Sustained efficacy and safety 3 years following infusion with etranacogene dezaparvovec in adults with severe or moderately severe hemophilia B in the Phase 3 HOPE-B clinical trial

#126

Steven W. Pipe[1], Paul van der Valk[2], Peter Verhamme[3], Peter Kampmann[4], Frank Leebeek[5], Michiel Coppens[6], Nigel Key[7], Nathan Visweshwar[8], Guy Young[9], Richard Lemons[10], Robert Klamroth[11], Niamh O'Connell[12], Sandra le Quellec[13], Paul E. Monahan[13], Cedric Hermans[14]

[1]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, US. [2]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands. [3]Center for Molecular and Vascular Biology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium. [4]Rigshospitalet, Copenhagen, Denmark. [5]Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands. [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands. [7]University of North Carolina, Chapel Hill, NC, US. [8]University of South Florida, Tampa, FL, US. [9]University of Southern California Keck School of Medicine, Children's Hospital Los Angeles, Los Angeles, CA, US. [10]University of Utah, Salt Lake City, UT, US. [11]Vivantes Klinikum im Friedrichshain, Berlin, Germany. [12]National Coagulation Centre, St. James's Hospital, Dublin, Ireland. [13]CSL Behring, King of Prussia, PA, US. [14]Division of Haematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium.

Introduction

- Etranacogene dezaparvovec, the successor of AMT-060 (**Figure 1**), is an approved liver-directed AAV5 gene therapy for hemophilia B[1–3]
- In the HOPE-B Phase 3 clinical trial, etranacogene dezaparvovec demonstrated superior bleed protection compared with factor IX (FIX) prophylaxis up to 24 months post-treatement[4,5]

Figure 1: Etranacogene dezaparvovec

AAV5, adeno-associated virus serotype 5; FIX, factor IX; hFIX, human factor IX.

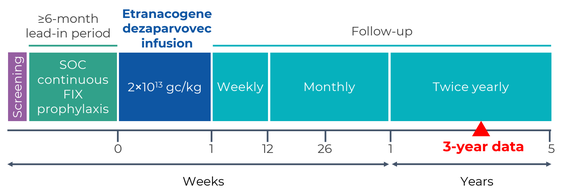
Objective

- **To report 36-month outcomes of etranacogene dezaparvovec from the Phase 3 HOPE-B trial in adult males with severe or moderately severe hemophilia B (FIX ≤2%; N=54)**

Methods

- The study design of the Phase 3 HOPE-B clinical trial (NCT03569891) is shown in **Figure 2**[4]
- The primary endpoint was the annualized bleeding rate (ABR) in the post-treatment period (Months 7–18) compared with the lead-in period, evaluated in a non-inferiority analysis[4]
  - Secondary endpoints included endogenous FIX activity, annualized FIX consumption, number of FIX infusions and adverse events (AEs)
- Participants were required to be on routine FIX prophylaxis prior to infusion (**Table 1**)[4]
  - Patients with pre-existing neutralizing antibodies (NAbs) to AAV5 were not excluded

Figure 2: Phase 3 HOPE-B open-label, single-arm study design[4]



FIX, factor IX; gc, genome copies; SOC, standard of care.

Results

STUDY PARTICIPANTS

- Only 2/54 patients did not complete 36 months follow-up:
  - One patient who was free of prophylaxis died (unrelated to treatment)
  - One patient who remained on prophylaxis withdrew consent for efficacy assessment

Table 1: Baseline characteristics[4,6]

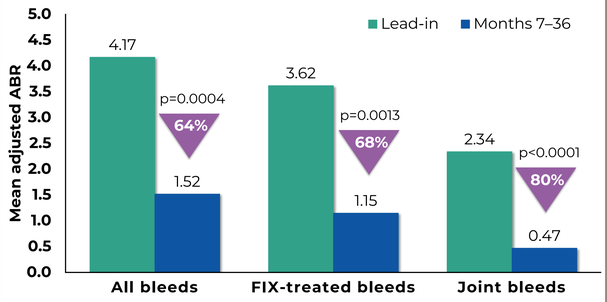
	Participants (N=54)
Mean age, years (range)	41.5 (19–75)
Hemophilia B severity, n (%)	
Severe [FIX<1%]	44 (81.5)
Moderately severe [FIX 1–2%]	10 (18.5)
History of infection, n (%)	
HIV+	3 (5.6)
Previous HBV	9 (16.7)
Previous HCV	31 (57.4)
Pre-existing AAV5 NAbs,* n (%)	21 (38.9)

AAV5, adeno-associated virus serotype 5; FIX, factor IX; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV+, human immunodeficiency virus-positive; NAb, neutralizing antibody.
*One participant had a titer of 3212 and 20 had a titer ≤678.

SUSTAINED HEMOSTATIC PROTECTION

- Mean adjusted ABR for all bleeds during Months 7–36 was reduced by 64% vs lead-in (p=0.0004; **Figure 3**)
- A 68% reduction in mean adjusted ABR for FIX-treated bleeds was observed between lead-in and Months 7–36 (p=0.0013)
- Overall, 61% (33/54) of participants experienced no joint bleeds at 36 months post-treatment

Figure 3: Mean adjusted ABR during ≥6-month lead-in vs Months 7–36 post-treatment

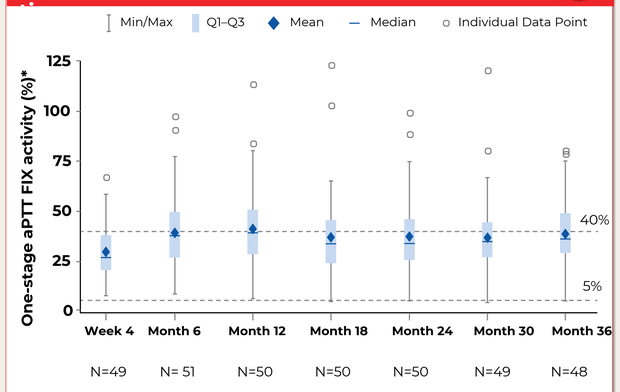


ABR, annualized bleeding rate; FIX, factor IX.

SUSTAINED ENDOGENOUS FIX ACTIVITY

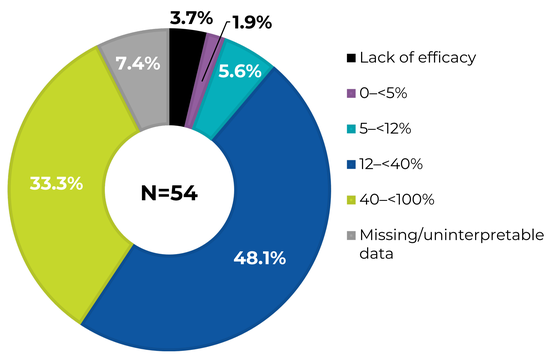
- Mean ± standard deviation (SD) FIX activity was sustained at 41.5 ± 21.7 IU/dL (n=50), 36.7 ± 19.0 IU/dL (n=50), and 38.6 ± 17.8 IU/dL (n=48) at 12 months, 24 months, and 36 months post-treatment, respectively (**Figure 4**)
- By Month 36, FIX activity levels were in the mild and normal range for 47/54 patients (87%; **Figure 5**)
  - Four patients (7.4%) had missing/uninterpretable data

Figure 4: Endogenous FIX activity levels over



*One-stage FIX activity assays. Only uncontaminated samples were included in analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use.
aPTT, activated partial thromboplastin time; FIX, factor IX.

Figure 5: FIX activity level* ranges at 36 months post-treatment



FIX, factor IX.
*Based on one-stage FIX activity levels from central laboratory results. Only "uncontaminated" samples were included in analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use.

REDUCED EXOGENOUS FIX USE

- 94.4% (51/54) of participants were free from continuous FIX prophylaxis through to Month 36 post-treatment
- FIX replacement use significantly decreased from lead-in by 96% (**Figure S1**; p<0.0001)

SAFETY

- A total of 93 treatment-related AEs occurred up to 36 months post-treatment with 97.8% reported in the first 6 months (**Table 2**)
- No treatment related serious AEs, FIX inhibitors or thromboembolic events occurred
- No new deaths, hepatocellular carcinoma, or late treatment-related alanine aminotransferase elevations were reported during Year 3

Table 2: Treatment-related AEs*

	At Month 36 follow-up	
	N (%)	# of events
At least 1 TRAE	38 (70.4)	93
ALT increased	9 (16.7)	10
Headache	8 (14.8)	9
Influenza like illness	7 (13.0)	8
AST increased	5 (9.3)	6
CPK increased	4 (7.4)	6
Dizziness	4 (7.4)	4
Fatigue	4 (7.4)	4
Nausea	4 (7.4)	4
Arthralgia	3 (5.6)	3

*Reported as MedDRA-PT and coded using MedDRA Version 26.0.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TRAE, treatment related adverse event.

Conclusions

- **Etranacogene dezaparvovec provides long-term, stable FIX Padua expression and superior bleed protection compared with FIX prophylaxis, with a favorable safety profile over 3 years post-treatment**

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5. Coppens M, et al. *Lancet Haematol*. Published online March 1, 2024. doi:10.1016/S2352-3026(24)00006-1
6. Pipe S, et al. Oral presentation at 65th ASH Annual Meeting 2023

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Disclosures

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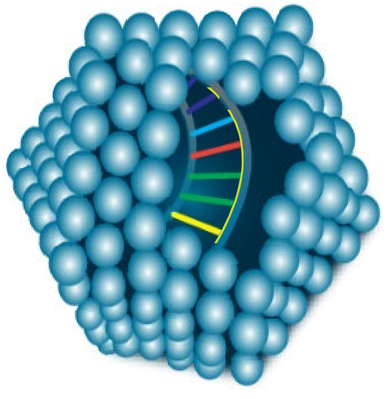
CSL Behring

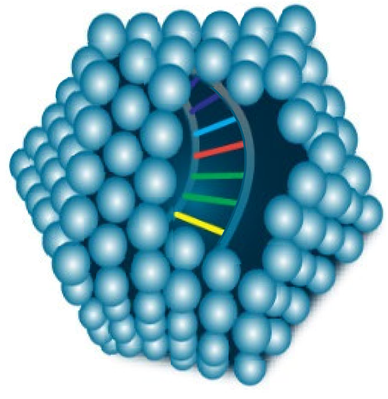
Figure 1: Etranacogene dezaparvovec

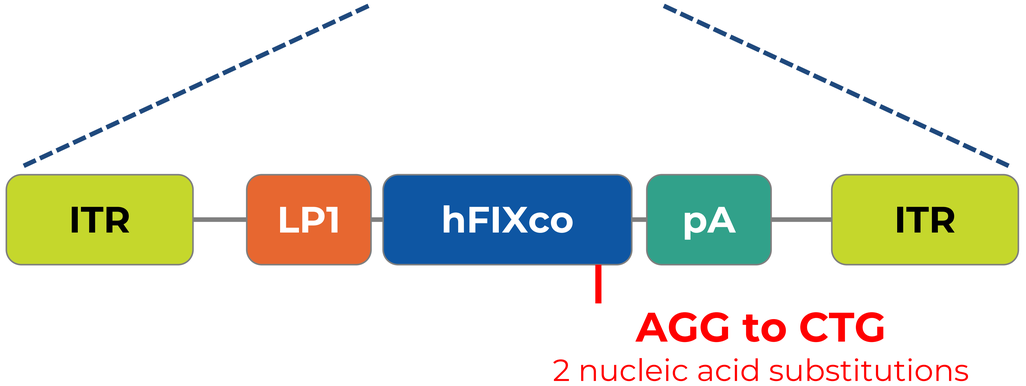
AMT-060 (AAV5-hFIX)



Wild-type **FIX**

Etranacogene dezaparvovec (Hemgenix®, AAV5-Padua hFIX)

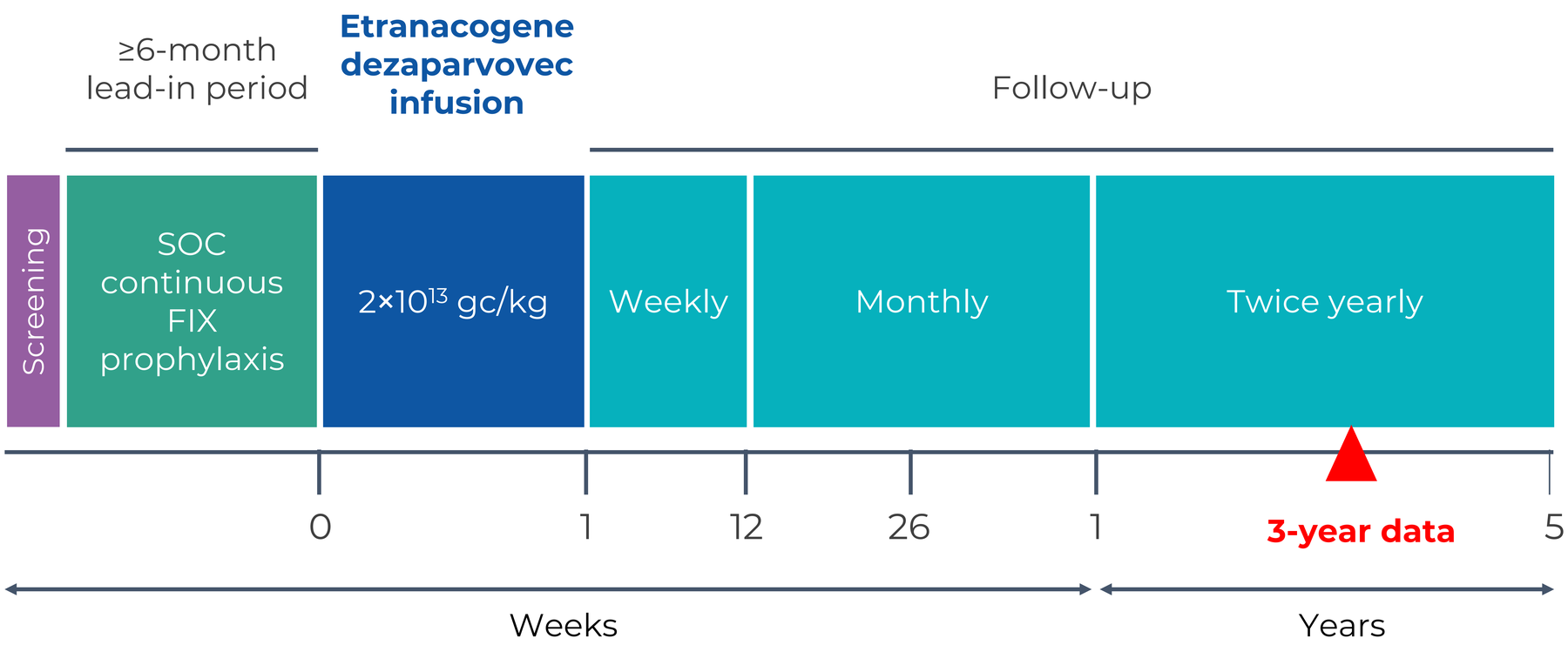




Highly active **FIX Padua variant** (R388L)

AAV5, adeno-associated virus serotype 5; FIX, factor IX; hFIX, human factor IX; ITR, inverted terminal repeat; LP1, liver promoter 1; pA, poly A.

Figure 2: Phase 3 HOPE-B open-label, single-arm study design



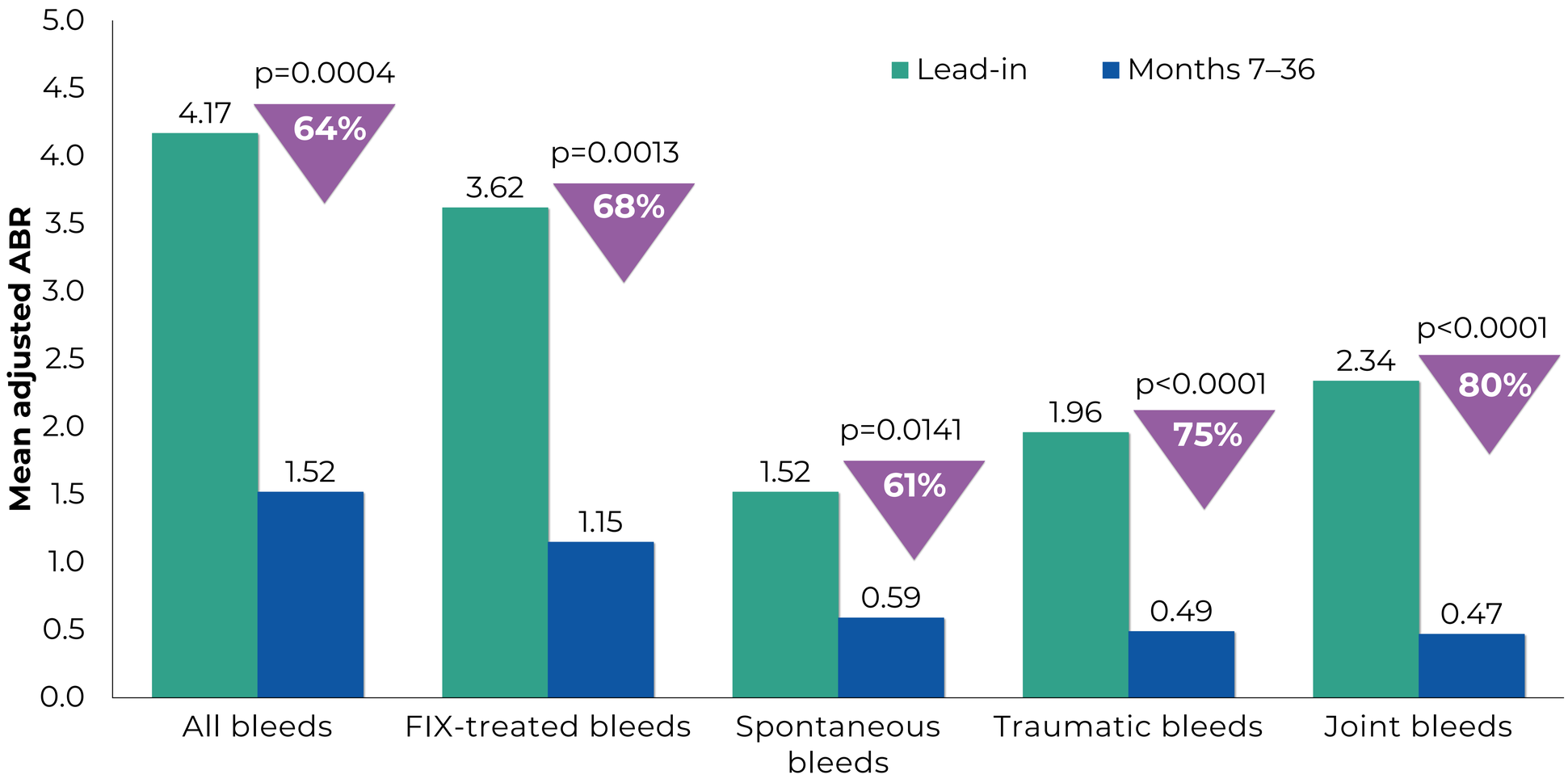
Key exclusion criteria:

- FIX inhibitors
- Active hepatitis B/C infection
- Uncontrolled HIV infection
- Evidence of advanced liver fibrosis

Pre-existing AAV5 NAbs were assessed but not used as an exclusion criteria

AAV5, adeno-associated virus serotype 5; FIX, factor IX; gc, genome copies; HIV, human immunodeficiency virus; NAb, neutralizing antibody; SOC, standard of care.

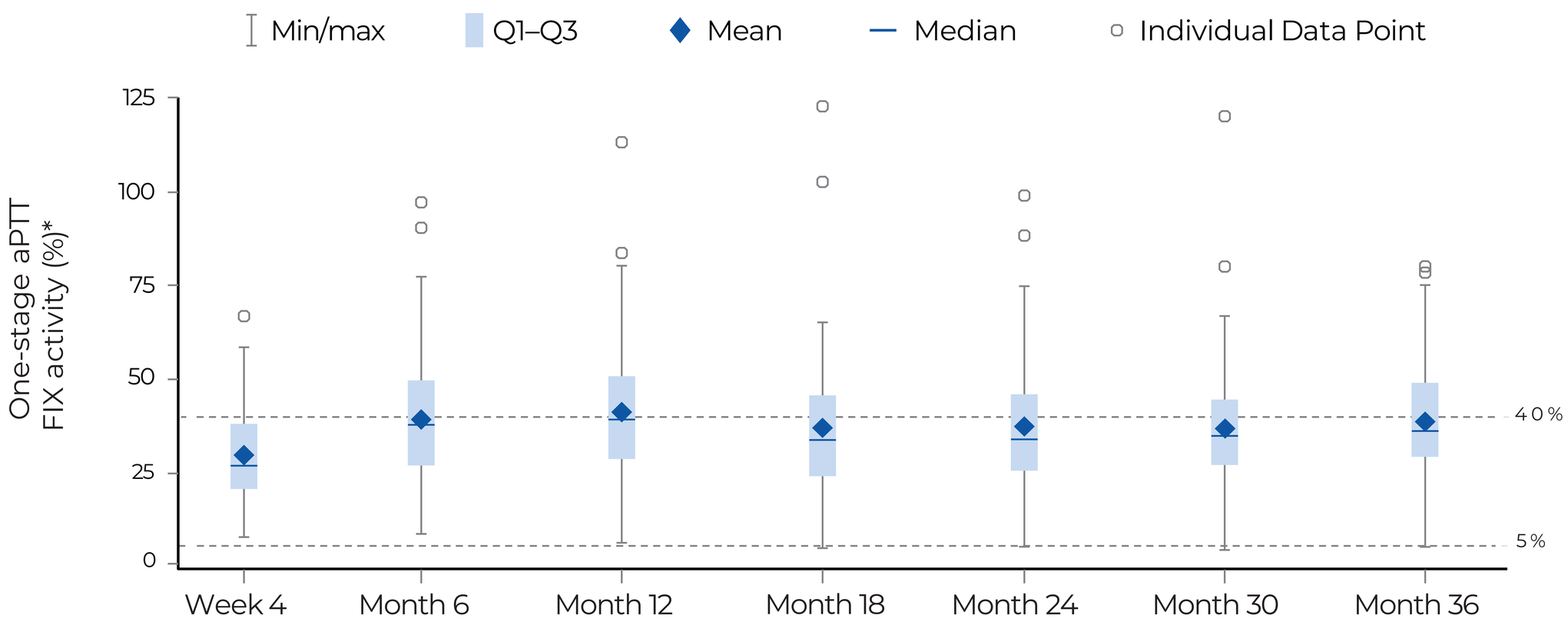
Figure 3: Mean adjusted ABR during ≥6-month lead-in vs Months 7–36 post-treatment



Etranacogene dezaparvovec stably reduced ABR by 64% and demonstrated superiority to prophylaxis in the lead-in period through 3 years post-treatment

Superiority was tested at a one-sided alpha level of 0.025 (p-value of ≤0.025 for post-dose / lead-in was statistically significant).
P-values were not adjusted for multiplicity.
ABR, annualized bleeding rate; FIX, factor IX.

Figure 4: Endogenous FIX activity levels over time



Number of participants with data:	49	51	50	50	50	49	48

Overall stable FIX activity levels over 3 years post-treatment

FIX activity levels	At year 3
Mean ± SD	38.6 ± 17.8
Median	36.0
IQR	29.5 – 48.1
Min – Max	4.8 – 80.3

*One-stage FIX activity assays. Only uncontaminated samples were included in analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use.
aPTT, activated partial thromboplastin time; FIX, factor IX; IQR, interquartile range; SD, standard deviation.

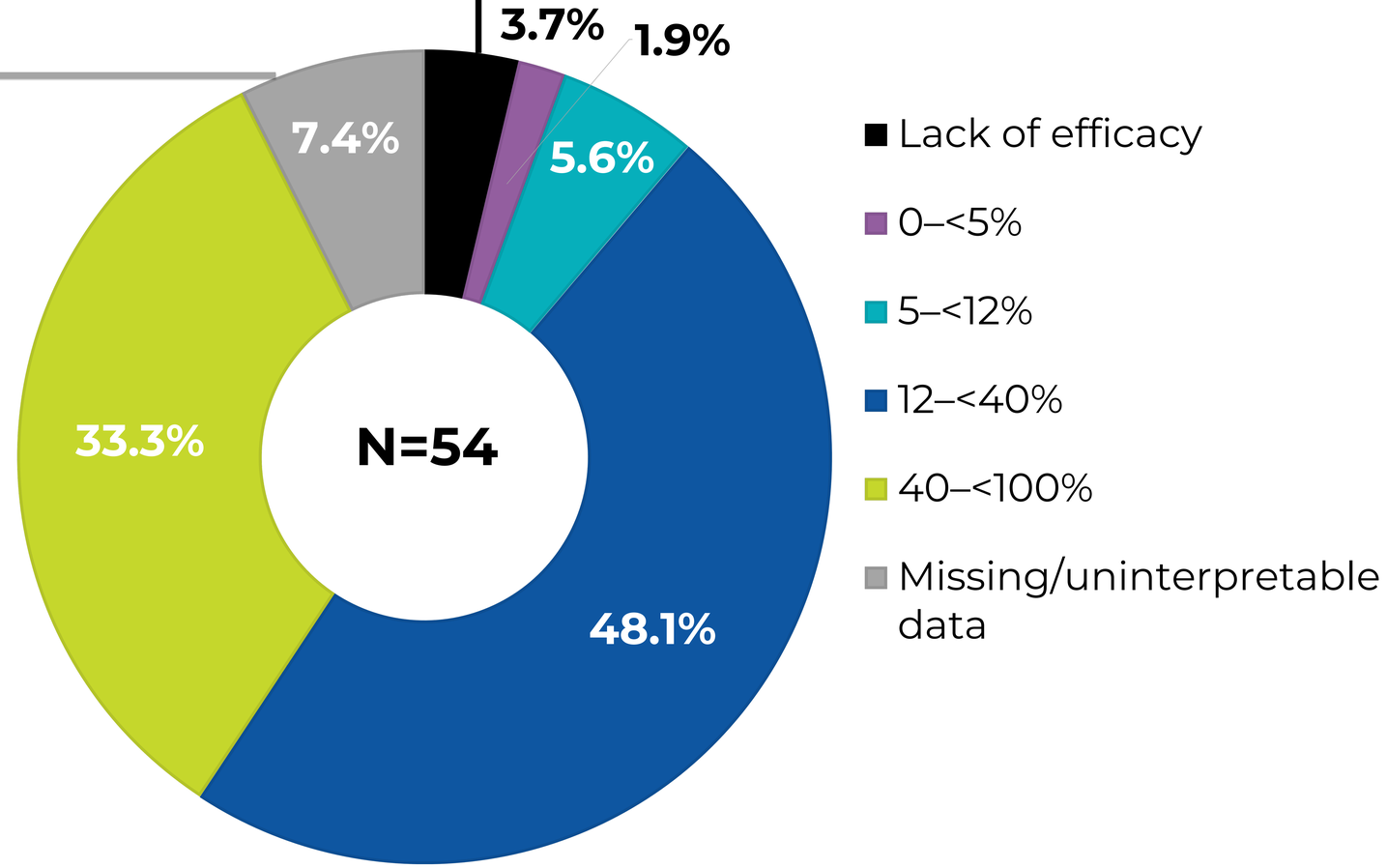
Figure 5: FIX activity level* ranges at 3 years post-treatment

2 (3.7%) lack of efficacy

- Participant with highest NAb titer
- Participant who received ~10% of the planned dose

4 (7.4%) missing/uninterpretable data

Reason for missing/uninterpretable data	Last FIX activity level*
Death at month 15 (unrelated to treatment)	43.7%
Liver transplant (HCC unrelated to treatment)	36.7%
Return to FIX prophylaxis at month 30	3.6%
Non-analyzable sample (hemolysis)	33.5%



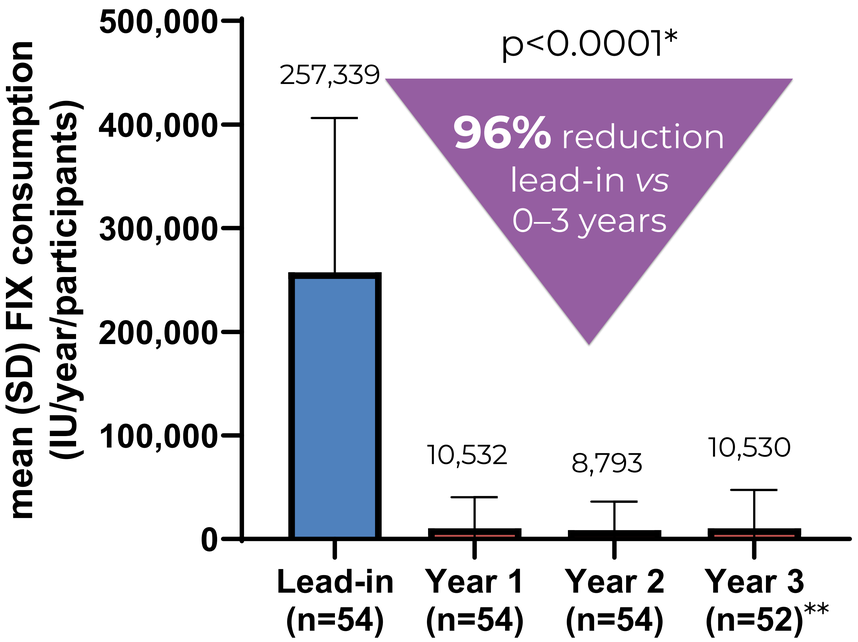
>87% of total participants were in the mild and normal FIX activity level range at 3 years post-treatment

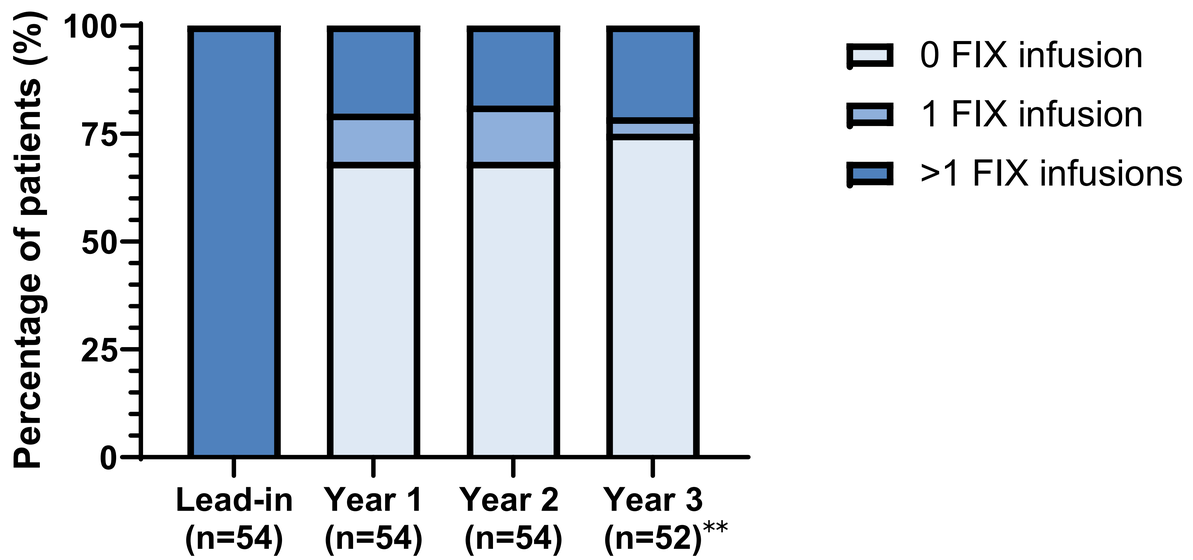
*Based on one-stage FIX activity levels from central laboratory results. Only “uncontaminated” samples were included in analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use

FIX, factor IX; HCC, hepatocellular carcinoma, NAb, neutralizing antibody.

Figure S1: Exogenous FIX use over 3 years of follow-up

94.4% (51/54) of participants were free from continuous prophylactic FIX infusions through 3 years post-administration





46.3% (25/54) of participants received no FIX infusions over 3-year period post-treatment

*p-value is calculated using a paired t-test comparing post-treatment and lead-in periods.
**One patient died (prophylaxis free) and another patient who remained on prophylaxis withdrew consent for efficacy assessment.
FIX, factor IX; SD, standard deviation.

Disclosures

SWP has received consultancy fees from Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, Equilibra Bioscience, GeneVentiv, HEMA Biologics, Freeline, LFB, Novo Nordisk, Pfizer, Regeneron/Intellia, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics, and uniQure; has received research funding from Siemens; and holds a membership on a scientific advisory committee for GeneVentiv and Equilibra Bioscience.

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SlQ and **PEM** are employees of CSL Behring.

CH has received consultancy and/or lecture fees from Bayer, Takeda, Roche, CSL Behring, Novo Nordisk, Pfizer, Sobi, LFB, OctaPharma, Uniqure and Biomarin.