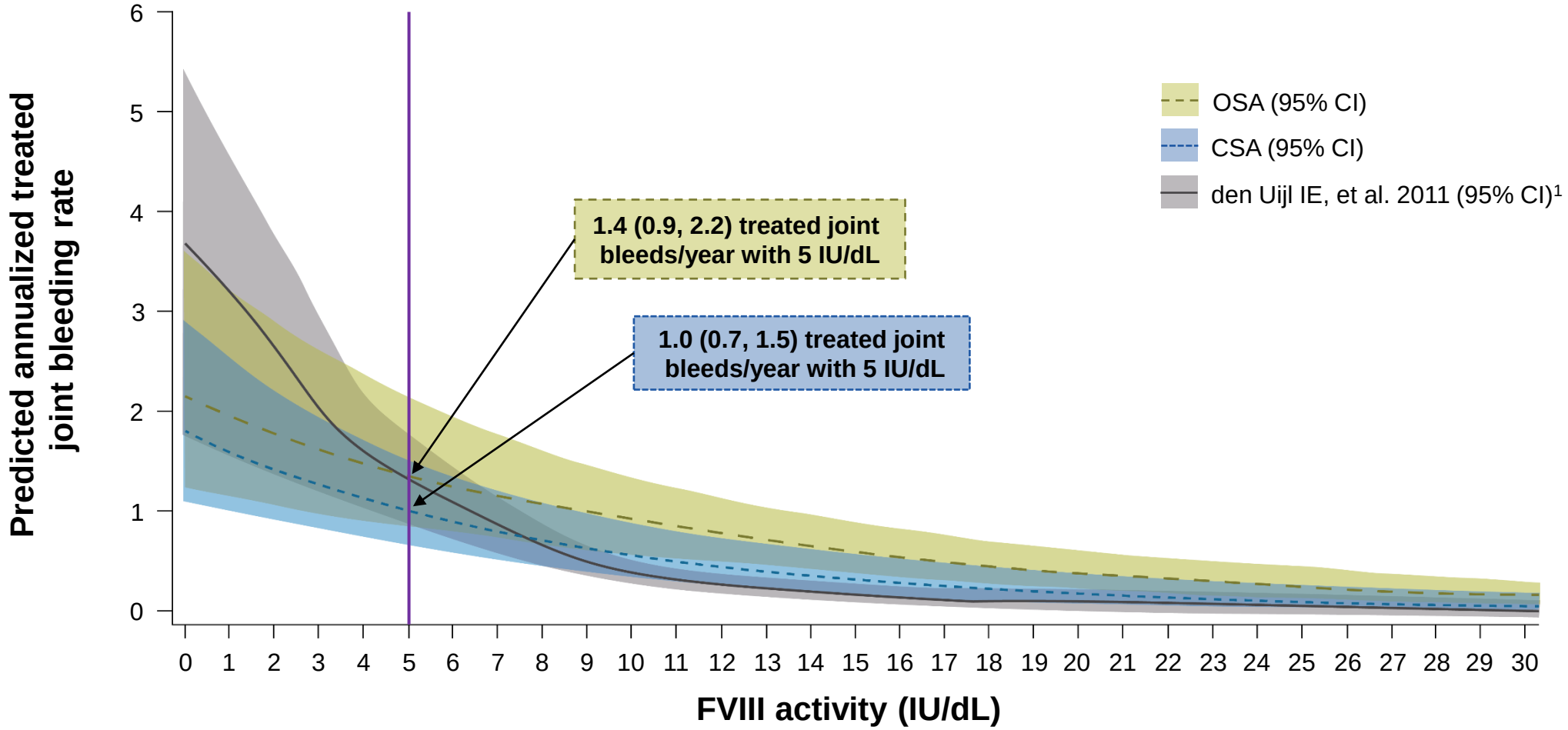

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1. den Uijl IE, et al. *Haemophilia.* 2011;17:41–4

Conclusions

- Safety results in year 2 were consistent with year 1 of the Phase 3 study
  - Four new SAEs unrelated to treatment with valoctocogene roxaparvovec
  - One new treatment-related Grade 3 AE of ALT elevation
- A single infusion of valoctocogene roxaparvovec provided robust hemostatic efficacy relative to FVIII prophylaxis for >2 years in the Phase 3 study
  - >80% of rollover participants had no treated bleeds each year in the absence of routine prophylaxis
  - 98% reduction in mean exogenous FVIII use overall
- Estimates of treated joint bleeding rates per transgene-derived FVIII activity align with epidemiological data in people with hemophilia A

AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; SAE, serious AE

Acknowledgements

- **Thank you to all the trial participants, their families, study-site personnel, and investigators**

- For their contributions to the abstract, we thank the investigators Emily Symington, Michael Wang, and Nigel Key, as well as Reena Mahajan and Divya Reddy of BioMarin Pharmaceutical Inc.
- Funding for this study was provided by BioMarin Pharmaceutical Inc.
- Medical writing and editorial support were provided by Kathleen Pieper of AlphaBioCom and funded by BioMarin Pharmaceutical Inc.