ISTH 2023 Highlights: AHA and GTR

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Disclosure of commercial support

I have relationships with for-profit and not-for-profit organizations over the past two years:

NATURE OF RELATIONSHIP	NAME OF THE FOR-PROFIT OR NOT-FOR-PROFIT ORGANIZATION	DESCRIPTION OF RELATIONSHIP
Any direct financial payments including receipt of honoraria	Hemalytic Inc	Consultant
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Patents on a drug, product or device	MacPopPK	IP co-owner
All other investments/relationship that could be seen as having the potential to influence the content of the educational activity	World Federation of Hemophilia	Co-Chair of the World Bleeding Disorders Registry / Gene Therapy Registry

Learning Objectives

Choose your own action words to start each objective

At the end of this presentation, participants will be better able to:

- Evaluate pros and cons of using Emicizumab as compassionate treatment for patient with acquired hemophilia
- Understand the need and value of prospective outcome collection (including patient reported outcomes) in patient with hemophilia undergoing gene therapy.

Emicizumab role in acquired hemophilia

- **0C.06.2: Matthias M Engelen et al. Emicizumab for Acquired Hemophilia A - A Case Series**
- **OC 06.3: Midori Shima et al. Results of the AGEHA trial (Phase III study of Emicizumab Prophylaxis for Acquired Hemophilia A).**
- **LB 01.2: Andreas Tiede et al. Emicizumab prophylaxis instead of immunosuppressive therapy in patients with acquired hemophilia A (AHA)**
- **PB0193: Praveen Gounder et al Financial impact of switching to emicizumab from conventional haemostatic agents in acquired haemophilia A**

Emicizumab for acquired Hemophilia A
– University Hospitals Leuven

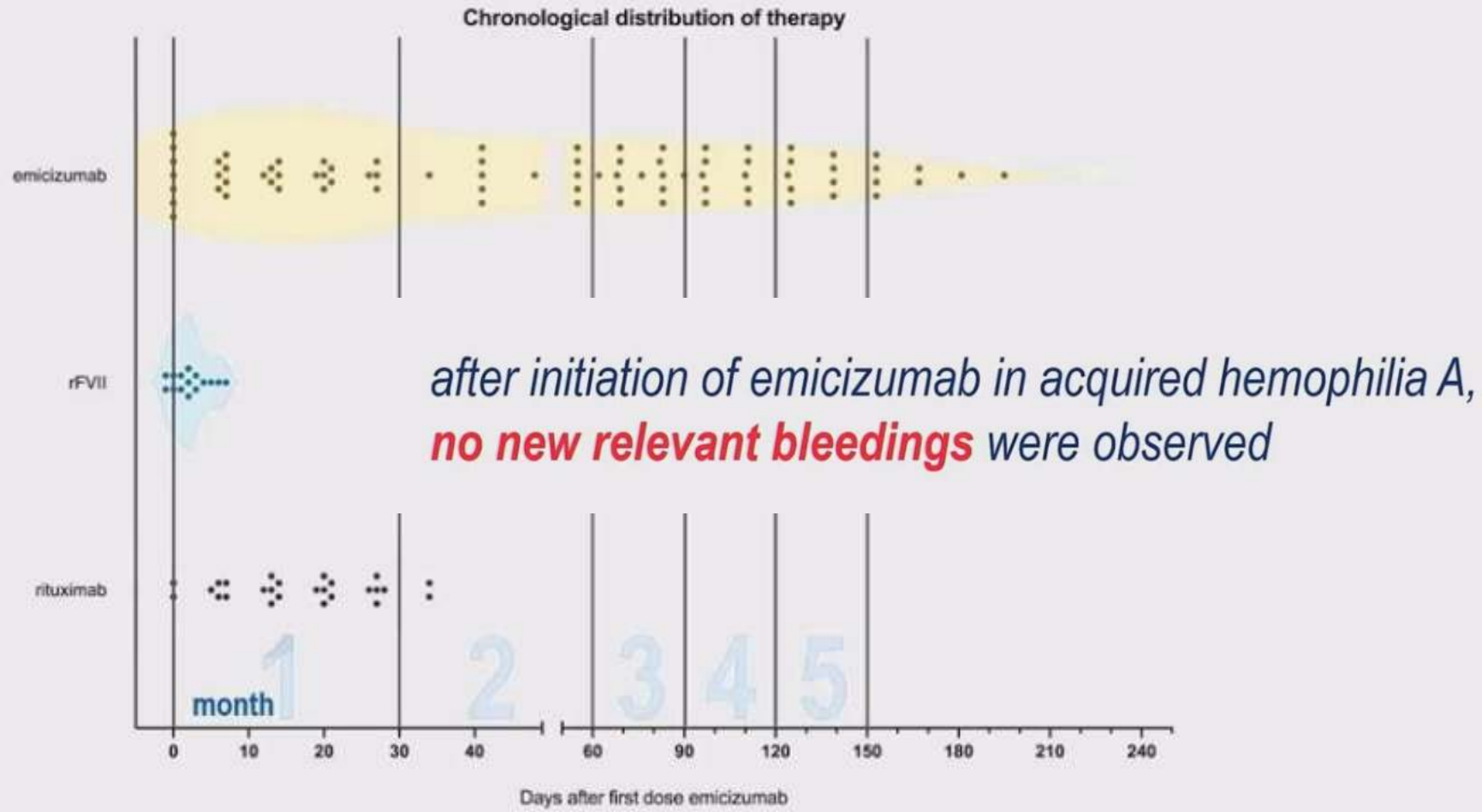
	Statistics	Patients
Baseline characteristics	***N***	**7**
Age, y	Median (IQR)	75 (68-78)
Male	*n/N* (%)	5/7 (71)
Caucasian ethnicity	*n/N* (%)	7/7 (100)
Cancer		
Active	*n/N* (%)	0/7 (0)
History of cancer	*n/N* (%)	1/7 (14)
Auto-immune disease	*n/N* (%)	1/7 (14)
History of bleeding	*n/N* (%)	0/0 (0)
History of thrombosis		
Venous thrombo-embolism	*n/N* (%)	0/0 (0)
Arterial thrombosis	*n/N* (%)	0/0 (0)

Bleeding phenotype	***N***	**7**
Spontaneous hematoma	*n/N* (%)	7/7 (100)
Intramuscular bleeding	*n/N* (%)	2/7 (29)
Haematuria	*n/N* (%)	2/7 (29)
Gastro-intestinal bleeding	*n/N* (%)	2/7 (29)
Major bleeding (ISTH criteria)	*n/N* (%)	6/7 (86)

Laboratory findings		
APTT		
At diagnosis (seconds)	Median (IQR)	90,8 (72,5-103)
Maximal (seconds)	Median (IQR)	103 (83,3-122,9)
FVIII activity		
At diagnosis (%)	Median (IQR)	0 (0-1)
Minimal (%)	Median (IQR)	0 (0-1)
FVIII inhibitor		
At diagnosis (BU/mL)	Median (IQR)	112 (31,9-190)
Maximal (BU/mL)	Median (IQR)	182 (104-228)

Matthias M Engelen et al. Emicizumab for Acquired Hemophilia A - A Case Series

	Treatment	Patients n/N (%)	Dose repetitions median (IQR)	Total dose in mg/kg median (IQR)
1 hemostasis	rFVIIa (eptacog alfa)	3/7 (43)		1.7 (1.2-2.2)
	Emicizumab	7/7 (100)	13 (9-15)	
2 immuno-suppression	Rituximab	7/7 (100)	4 (4-4)	
	Methylprednisolone	6/7 (86)	Individualized tapering	

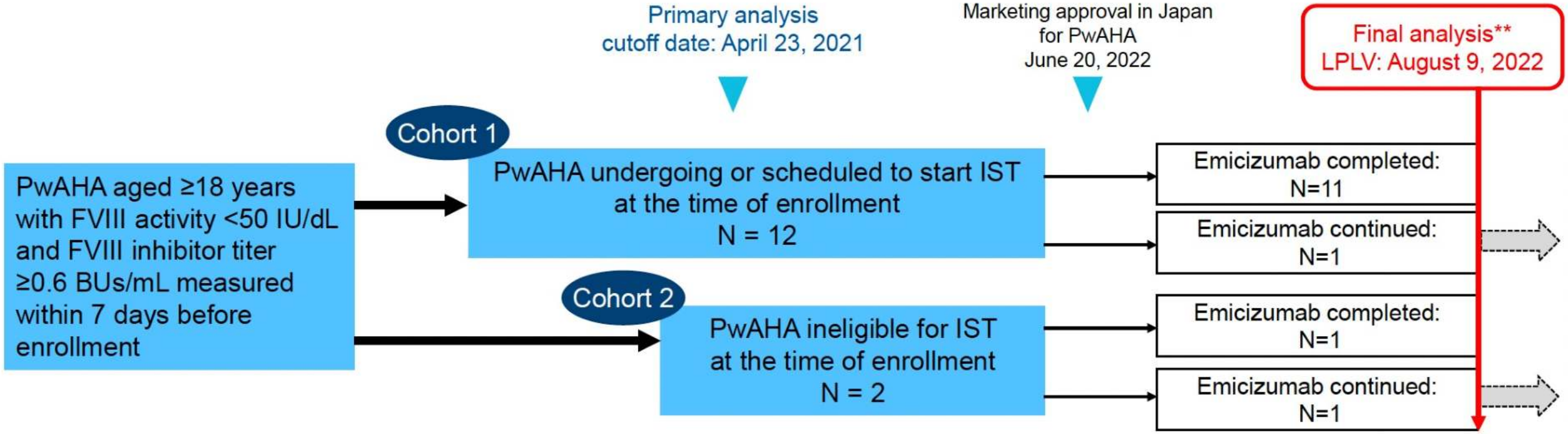


after initiation of emicizumab in acquired hemophilia A,
no new relevant bleedings *were observed*

Matthias M Engelen et al. Emicizumab for Acquired Hemophilia A - A Case Series

Prospective, Multicenter, Open-label Phase III Study (AGEHA*) of Emicizumab Prophylaxis in PwAHA

- The results of primary analysis have been reported previously; however, only Cohort 1 patients who started emicizumab treatment under immunosuppressive therapy (IST) were included [1]
- This final analysis included Cohort 2 data and long-term observation data of Cohort 1 (at primary analysis: up to 208 days ➡ at final analysis: up to 639 days)



*Clinical trial identification code: JapicCTI-205151
**The study was completed when all 2 patients who were still on emicizumab treatment were switched to commercial emicizumab

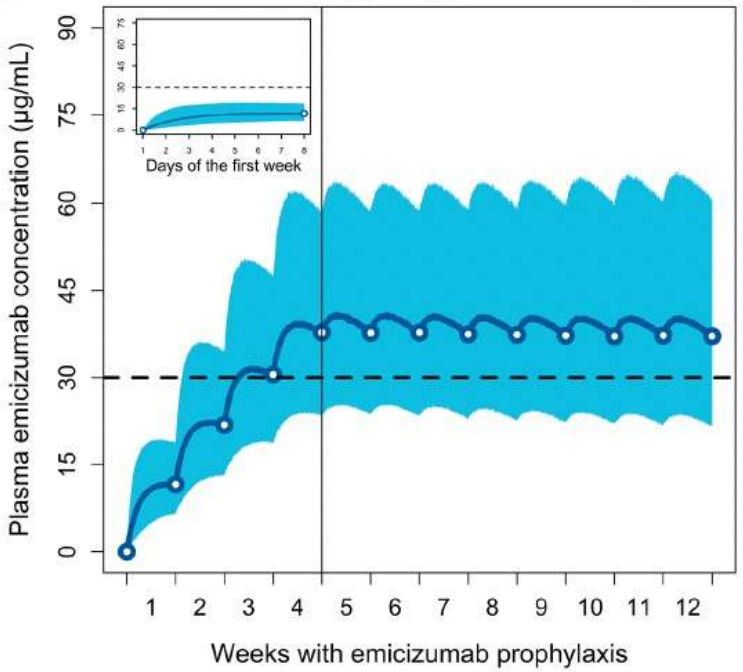
BU, bethesda units; FVIII, factor VIII; IU, international units; LPLV, last patient last visit; PwAHA, patients with acquired hemophilia A

[1] Shima et al. *J Thromb Haemost.* 2023 Mar;21(3):534-545

Modified Dosing Regimen for Acquired Hemophilia A

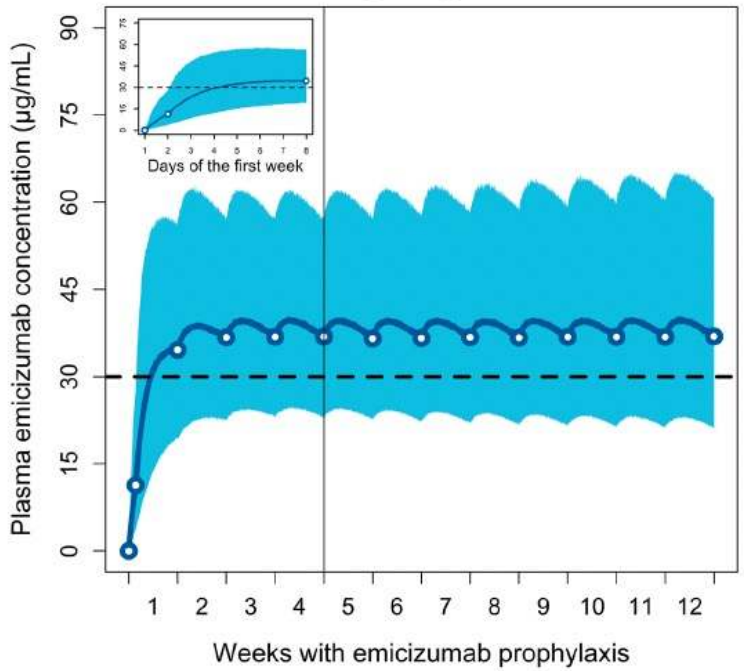
- PK simulation guided selection of a modified “one-week loading regimen” for acquired hemophilia A (AHA) to achieve rapid maximization and stabilization of the effect of emicizumab within one week.

Approved QW dosing regimen for CHA



Loading: 3 mg/kg QW for the first 4 weeks
Maintenance: 1.5 mg/kg QW from the 5th week onwards

Modified QW dosing regimen for AHA



Loading: 6 mg/kg on the 1st day and 3 mg/kg on the 2nd day of the 1st week
Maintenance: 1.5 mg/kg QW from the 2nd week onwards

Solid curve: simulated median profile;
Open circles: simulated median trough levels;
Shaded area: simulated 5th to 95th percentile range;
Vertical solid line: anticipated last trough time point before achieving partial remission in approximately half of patients;
Horizontal dashed line: target efficacious exposure of > 30 µg/mL

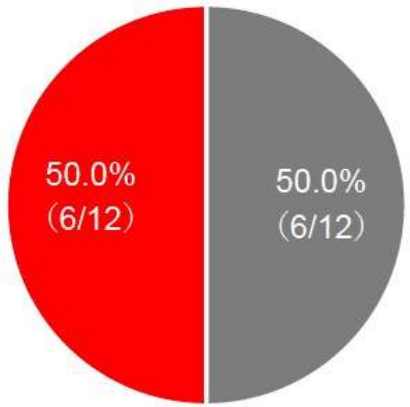
The observed PK profile of emicizumab in the primary analysis was almost consistent with this PK simulation

CHA, congenital hemophilia A; PK, pharmacokinetics; QW: once a week

Proportions of Patients with or without Treated Bleeds

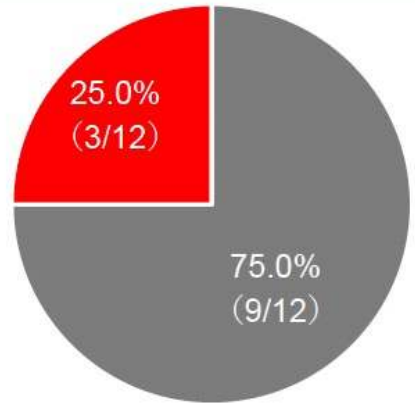
Cohort 1

Pre-treatment Period



Median (range) duration: 68.0 (17-168) days

On-treatment Period

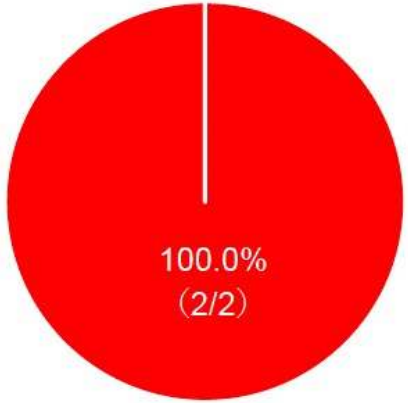


Median (range) duration: 44.5 (8-639) days

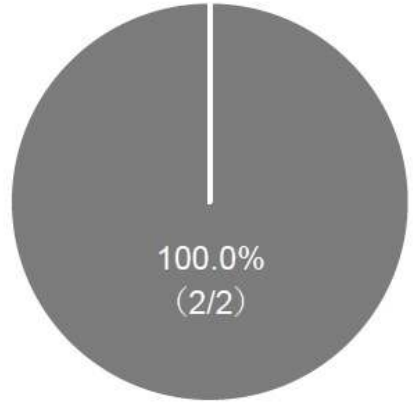
≥1 Treated Bleeds

Zero Treated Bleeds

Cohort 2



Median (range) duration: 95.5 (23-168) days



Median (range) duration: 257 (64-450) days

≥1 Treated Bleeds

Zero Treated Bleeds

Safety Summary

- Asymptomatic, non-serious DVT considered related to emicizumab was reported in 1 patient in the primary analysis, and no other TE/TMA occurred thereafter
- No injection site reactions occurred at any point in the study

	Cohort 1 N=12	Cohort 2 N=2
Total number of AEs	95	25
Total number of patients with ≥1 AE, n (%)	12 (100)	2 (100)
AE with fatal outcome[a] Serious AE[b] Emicizumab related AE[c]	1 (8.3) 5 (41.7) 3 (25.0)	0 1(50.0) 2 (100)
Total number of patients who developed ADAs[d], n (%)	2 (16.7)	0

[a]Exacerbation of concomitant disease (CKD) in 1 patient not related to emicizumab
[b]Cholangitis acute and cholangitis chronic in 1 patient, cholelithiasis and shock haemorrhagic in 1 patient, pneumonia, CKD, orthostatic hypotension, and Basedow's disease in 1 patient each
[c]Thrombocytopenia, prothrombin fragment 1+2 increased, DVT, Basedow's disease, and rash in 1 patient each. DVT was an asymptomatic and non-serious event, which may also be associated with bed rest and prednisolone.
[d]1 of whom had decreased emicizumab exposure that was considered attributed to the ADAs detected after completing emicizumab administration ($t_{1/2}$ of the patient: 9.77 days, $t_{1/2}$ in overall population: 34.2 ± 14.3 days [mean ± SD])

ADA, anti-drug antibody; AE, adverse event; CKD, chronic kidney disease; DVT, deep vein thrombosis; SD, standard deviation; $t_{1/2}$, half-life; TE, thromboembolic event; TMA, thrombotic microangiopathy

GTH Acquired Hemophilia Working Group

Emicizumab prophylaxis instead of immunosuppressive therapy in patients with acquired hemophilia A (AHA)

Andreas Tiede et al. LB 01.2

Objectives of the GTH-AHA-EMI trial

- Assess efficacy of emicizumab to prevent new bleeds
- Establish safety of emicizumab in this elderly and fragile population of patients
- Postpone immunosuppression for at least 12 weeks

Results of the GTH-AHA-EMI trial

- Emicizumab was **effective** to prevent bleeds in AHA according to a predefined efficacy criterion
- Emicizumab was **safe** (thromboembolic events in 2 out of 47 pts)
- IST was safely deferred and overall survival was promising

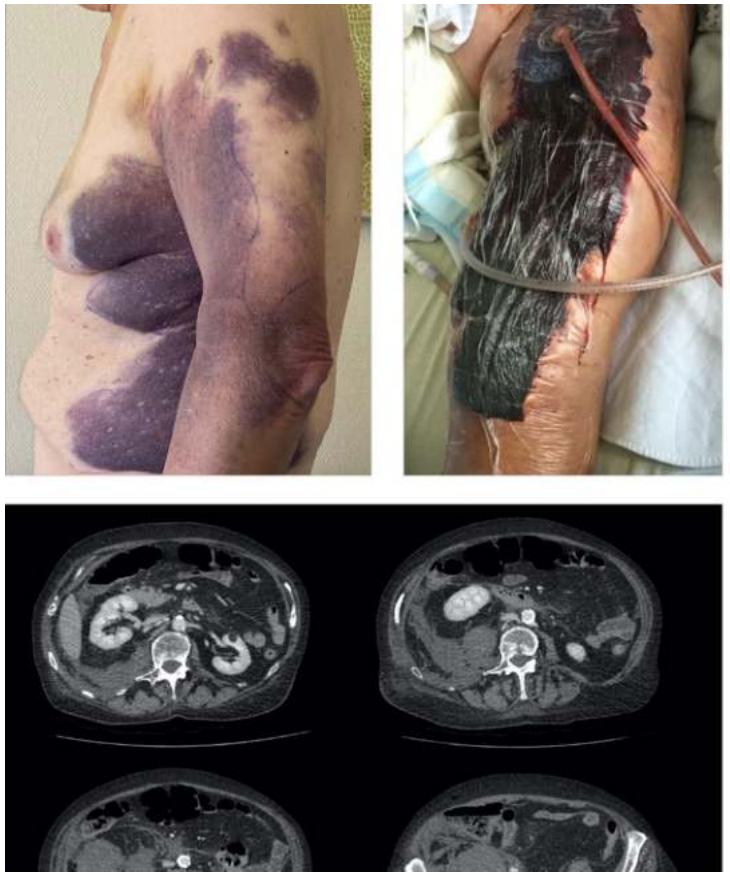


Figure: Tiede et al. J Thromb Haemost. 2021;19:637–644.

Study overview

- Single-arm, open label, multicenter (Germany, Austria)
- Emicizumab accelerated loading regimen
  - Day 1: 6 mg/kg, day 2: 3 mg/kg
- Emicizumab maintenance
  - 1.5 mg/kg qw for 12 weeks
- Immunosuppression not allowed until end of primary efficacy period (12 weeks)
- Primary endpoint: clinically relevant breakthrough bleeds

Baseline characteristics

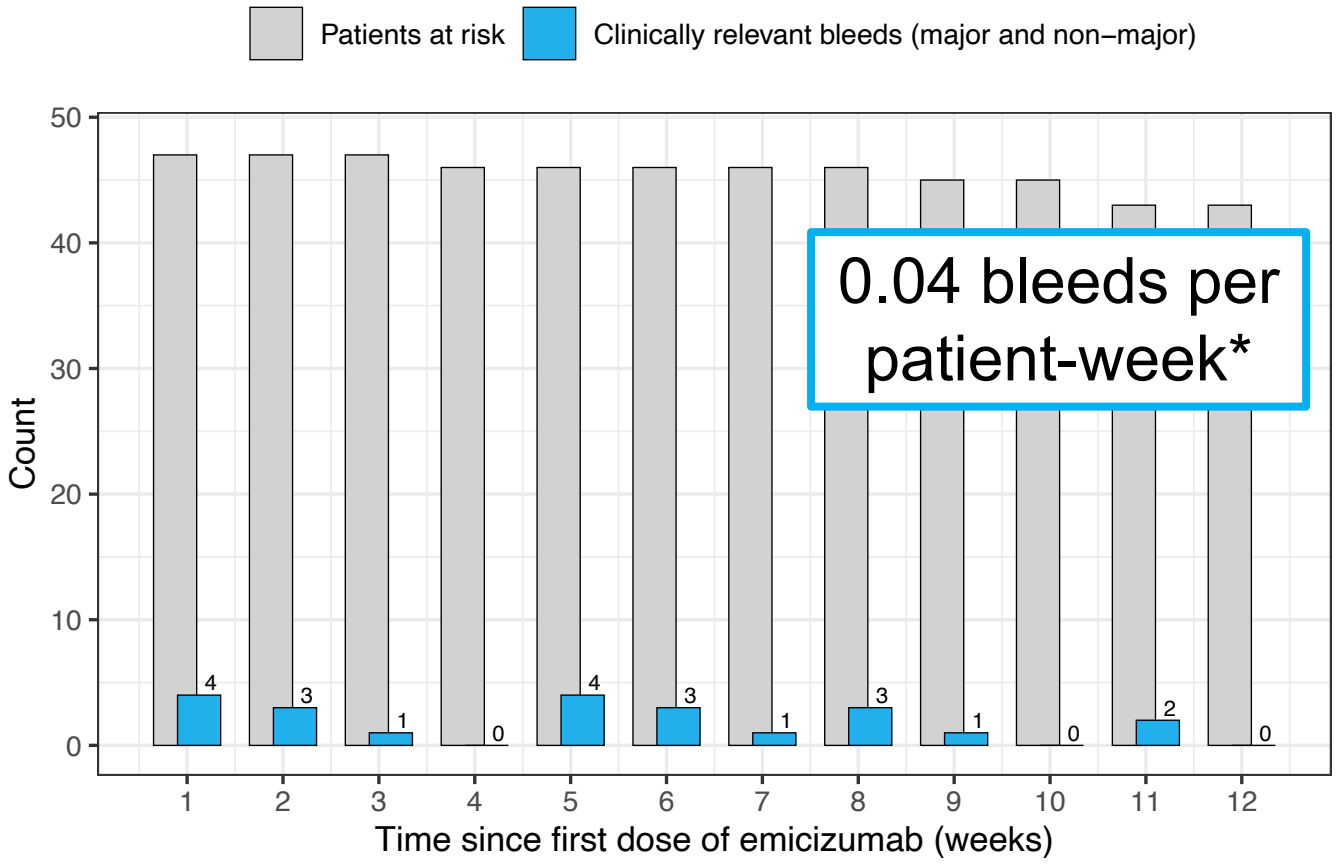
Characteristic	N = 47
Age	
Median (IQR) – yr	76 (66-80)
Sex – no. (%)	
Female	23 (49)
Male	24 (51)
Factor VIII activity in IU/dl	
Median (IQR) – IU/dl	1.4 (0.3-5.6)
Factor VIII inhibitor	
Median (IQR) – BU/ml	12.2 (4.0-47.2)

Statistics

Predefined efficacy criterion (emicizumab considered effective if bleed rate significantly below that of IST-treated patients in historic GTH-AH 01/2010 study)

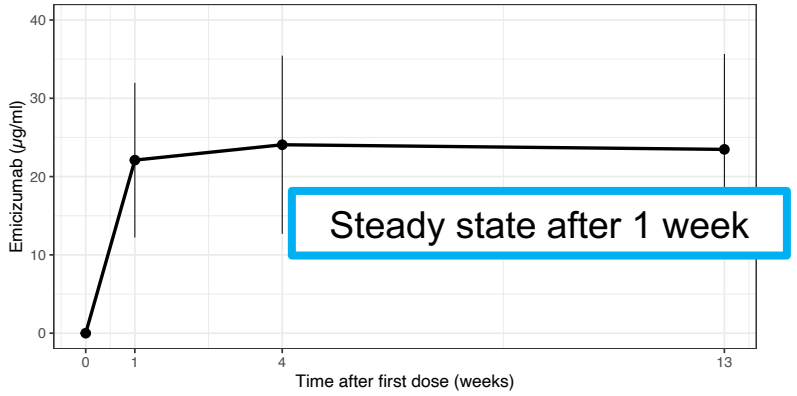
Andreas Tiede et al. LB 01.2

Clinically relevant bleeds

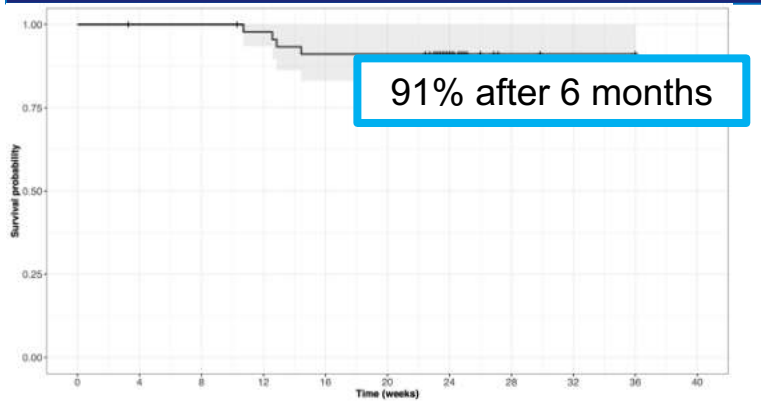


** below predefined efficacy criterion ($p < 0.001$)*

Pharmacokinetics



Overall survival

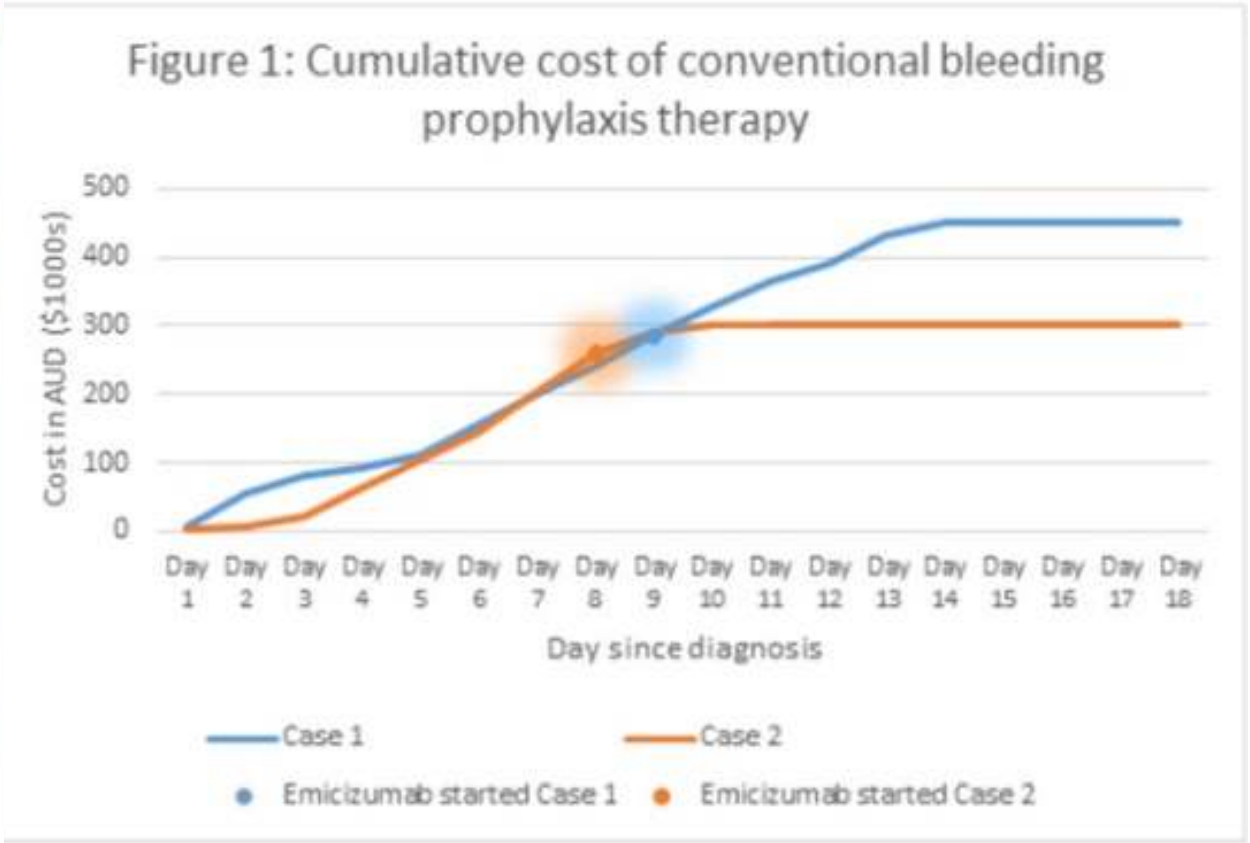


Financial impact of switching to emicizumab from conventional haemostatic agents in acquired haemophilia A

PB0193: Praveen Gounder et al Financial impact of switching to emicizumab from conventional haemostatic agents in acquired haemophilia A

Table 1: Summary of clinical details and costs

	Case 1	Case 2	Case 3
Age (years)	83	92	51
Gender	M	M	M
Weight (kg)	57.0	75.7	75.0
FVIII level at presentation (%)	6%	<1%	3%
Inhibitor level at presentation (BU)	13.7	266	8.3
Sites of bleeding	Cutaneous, urinary tract, muscle and gastrointestinal	Oral mucosa, cutaneous (limb)	Numbered according to admission (1) Haematemesis and retroperitoneal haematoma (2) Upper limb haematoma (3) Thigh haematoma (4) Thigh haematoma
Conventional haemostatic therapies	rFVIIa FEIBA	rFVIIa FEIBA	rFVIIa
Duration of emicizumab	4 weeks	3 weeks (ongoing)	12 weeks
Cost of conventional haemostatic therapy (AUD)	$450,970	$302,380	$3,696,250 (cumulative cost across 4 admissions)

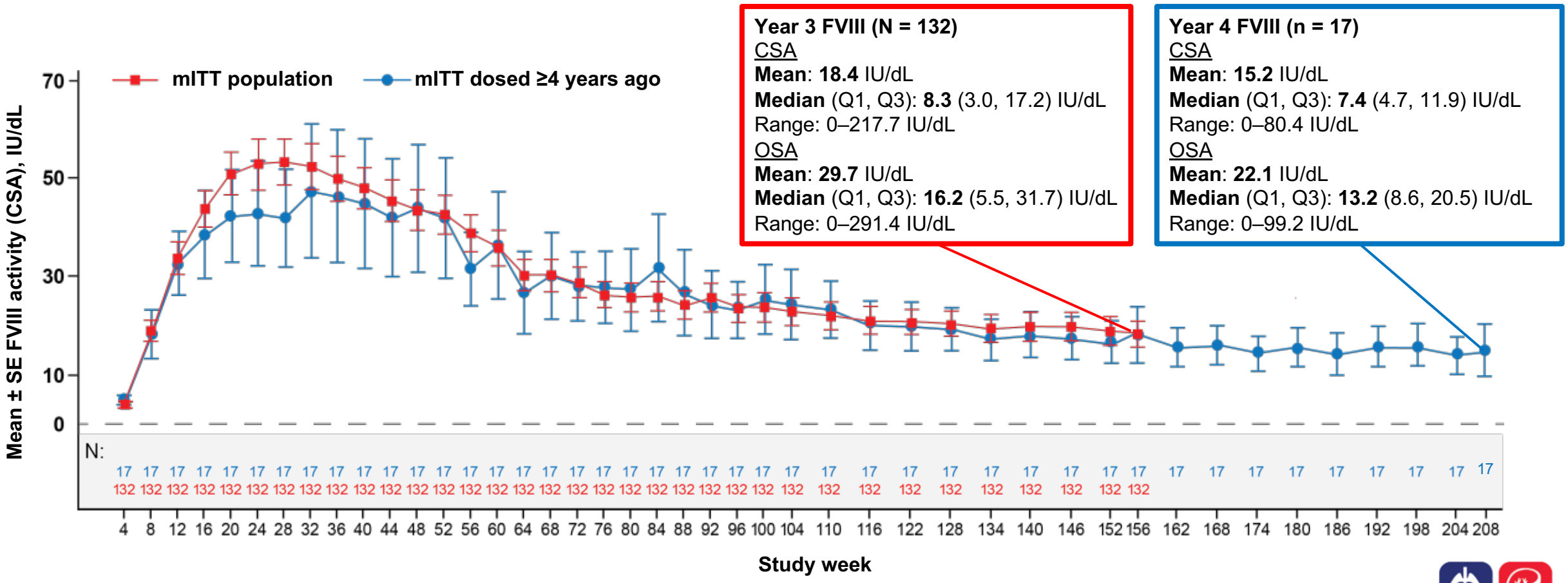


Emicizumab achieved haemostasis rapidly, did not potentiate DIC and appeared to significantly reduce the cumulative financial burden of rFVIIa and FEIBA. Full cost effectiveness studies are warranted.

Clinical outcomes in hemophilia gene therapy

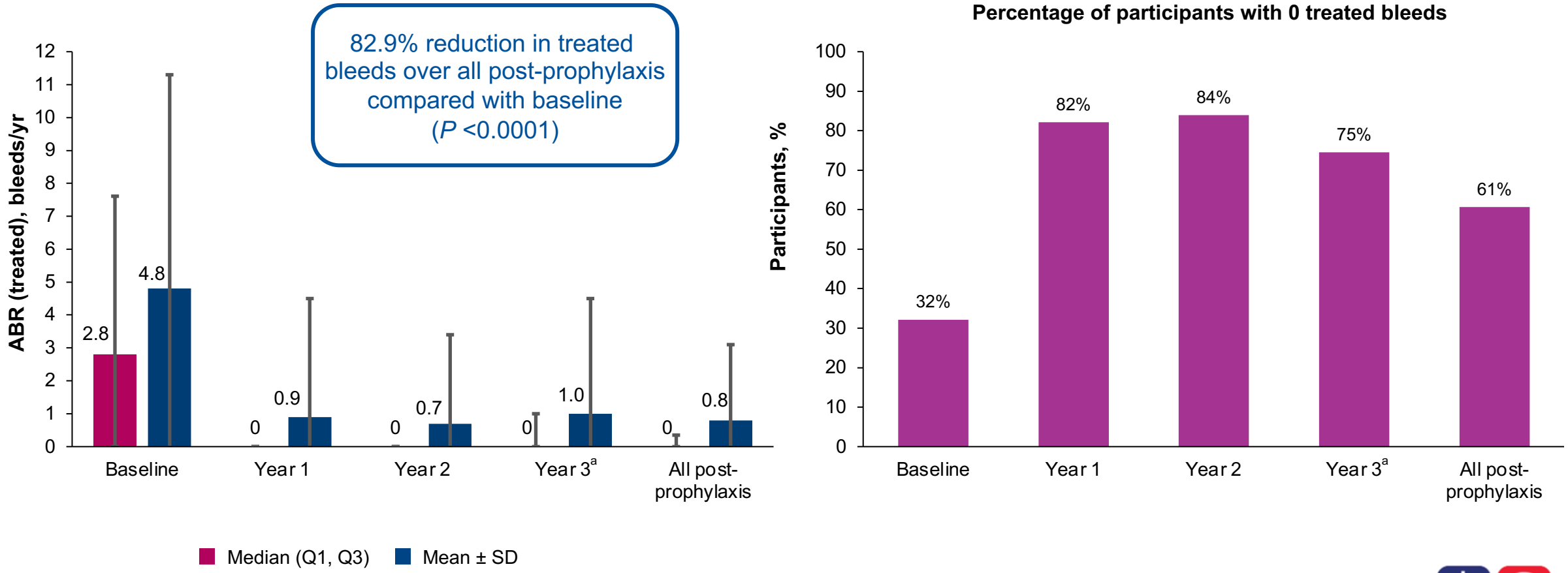
- **OC 20.1 Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1**
  - Johnny Mahlangu
- **OC 20.2 Gene therapy in hemophilia A: The impact of valoctocogene roxaparvovec on patient outcomes – initial results from Patient Reported Outcomes, Burdens and Experiences (PROBE) from the GENEr8-1 trial.**
  - Mark W. Skinner
- **OC 20.5 The WFH Gene Therapy Registry: A Collaborative Approach Towards a Global Resource for the Long-term Follow-up of People with Hemophilia Treated with Gene Therapy**
  - Barbara Konkle

Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1



For participants who discontinued the study, missing FVIII values post-discontinuation were imputed to be 0 IU/dL through the data cutoff date for the analysis.
CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intent-to-treat; OSA, one-stage assay; SE, standard error; Q, quartile.

Reduction in treated bleeds maintained over 3 years

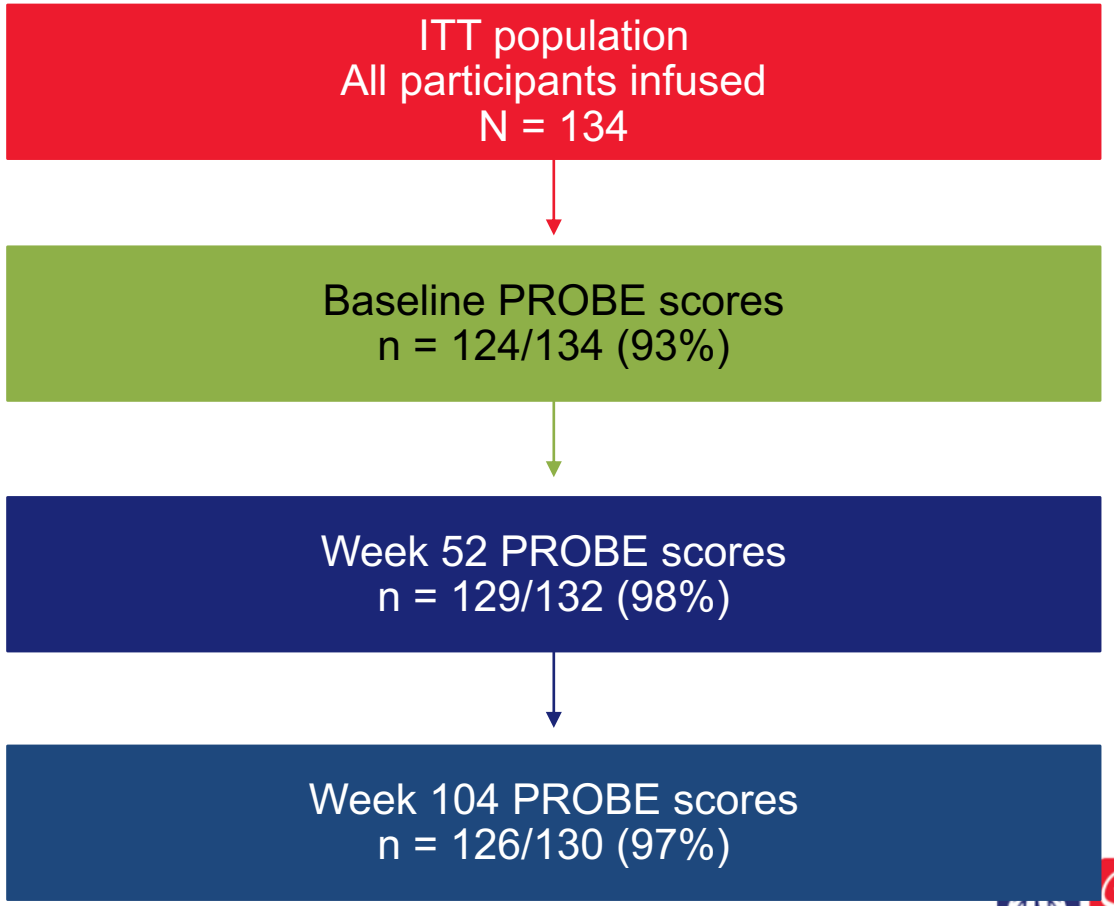


Rollover population (N = 112)

Missing data were not imputed. [a]Year 3 data were based on N = 110 due to participants who discontinued from the study.
ABR, annualized bleeding rate; SD, standard deviation; Q, quartile.

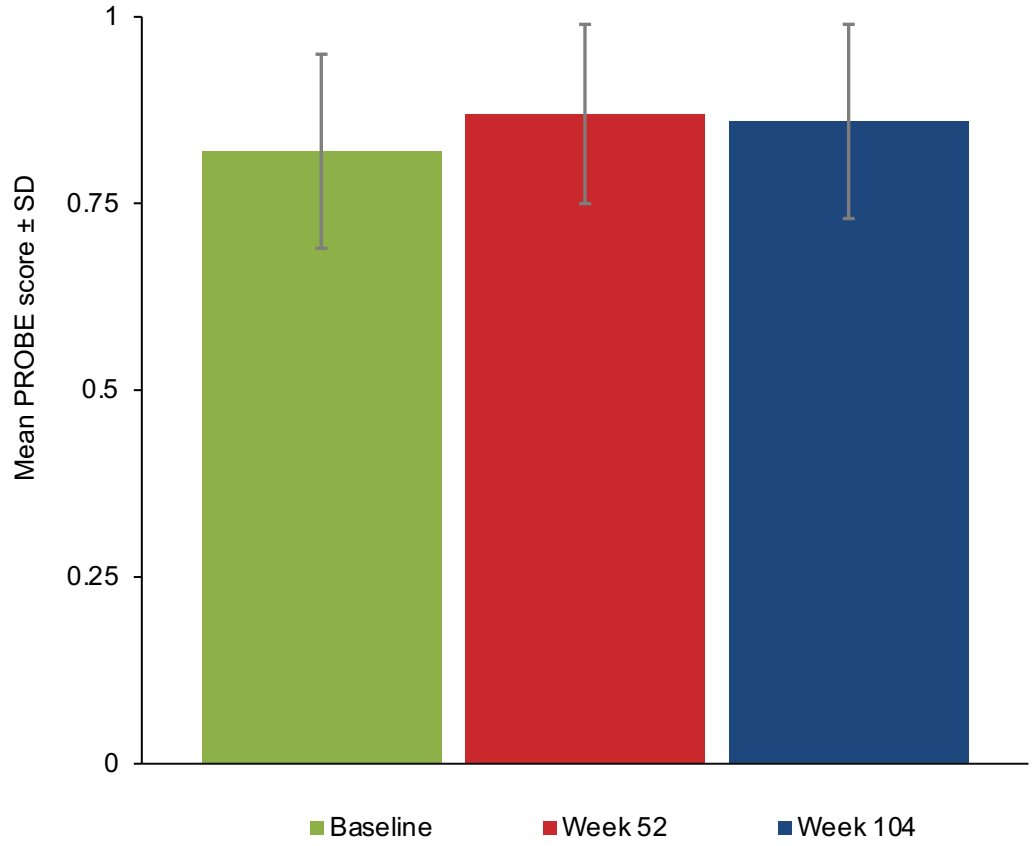
Participant characteristics and disposition

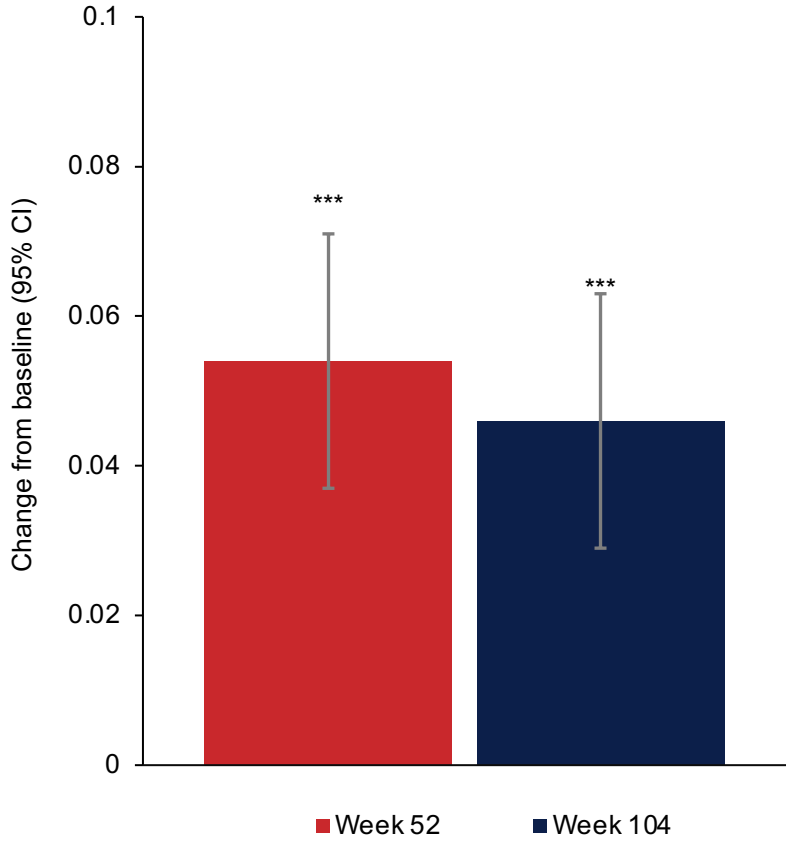
Baseline characteristics[1]	ITT (N = 134)
Age, years, mean ± SD	31.7 ± 10.3
Race, n (%)	
White	96 (71.6)
Asian	19 (14.2)
Black or African American	15 (11.2)
Hawaiian or Pacific Islander	1 (0.7)
Not provided	3 (2.2)
Hispanic or Latino ethnicity, n (%)	7 (5.2)
BMI, kg/m², mean ± SD	25.3 ± 4.6
Medical history, n (%)	
Hepatitis B	20 (14.9)
Hepatitis C	41 (30.6)
HIV	2 (1.5)
Number of problem joints,[a] n (%)	
0	97 (72.4)
1	17 (12.7)
2	9 (6.7)
3	8 (6.0)
>3	3 (2.2)



[a]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; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.
1. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25.

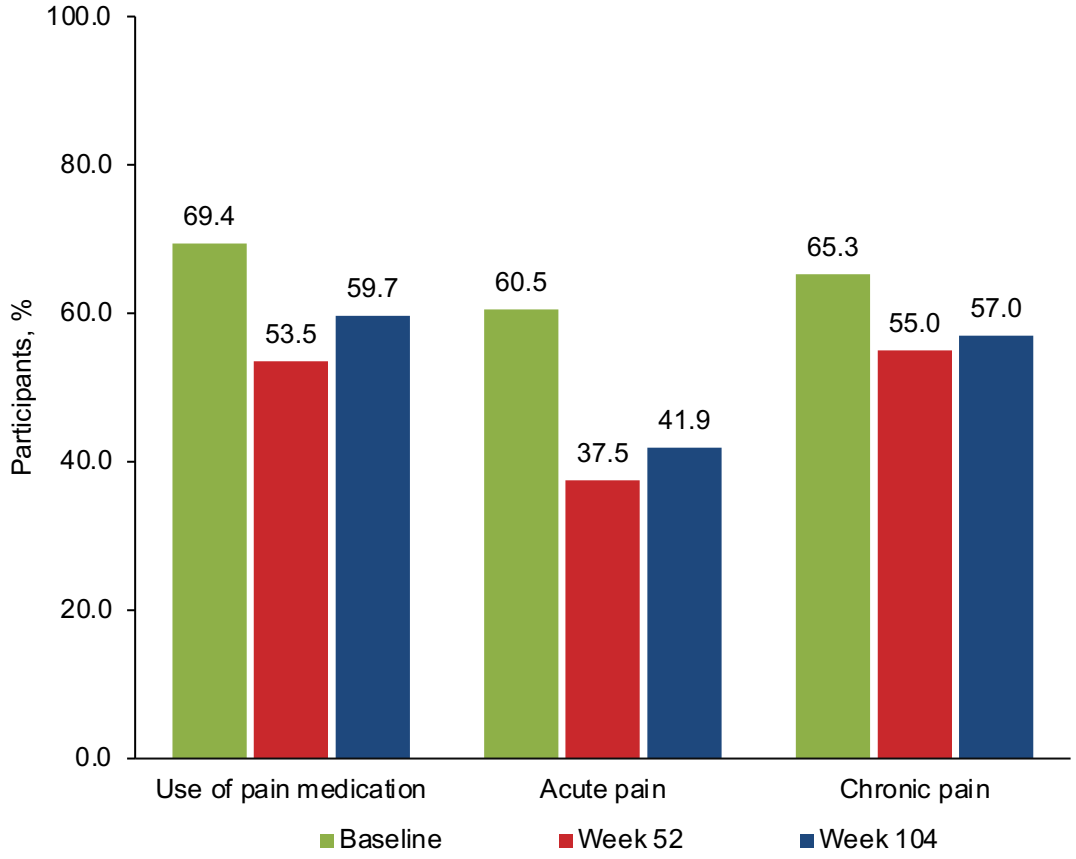
PROBE total scores improved at weeks 52 and 104

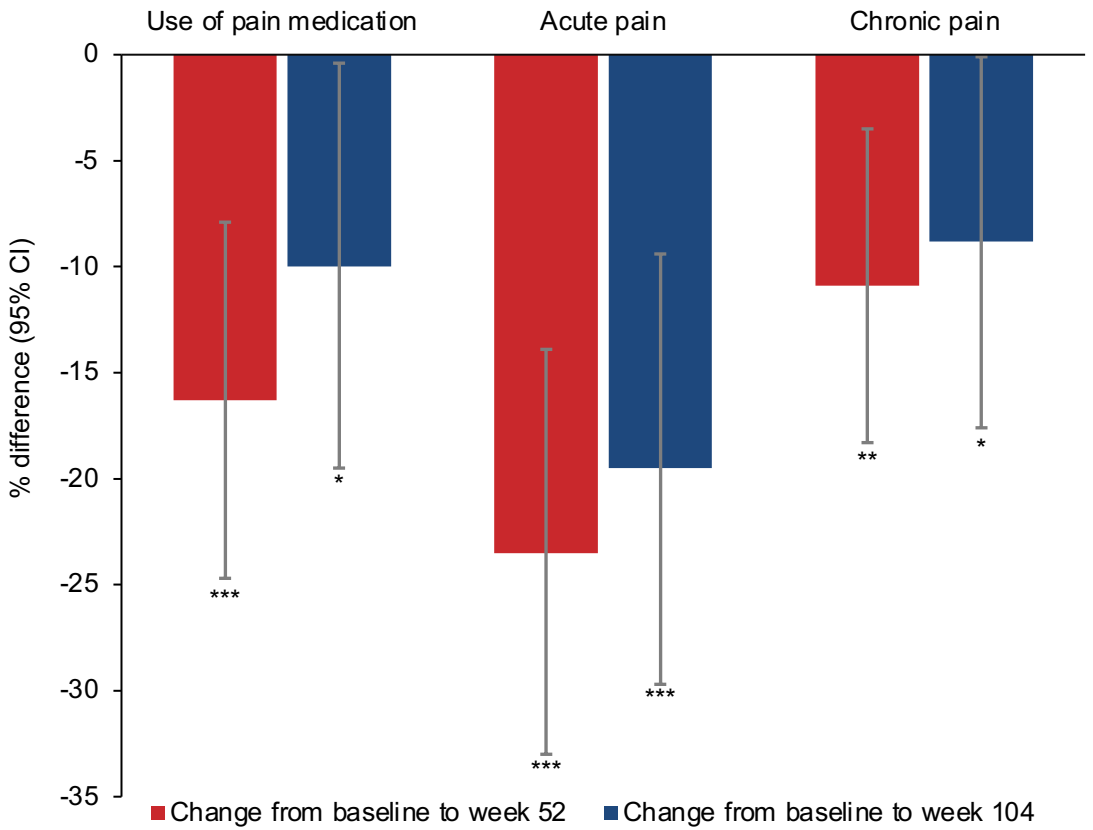




***P <0.001 compared to baseline using a linear mixed model. Data are mean ± SD or change from baseline (95% CI).
CI, confidence interval; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.

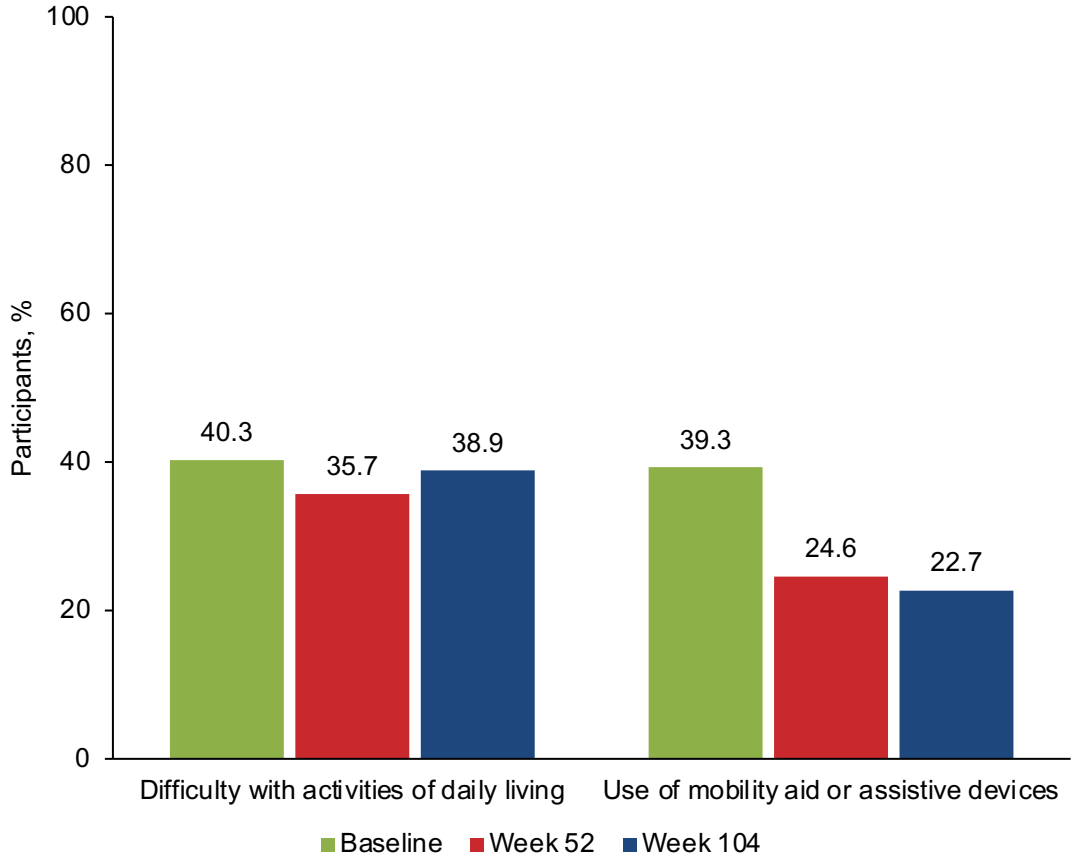
Outcomes for pain improved

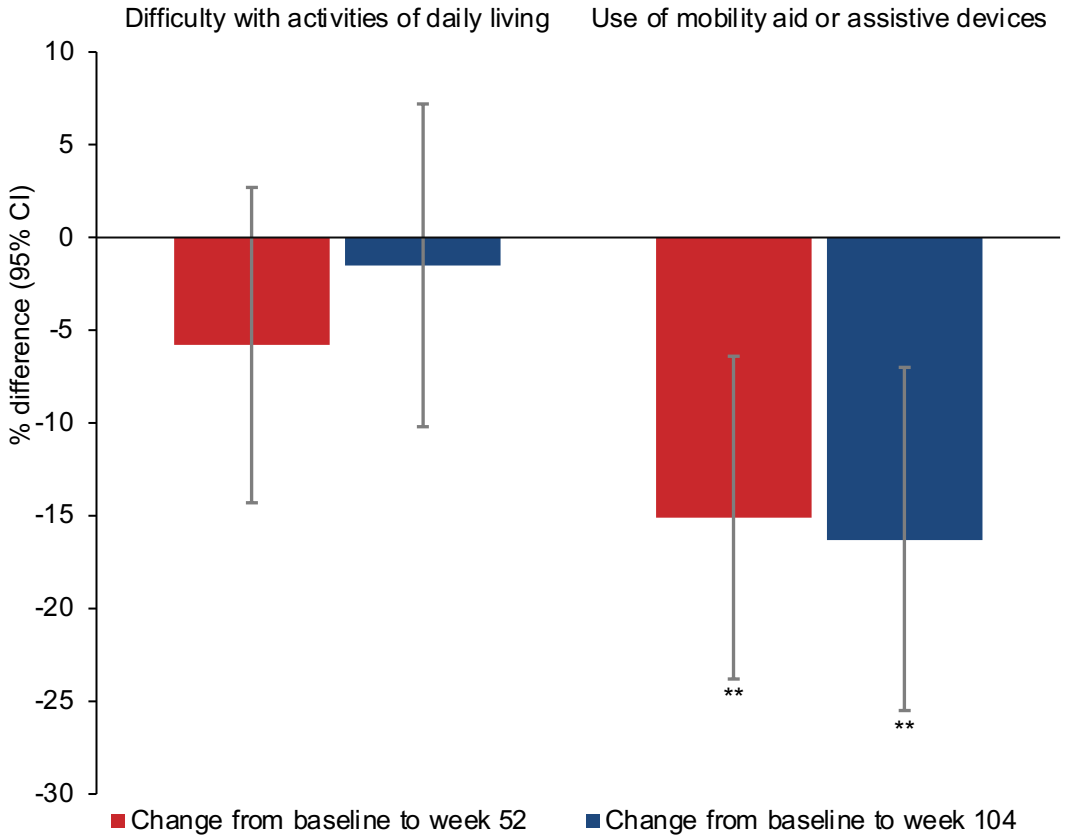




*P <0.05, **P <0.01, ***P <0.001 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

Outcomes for activities of daily living and mobility improved





**P <0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

GTR Objectives

Primary Objective

- to determine the long-term safety of factor VIII and factor IX gene therapies in patients with hemophilia

Secondary Objective

- to determine the long-term efficacy and the durability of factor VIII and factor IX gene therapies in patients with hemophilia;
- to assess long-term quality of life (EQ-5D-5L) and burden of disease (PROBE) post gene-therapy infusion.

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders. Core data set on safety, efficacy and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020 Oct. https://doi.org/10.1111/jth.15023

Data Collection

Data will be collected at:

- Baseline / Vector infusion
- Follow-up visits
  - Month 3, 6, 9, 12, 18, 24
  - Annually thereafter

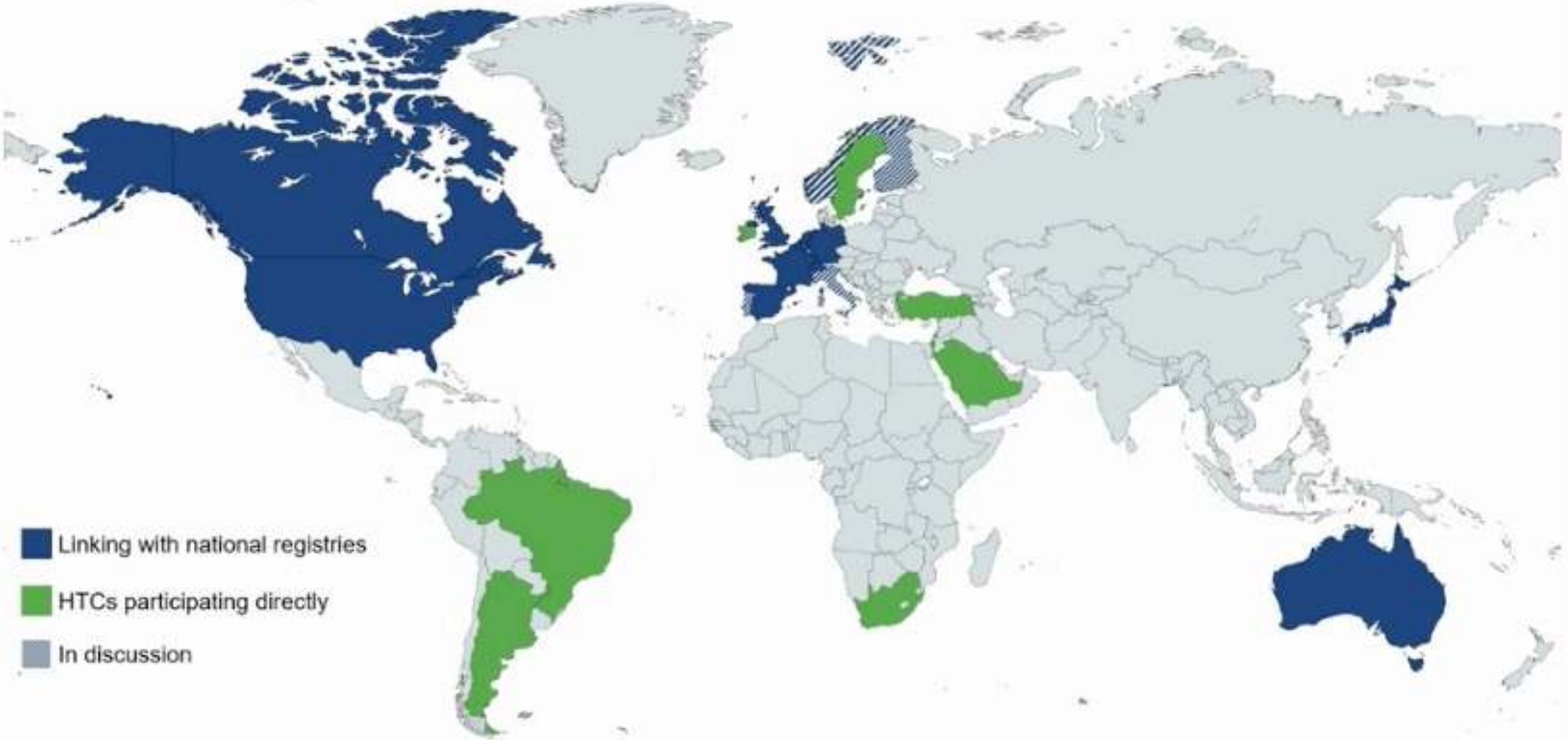
Data will be captured in the registry in one of 2 ways:

- Through data transfer from existing national hemophilia registries
- Directly via participating HTCs

Capture both post-regulatory approval and clinical trial participants

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders. Core data set on safety, efficacy and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020 Oct. https://doi.org/10.1111/jth.15023

Implementation Partners - Global



Questions?

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