CSL Gene Therapy

Data E-Flipbook

This self-directed learning tool summarizes data from the CSL Behring Gene Therapy Clinical Trial Program for Hemophilia B

CSL Behring Gene Therapy Clinical Trial Program

USA-HGX-0220

User Guide

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IMPORTANT SAFETY INFORMATION

Warning and Precautions

Infusion Reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved.

Hepatotoxicity/Hepatocellular Carcinoma

Post-dose, monitor for elevated transaminase levels. Consider corticosteroid treatment should elevations occur. The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. For patients with preexisting risk factors for hepatocellular carcinogenicity, perform regular (eg, annual) abdominal ultrasound and alpha-fetoprotein testing following administration.

Immune-mediated neutralization of the AAV5 vector capsid

Preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired levels.

Monitoring Laboratory Tests

In addition to monitoring liver function, monitor for Factor IX activity and Factor IX inhibitors after administration.

Adverse Reactions

The most common adverse reactions (incidence ≥5%) were elevated ALT, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, nausea, malaise, and elevated AST.

Indication

HEMGENIX®, etranacogene dezaparvovec-drlb, is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

HEMGENIX is for single use intravenous infusion only.

Contraindications: None.

Please see full prescribing information for HEMGENIX.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Introduction

Understanding Hemophilia B

Hemophilia B (HB) is a rare, monogenic, X-linked congenital bleeding disorder characterized by a deficiency of coagulation factor IX (FIX)[1,2]

HB affects mostly men; women are usually heterozygous carriers of 1 mutated gene[1,3]

Figure 1

Global HB prevalence at birth: **5/100,000 males[4]**

People living with HB (PWHB) **globally in 2020: 37,998[4]**

Classification of HB severity is characterized by FIX activity[1]

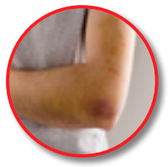
Table 1. HB severity classification[1]

Severity	Clotting factor level	Bleeding episodes
Severe	<1 IU/dL (<0.01 IU/mL) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1–5 IU/dL (0.01–0.05 IU/mL) or 1%–5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5–<40 IU/dL (0.05–<0.40 IU/mL) or 5%–<40% of normal	Severe bleeding with major trauma or surgery; rare spontaneous bleeding

IU, international unit.

~80% of bleeding episodes occur in the joints[1]

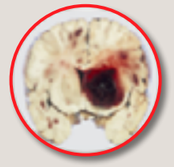
Elbow



Knee

Ankle

Incidence: 0.29%–0.54%[5]



PWH with severe disease are at greater risk of **life-threatening bleeding episodes** such as **intracranial hemorrhages[5,6]**

HB unmet need

Standard of care is lifelong coagulation factor replacement, either prophylactic or episodic, with guidelines recommending prophylaxis for improved clinical outcomes[1,7–10]

Treatment burden

Joint damage

Inhibitor development

High lifetime treatment costs

Pain and limits on activity

Introduction

What Is Gene Therapy?

Gene therapy is a transformative treatment to address underlying genetic mutations[10,11]

There are 4 basic gene therapy approaches

Gene replacement

Functional gene replaces a mutated, nonworking gene[12]

Gene silencing

Inactivation of toxic effect of mutated gene[12]

Gene addition/ transfer

Overexpression of exogenous gene to impact cellular function[12]

Gene editing

Permanent manipulation of genome[12]

Gene therapy aims for durable expression of the therapeutic gene or *transgene* at a level sufficient to ameliorate disease symptoms with minimal adverse events (AEs)[13]

The vector

Gene delivery vehicles or **vectors** perform **efficient gene delivery** to the target cells/tissues

- There are 2 types of vectors: viral and nonviral (polymers, lipids, peptides, inorganic materials, or hybrid systems)[12,14]

Ideal vector characteristics

Allows for a single administration with durable effect[15,16]

Delivers therapeutic gene to the appropriate organ[15]

Favorable immunologic profile allowing broad use[16]

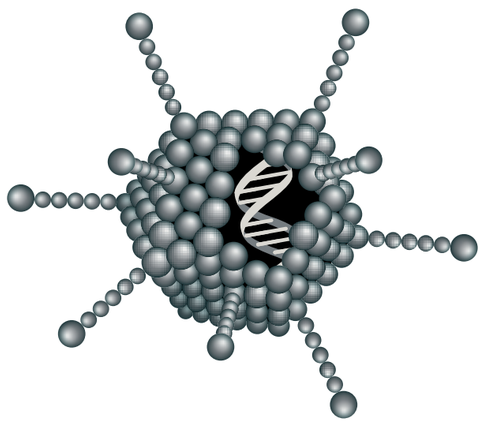
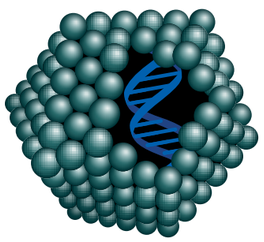
Minimal off-target effects[15]

The adeno-associated virus (AAV)

AAV was discovered in 1965 and belongs to the genus *Dependoparvovirus* within the family *Parvoviridae*[12,17,18]

AAVs are not associated with disease and do not replicate without a helper virus such as adenovirus (Figure 2)[19]

Figure 2. Differences between adenovirus and AAV[12,17]

Adenovirus	AAV
	

AAV as a Vector for Gene Delivery

Exposure to wild-type (WT) AAV during childhood often results in **persistent titers of AAV antibodies or neutralizing antibodies (NAbs)** sufficient to neutralize subsequent AAV infection[20–23]

- Seroprevalence of AAV NAbs **varies** by age, geographic location, and serotype[21–24]

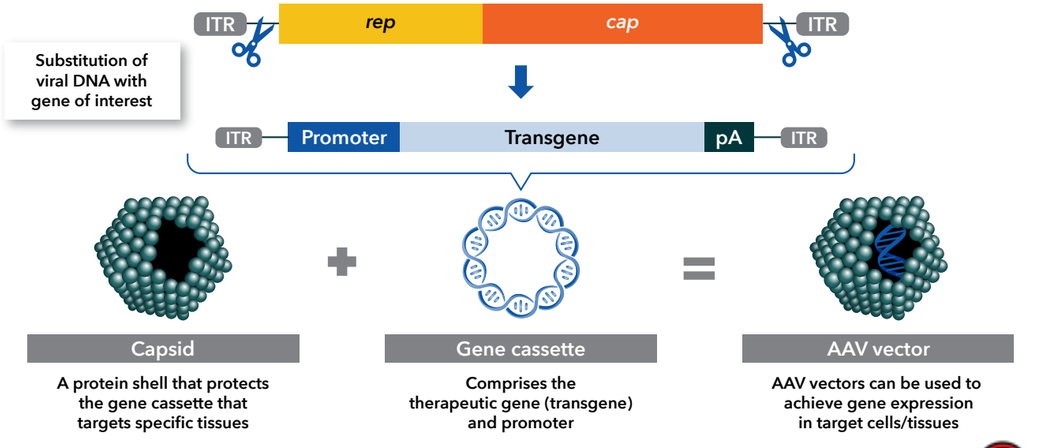
Recombinant AAV (rAAV) vectors are leading platforms for gene therapy[17]

Vector design

rAAV vectors are derived from wild-type (WT)[17,18] (Figure 3)

- The viral genome of WT AAV is replaced with the gene cassette, which comprises the promoter and the transgene[12,19]
- The inverted terminal repeats (ITRs) are retained to guide genome replication and packaging during vector production[17,18]

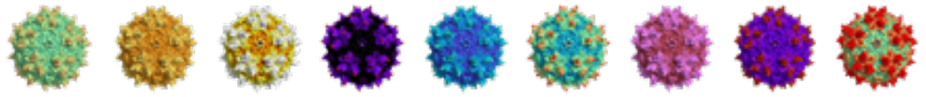
Figure 3. Anatomy of an AAV vector[12,18,19]



AAV serotypes

AAV vector-promoter combination results in efficient, tissue-specific expression[25] (Table 2)

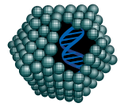
Table 2. AAV serotypes[25]



	AAV1	AAV2	AAV3	AAV4	AAV5	AAV6	AAV7	AAV8	AAV9
Bio-distribution (mouse model)	Liver, heart, sk muscle, adipose, CNS	Liver, heart, muscle	Heart, liver	Heart, lung, liver	Liver	Liver, heart, sk muscle	Liver, sk muscle	Heart, liver, CNS, muscle	Liver, heart, CNS, lung, sk muscle
Large animal model	Heart, CNS, sk muscle	CNS, eye		Eye	Liver, CNS	Heart, CNS, sk muscle		Liver, eye, CNS	Heart, CNS, sk muscle

CNS, cemtral nervous system.
SK muscle, skeletal muscle.

AAV vector



Advantages[26,27]

- Transduction into a range of tissues
- Long-term gene expression
- Poor integration into the host genome
- Low pathogenicity
- Low immunogenicity

Potential challenges[26,27]

- Gradual loss of transgene expression
- Preexisting humoral immunity to WT AAV

Introduction

CSL Hemophilia B Gene Therapy Clinical Development Program

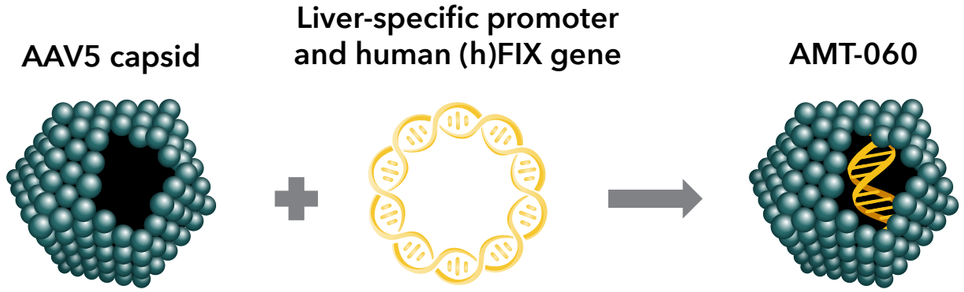
Clinical development program

Currently assessing single-administration gene therapy for severe/moderately severe HB[28-30]

	Etranacogene dezaparvovec-drlb	
AMT-060 phase 1/2	**Phase 2b**	**HOPE-B phase 3**
Cohort 1 (n=5) received AMT-060 **5 × 10^{12} gc/kg**	Participants (n=3) received etranacogene dezaparvovec-drlb **2 × 10^{13} gc/kg**	Participants (n=54) received etranacogene dezaparvovec-drlb **2 × 10^{13} gc/kg**
Cohort 2 (n=5) received AMT-060 **2 × 10^{13} gc/kg**		
Safety evaluation and proof of concept[28] Determine safety profile of a single intravenous (IV) infusion of AMT-060	**Safety and efficacy evaluation[29]** Determine efficacy and safety of a single IV infusion of etranacogene dezaparvovec-drlb	**Safety and efficacy evaluation[30]** Determine efficacy and safety of a single IV infusion of etranacogene dezaparvovec-drlb

gc, genome copy.

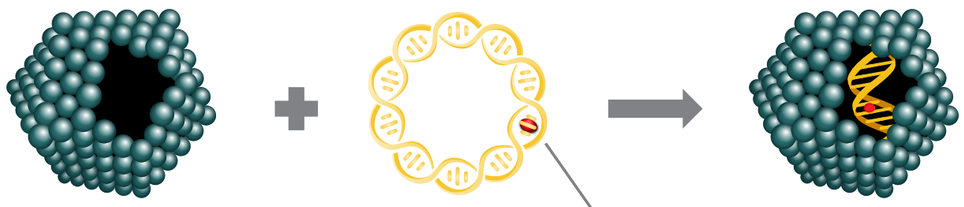
What is AMT-060?[28]



Previously tested in humans without sign of cellular immune activation

AMT-060 – WT hFIX

What is etranacogene dezaparvovec-drlb?[29,31]



Previously tested in humans without sign of cellular immune activation

Padua variant (highly active)

AGG to CTG in gene resulting in **R338L** in protein

Introduction

What is the difference between AMT-060 and etranacogene dezaparvovec-drlb?

AMT-060		Etranacogene dezaparvovec-drlb
AAV5-hFIX		AAV5-hFIXco-Padua
	vs	

Single difference is a **single amino acid substitution (R338L)**, termed the Padua variant, in the FIX gene[29]

Etranacogene dezaparvovec-drlb is the enhanced version of AMT-060, delivering the hyperactive Padua variant[29]

The switch of transgene was not expected to influence other previously reported safety characteristics of AMT-060 at the established dose of 2×10^{13} gc/kg[28,29]

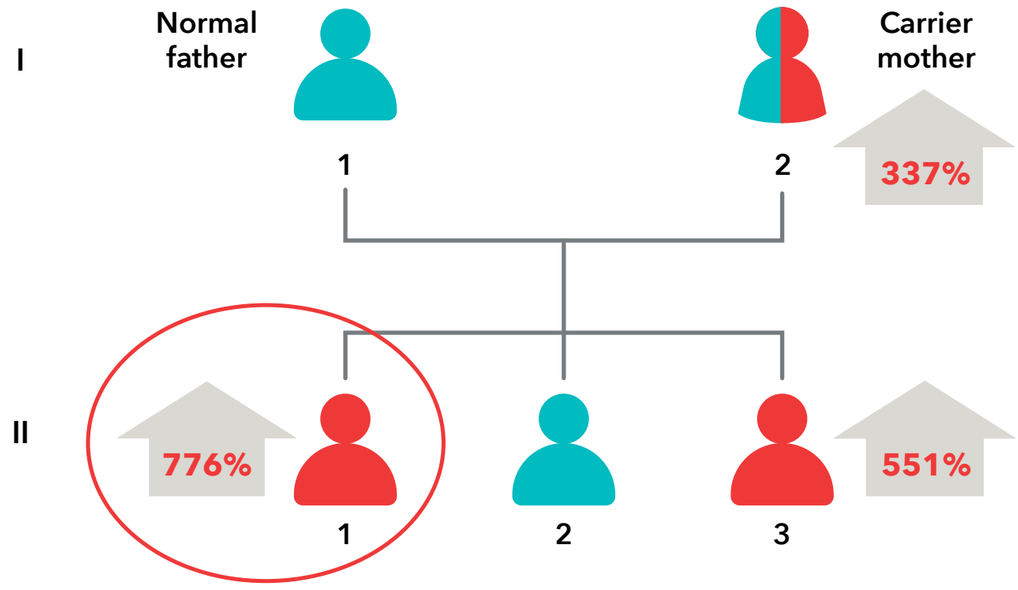
In silico analyses indicated no increased risk of potential immunogenicity for the FIX-Padua protein compared with the WT FIX protein[32]

The Padua Variant

The substitution of leucine for arginine at position 338 (R338L) in the FIX gene results in a hyperfunctional FIX[33]

The increased coagulant activity of FIX has an X-linked inheritance pattern[33] (Figure 4)

Figure 4. Padua variant inheritance pattern[33]



The mutation leads to an **~8-fold increase** in FIX activity vs WT FIX[33]

AMT-060 Program Overview

AMT-060 Phase 1/2 Study

Phase 1/2, open-label, uncontrolled, single-dose, dose-ascending, multicenter trial investigating rAAV5-hFIX (AMT-060) in adult patients with severe or moderately severe HB (NCT02396342)[28,34-37]

Study objectives and endpoints

Determine the number of patients who experienced AEs after a single IV infusion of AMT-060 over a 5-year period[28]

Safety[28]

- Treatment-related adverse events (TRAEs)
- NAbs to AAV5
- Antibodies against FIX (including inhibitors)
- Total IgM and IgG against AAV5
- AAV capsid-specific T cells
- AMT-060 vector shedding
- Inflammatory markers

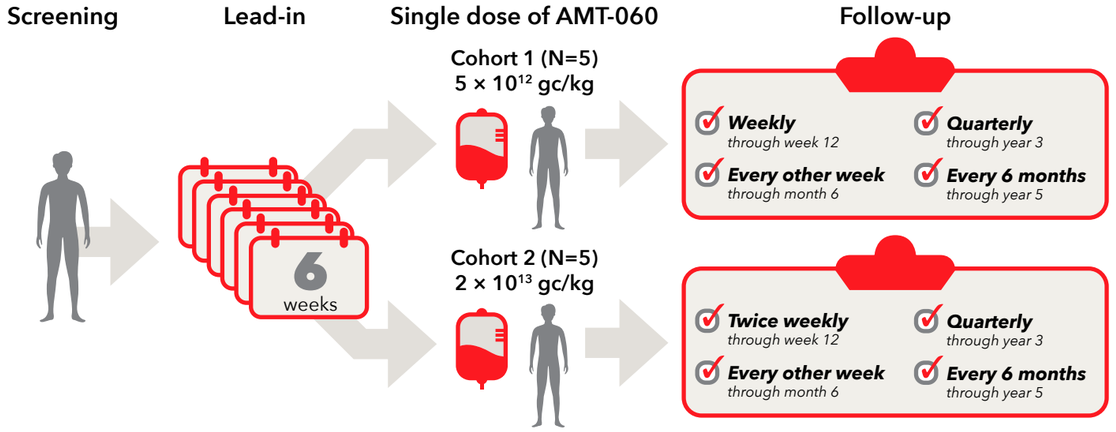
Therapeutic effect[28]

- FIX activity levels
- FIX consumption

Ig, immunoglobulin.

Study design

Figure 5. AMT-060 phase 1/2 study design[28]



Prophylaxis was tapered and discontinued by 12 weeks if FIX activity levels were maintained at ≥2 IU/dL.

Key inclusion criteria[28]

- Males age >18 years
- Congenital severe or moderate HB
- On prophylaxis or on-demand therapy
- Current/past ABR of ≥4 or chronic hemophilic arthropathy
- >150 previous exposure days of FIX protein

Key exclusion criteria[28]

- FIX inhibitors (≥0.6 BU/mL)
- Presence of NAbs to AAV5[a]
- ALT and/or AST >2 × ULN, total bilirubin >2 × ULN, ALP >2 × ULN, creatinine >1.5 × ULN
- Any coagulation disorder other than HB
- Active or untreated HIV, HBV, HCV infections
- Body mass index <16 or ≥35 kg/m^2

[a]Criterion was revisited; a subsequent analysis found preexisting AAV5 NAbs in 3 of the 10 participants.[37]
ABR, annualized bleeding rate; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BU, Bethesda unit; HBV, hepatitis B virus; HCV, hepatitis C virus; ULN, upper limit of normal.

AMT-060 Program Results

Baseline characteristics

Table 3. Baseline characteristics[28,36]

Variable	Cohort 1 (n=5)	Cohort 2 (n=5)
Age, y	69 (35–72)	35 (33–46)
Weight, kg	85 (71–89)	84 (71–96)
FIX use[a] Prophylaxis, IU/week Annualized mean, IU/year	 4000 (2000–8000) 354,800	 4000 (4000–10,500)[b] 173,200
Mean no. of bleeds in the year before enrollment, total Spontaneous Traumatic Unknown	14.4 9.8 2.8 1.8	4.0[c] 3.0 1.0 0.0
Hemophilia Joint Health Scores[d]	27 (2, 49)	6 (0, 17)
HIV-positive status, n	1	0
Prior hepatitis C infection, n	4	2
AAV5 NAb+, luciferase assay	3	0

Values are median (minimum, maximum) unless otherwise stated. [a]Every other day used as 3.5 × per week for calculations. [b]One participant in cohort 2 received on-demand treatment and is therefore not included. [c]Historical bleed data missing for 1 participant in cohort 2 who is therefore not included. [d]Joint status was assessed using the Haemophilia Joint Health Score version 2.1.

Long-term safety profile of AMT-060

- Reported **TRAEs** (Table 4)[36]
- Three **treatment-related serious adverse events (SAEs)** occurred within the first 3.5 months[28,35,36,a]
- Three **treatment-unrelated SAEs** were also reported[36,b]
- **No participants** developed FIX inhibitors[28,35,36]

[a]Treatment-related SAEs included short, self-limiting fever in first 24 hours post-AMT-060 (1 participant) and mild, asymptomatic elevations in liver enzymes (2 participants; 1 in each cohort). [b]Treatment-unrelated SAEs included ureteral calculi and renal colic (1 participant), myelopathy (1 participant), and death due to natural causes after 5-year visit (1 participant).

Table 4. AMT-060 TRAE[36]

TRAEs[a], n (E)	Cohort 1 (n=5)	Cohort 2 (n=5)
Any TRAE	**4 (5)**	**3 (10)**
Liver enzyme increased	1 (1)	2 (3[b])
Pyrexia	1 (1)	2 (2)
Anxiety	1 (1)	1 (1)
Drug ineffective	1 (1)	0
Joint swelling[c]	1 (1)	0
Palpitations	0	1 (1)
Headache	0	1 (1)
Prostatitis	0	1 (1)
Rash	0	1 (1)

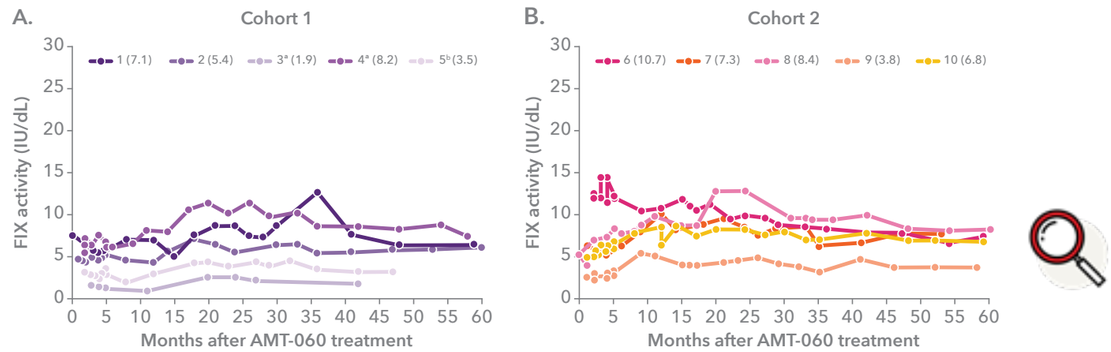
[a]TRAE reported as possibly/probably related to treatment by the investigator. [b]Two events reported in the same participant. [c]This TRAE occurred in year ~3 post-AMT-060.
n, number of participants with events; E, number of events.

FIX activity for up to 5 years in all participants

Cohort 1
5.2% (95% CI, 2.0–8.4)

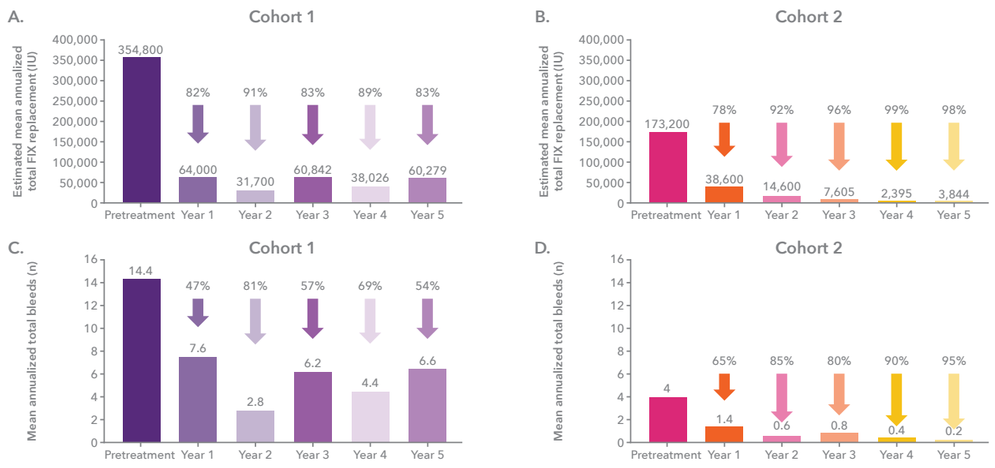
Cohort 2
7.4% (95% CI, 4.3–10.5)

Figure 6. FIX activity for up to 5 years[36]



FIX replacement use and occurrence of bleeding

Figure 7. FIX use and bleeds for up to 5 years[36]



Haemophilia Joint Health Score
decreased in both cohorts[36]

Etranacogene dezaparvovec-drlb Phase 2b Overview

Etranacogene dezaparvovec-drlb Phase 2b study

Phase 2b, open-label, single-dose, single-arm, multicenter trial investigating etranacogene dezaparvovec-drlb in adult patients with severe or moderately severe HB (NCT03489291)[29,38]

Study endpoints

Primary endpoint[29]

- ≥5% FIX activity (central 1 stage aPTT) at 6 weeks after dosing

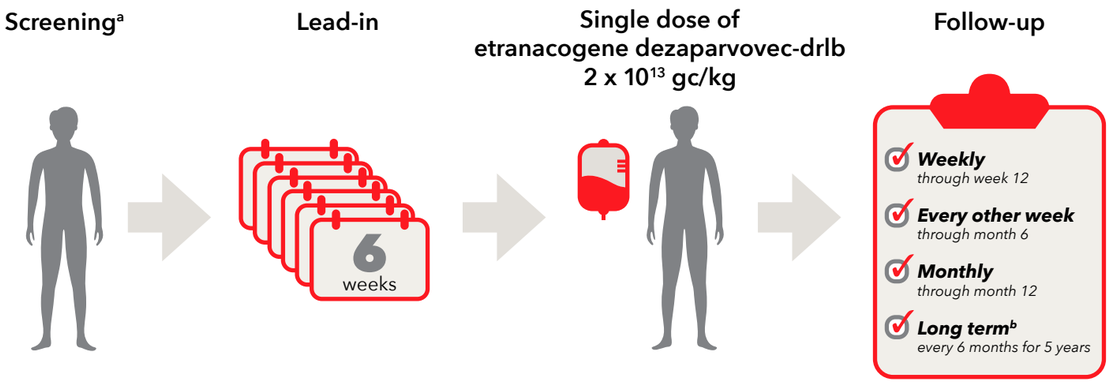
Secondary endpoints[29]

- FIX activity at other time points (aPTT and chromogenic assay)
- FIX replacement use
- Occurrence of bleeding (ABR)
- Safety

aPTT, activated partial thromboplastin time.

Study design

Figure 8. Phase 2b study design[29]



Two participants had previously failed screening for another gene therapy trial because of preexisting NAbs for the vector serotype used in that study. [a]Included assessment of eligibility parameters and historical bleeds and FIX replacement (based on medical records). Recording of bleeds and FIX replacement before and after etranacogene dezaparvovec-drlb treatment was registered in an electronic diary. [b]No electronic diary recording during long-term follow-up.

Key inclusion criteria[29]

- Males age ≥18 years
- Diagnosed with congenital hemophilia B classified as severe or moderately severe
- FIX activity ≤2% of normal
- >20 previous exposure days of treatment with FIX protein

Key exclusion criteria[29]

- History of FIX inhibitors or positive test at screening
- Any of the following >2 × ULN at baseline: AST, ALT, ALP, creatinine, and bilirubin
- Active HIV, HBV, HCV (controlled HIV, cleared HBV/HCV were permitted)

Etranacogene dezaparvovec-drlb Phase 2b Results

Baseline characteristics

Table 5. Baseline characteristics[29]

Characteristic	Participant		
	1	2	3
Age, y	43	50	47
Weight, kg	89	81	82
HIV status	Negative	Positive, controlled	Positive, controlled
Hepatitis B/C[a]	Hepatitis C; resolved	Hepatitis C; resolved	Hepatitis C; resolved
HB status[b]	FIX = 1%	FIX <1%	FIX <1%
ABR 1 y before screening	3	1	5
AAV5 NAb status (titer)[d]	Positive (48)	Positive (44)	Positive (25)

Participants 2 and 3 were excluded from another AAV-based gene therapy trial for hemophilia B based on anti-AAV titer. [a]All participants were hepatitis B negative. [b]All participants were using extended half-life FIX as prophylaxis. [c]Total bleeds (treated and untreated). [d]AAV NAb data from screening visit, considered positive if titer ≥2.

Safety at 3.0 years of follow-up

General safety

- Two TRAEs[a] in 1 participant[29]
- One SAE unrelated to treatment[29,31,39,40]

Liver specific

- One isolated AST elevation[a] at 18 months in 1 participant (62 U/L; ULN 34)[29,31,39,40]

Immune Response

- No FIX inhibitor development[40]
- No requirement for immunosuppression[40]
- Sustained FIX expression[40]

[a]Self-limiting headache and elevated CRP; resolved without intervention.
SAE, serious adverse event.

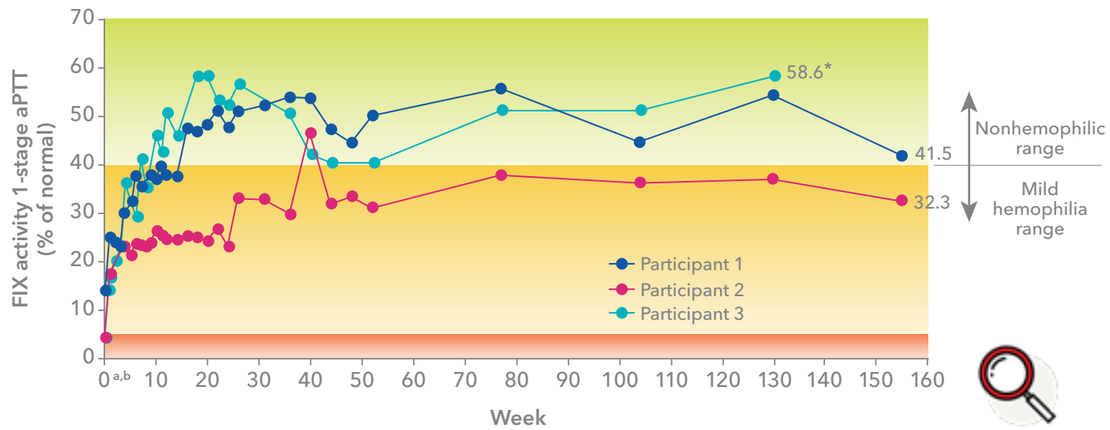
FIX activity for up to 3 years

6 weeks — Mean FIX activity = 31% (23.9% - 37.8%)[29,31,39,40]

3 years — Mean FIX activity = 36.9% (32.3% - 41.5%)[40]

Data unavailable for participant 3 at the 3-year mark

Figure 9. FIX activity during 3 years after etranacogene dezaparvovec-drlb treatment[40]



[a]Samples at baseline and week 1 may have included activity from exogenous FIX replacement.
[b]Week 0 reflects FIX activity before etranacogene dezaparvovec-drlb treatment.

*Measured at the last time point of uncontaminated sample for participant 3 (2.5 years). Uncontaminated FIX activity measured by using a one-stage aPTT assay.

Occurrence of bleeding

Table 6. Occurrence of bleeding[40]

Participant	Bleeds	
	Before treatment	After treatment
1	3 spontaneous (severe)	0
2	1 spontaneous (moderate)	0
3	6 spontaneous[a] (2 moderate, 4 mild)	2 (1 traumatic, 1 spontaneous/mild)

Two bleeds were reported in Participant 3 during the 3-year follow-up period. Both bleeds were treated with a single dose of FIX 2 days after the start of the bleed. [a]One bleed occurred after enrollment but before dosing.

Etranacogene dezaparvovec-drlb HOPE-B Overview

HOPE-B Phase 3 Study

Health outcomes with Padua gene: Evaluation in hemophilia B (HOPE-B)

Phase 3, open-label, single-dose, multicenter, multinational trial investigating the efficacy and safety of etranacogene dezaparvovec-drlb in patients with severe or moderately severe HB (NCT03569891)[30,41]

Study endpoints

Primary endpoint[30]

- ABR (all bleeds) comparison of etranacogene dezaparvovec-drlb and prophylaxis for noninferiority between the lead-in phase and the 52 weeks following stable FIX expression (months 7-18 post-treatment)

Secondary endpoints[30]

- FIX activity (1-stage assay) at 6, 12, and 18 months
- FIX consumption
- AsBR and AjBR
- FIX activity correlated to pre-existing AAV5 NAb titers
- Non disease specific patient-reported outcomes

Exploratory endpoint[30]

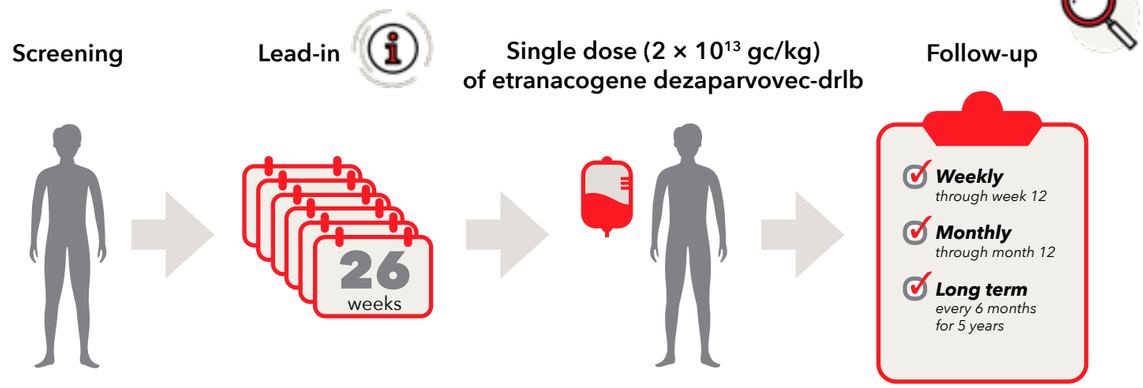
- Hemophilia-specific patient reported outcomes (Hem-A-QoL)

HOPE-B continues to evaluate the efficacy and safety of a single dose of etranacogene dezaparvovec-drlb (2 × 10^{13} gc/kg) for a follow-up period of 5 years[30,41]

AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate.

Study design

Figure 10. HOPE-B study design[30]



Pre-existing NAbs allowed. No prophylactic immunosuppression was required.

Key inclusion criteria[30]

- Male aged ≥18 years
- Diagnosed with severe or moderately severe congenital HB
- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months
- >150 exposure days of treatment with factor IX

Key exclusion criteria[30]

- History of FIX inhibitors
- Positive FIX inhibitor test at screening
- Positive HIV test, not controlled with antivirals
- Active infection with hepatitis B or C virus
- Evidence of advanced liver disease

Etranacogene dezaparvovec-drlb HOPE-B Results

Patient disposition

54 patients dosed; 53 patients completed 18 months of follow-up.[30]
52 patients completed 24 months.[42]

Table 7. Baseline characteristics[42]

	Full analysis set (N=54)
Age, mean (SD; minimum–maximum), y	41.5 (15.8; 19–75)
Severity of HB at diagnosis, n (%)	
Severe, FIX <1%	44 (81)
Moderately severe, FIX ≥1% and ≤2%	10 (19)
Positive HIV status, n (%)	3 (6)
Prior HBV infection, n (%)	9 (17)
Prior HCV infection, n (%)	31 (57)
Prescreening FIX treatment, n (%)	
Extended half-life	31 (57)
Standard half-life	23 (43)
Detectable NAbs at baseline, n (%)	21 (39)
Participants with zero bleeds at lead-in, n (%)	14 (26)

Safety

General safety

Most common Treatment Related Adverse Events[30]

- Transient transaminitis
- Headaches
- Infusion-related reactions
- Influenza-like illness

Serious Adverse Events

- One death reported; unrelated to study treatment[30]
- One case of hepatocellular carcinoma; unrelated to study treatment[30]

ABR, FIX replacement use, and quality-of-life score

Primary endpoint: ABR months 7-18[30]

- 64% reduction in ABR (4.19 to 1.51; *P<0.001*)

Secondary endpoint: FIX replacement use[30]

- Mean (SD) difference in FIX consumption was –248,825 IU/year/patient (*P*<0.001)

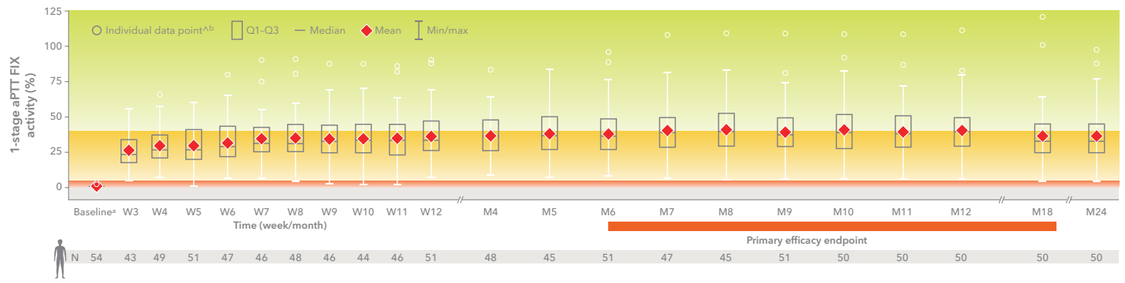
Exploratory endpoint: Quality-of-life score[30]

- Improvement in Hemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL) score

FIX activity

Mean (SD; minimum–maximum) FIX of 36.7% (±19.0; 4.7–99.2) at Year 2

Figure 11. FIX activity during 24-month post-treatment period[42]



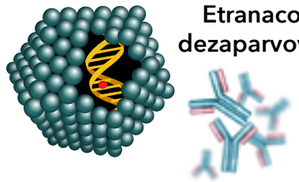
[a]Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.

[b]Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.

aPTT=activated partial thromboplastin time; CRF=case report form; FIX=factor IX; M=Month; W=Week

Etranacogene dezaparvovec-drlb HOPE-B Neutralizing Antibody Overview

Neutralizing Antibodies Against the AAV5 Capsid of Etranacogene dezaparvovec-drlb: HOPE-B



Neutralizing antibodies (NAbs) against AAV5 capsid proteins are common in the general population[26,27]

In the HOPE-B clinical trial program, the presence of AAV5 NAbs was not an exclusion criterion[43]

Baseline demographics in HOPE-B according to baseline AAV5 NAb status

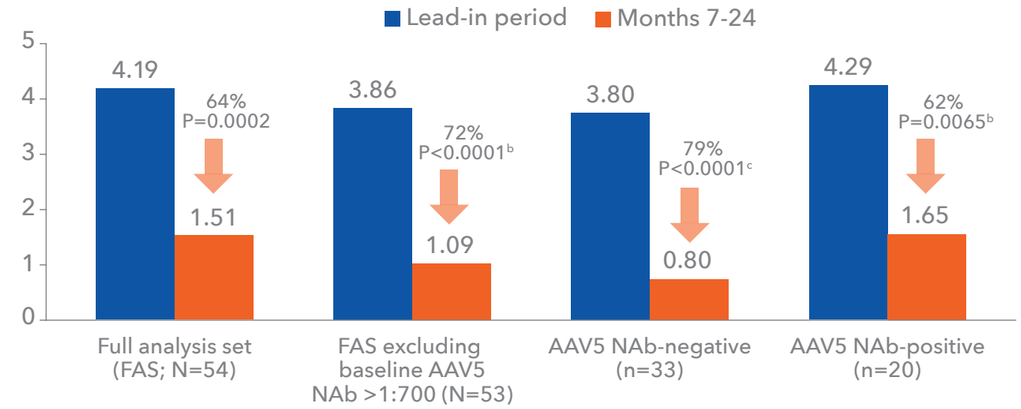
Table 10. Baseline demographics according to baseline AAV5 NAb status[43]

	Baseline NAb status		
	AAV5 NAb-positive	AAV5 NAb-negative*	All
Number of patients	21	33	54
Maximum titer	3212.3	–	
Median titer (Q1-Q3)	56.9 (23.3-198.9)	–	
Age, mean (SD, minimum-maximum), years	44.5 (17.5, 19-75)	39.5 (14.5, 21-73)	41.5 (15.8, 19-75)
Severity of HB at diagnosis, n (%)			
Severe (FIX <1%)	16 (76)	28 (85)	44 (82)
Moderately severe (FIX ≥1% and ≤2%)	5 (24)	5 (15)	10 (19)
Positive HIV status, n (%)	1 (5)	2 (6)	3 (6)
Prior hepatitis B, n (%)	5 (24)	4 (12)	9 (17)
Prior hepatitis C, n (%)	14 (67)	17 (52)	31 (57)
Pre-screening FIX treatment, n (%)			
Extended half-life	14 (67)	17 (52)	31 (57)
Standard half-life	7 (33)	16 (49)	23 (43)

*Lower limit of detection for Nab assay: 7

ABR[a] (all bleeds) according to baseline AAV5 NAb status

Figure 14. ABR according to baseline AAV5 NAb status[43]



[a]Adjusted ABR and comparison of ABR between the lead-in and post-treatment periods was estimated from a repeated measures generalized estimating equations negative binomial regression modelaccounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate. [b]Post-hoc analysis not controlled for Type I error. [c]Subgroup analysis not controlled for Type I error.

FIX activity[a] at 24 months according to baseline AAV5 NAb status

Table 11. FIX activity according to baseline AAV5 NAb status[43]

	Baseline NAb status	
FIX activity (%) at 24 months[a]	AAV5 NAb-positive n=17	AAV5 NAb-negative n=33
Median (minimum-maximum)	33.50 (9.1-88.3)	35.40 (4.7-99.2)
Mean (SD)	32.98 (18.50)	38.55 (19.19)

[a]One-stage FIX activity assays. Only samples uncontaminated with exogenous FIX were included in analysis. LS mean from repeated measures linear mixed model with visit as a categorical covariate.

Safety according to baseline NAb status[43]

- Safety profile similar across NAb subgroups
- Over 24 months, corticosteroid-treated transaminase elevations occurred in 6/33 (18%) of NAb-negative participants and 3/21 (14%) of NAb-positive participants
- Infusion-related reactions occurred in 2/33 (6%) of NAb-negative participants and 5/21 (24%) of NAb-positive participants, respectively (p=0.0956)

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Abbreviations

AAV, adeno-associated virus
ABR, annualized bleeding rate
AE, adverse event
AjBR, annualized joint bleeding rate
ALP, alkaline phosphatase
ALT, alanine transaminase
aPTT, activated partial thromboplastin time
AsBR, annualized spontaneous bleeding rate
AST, aspartate transaminase
BU, Bethesda unit
CNS, central nervous system
CPK, creatine phosphokinase
E, number of events
HB, hemophilia B
HBV, hepatitis B virus
HCV, hepatitis C virus
HOPE-B, Health Outcomes with Padua gene; Evaluation in Hemophilia B
FIX, factor IX
gc, genome copy
h, human
Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults
Ig, immunoglobulin
IU, international unit
ITR, inverted terminal repeat
IV, intravenous
n, number of participants
NAb, neutralizing antibody
pA, polyadenylation sequence
PWHB, people living with hemophilia B
rAAV, recombinant adeno-associated virus
SAE, serious adverse event
sk, skeletal
TRAE, treatment-related adverse event
ULN, upper limit of normal
WT, wild type

Figure 1. HB inheritance pattern[3]

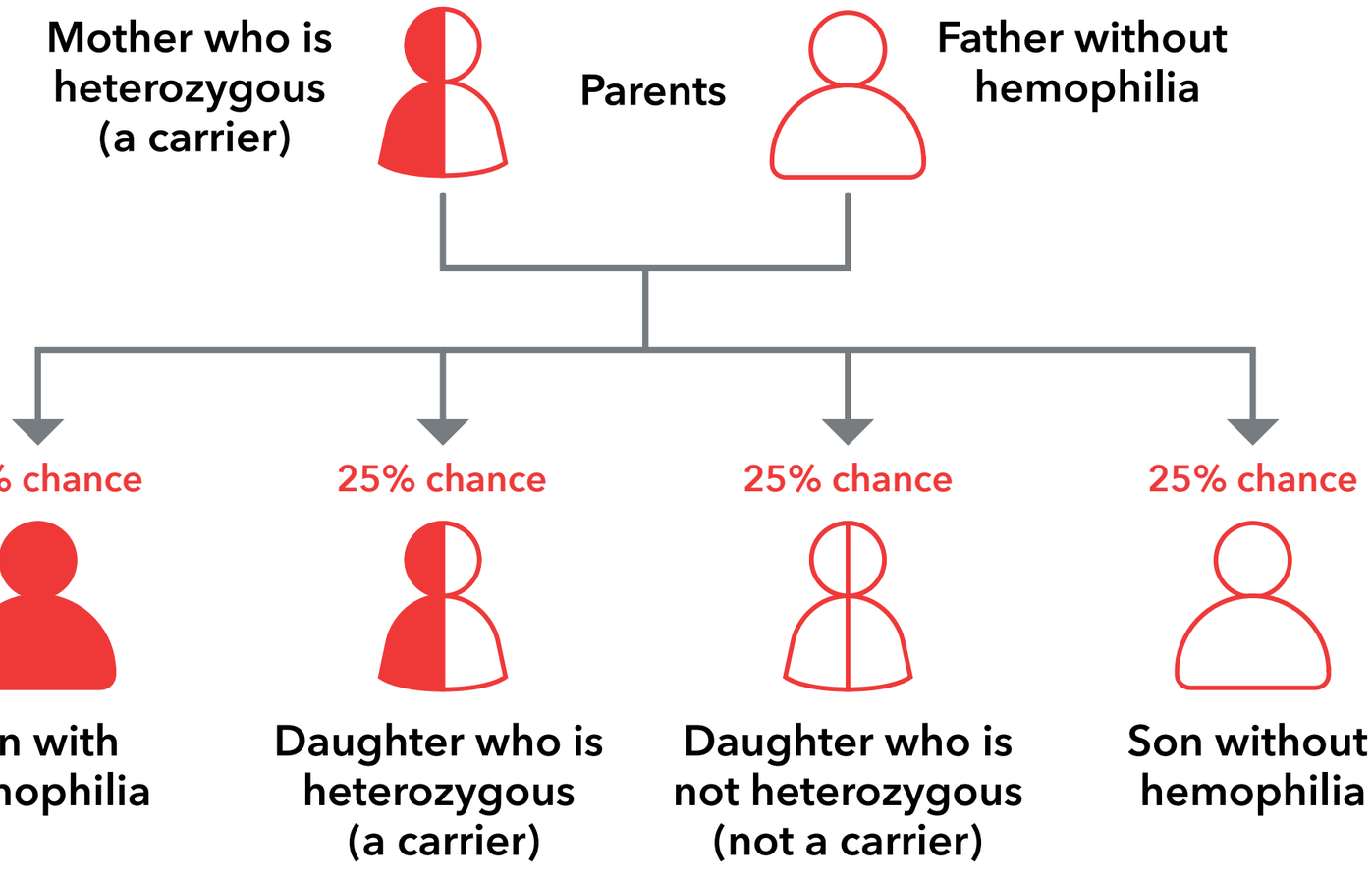
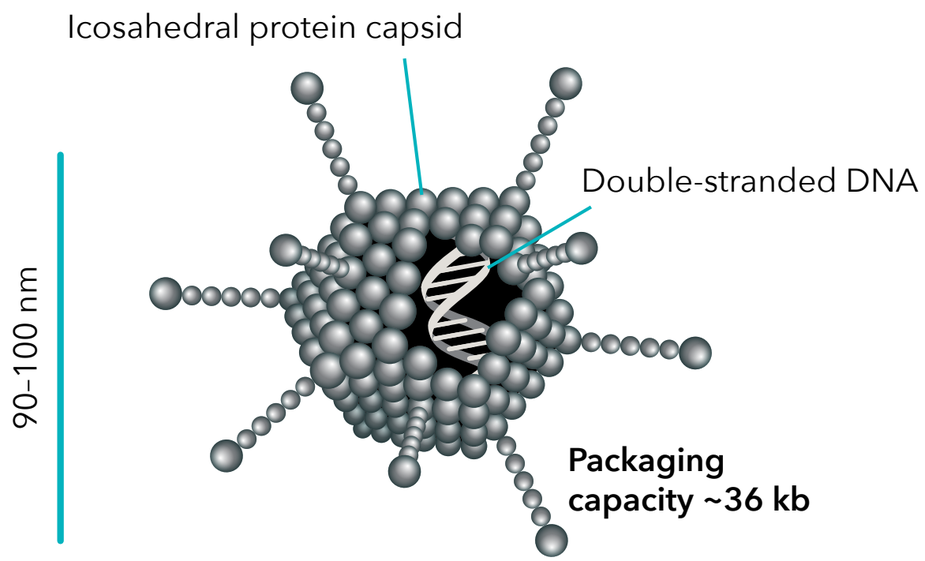


Figure 2. Differences between the adenovirus and AAV[12,17]

Adenovirus



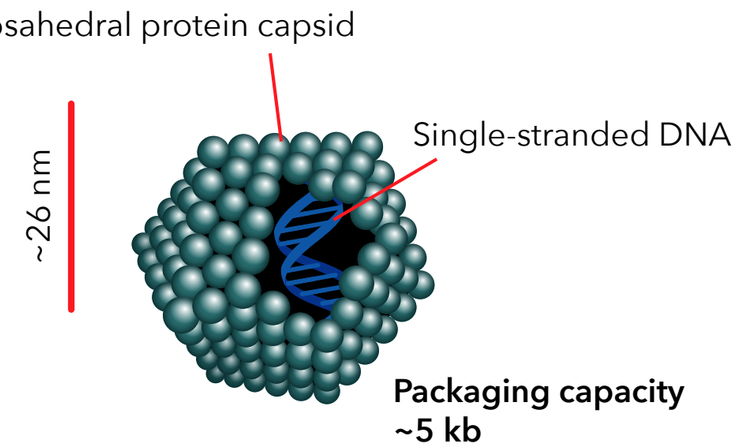
Virus

- Pathogenic; known to cause infections in humans (eg, upper respiratory tract infections)
- Can replicate in host cells without a helper virus

Vector

- Large packaging capacity
- Highly immunogenic and inflammatory
- Possible candidates for cancer immunotherapy and novel vaccines (eg, Ebola, influenza)

AAV



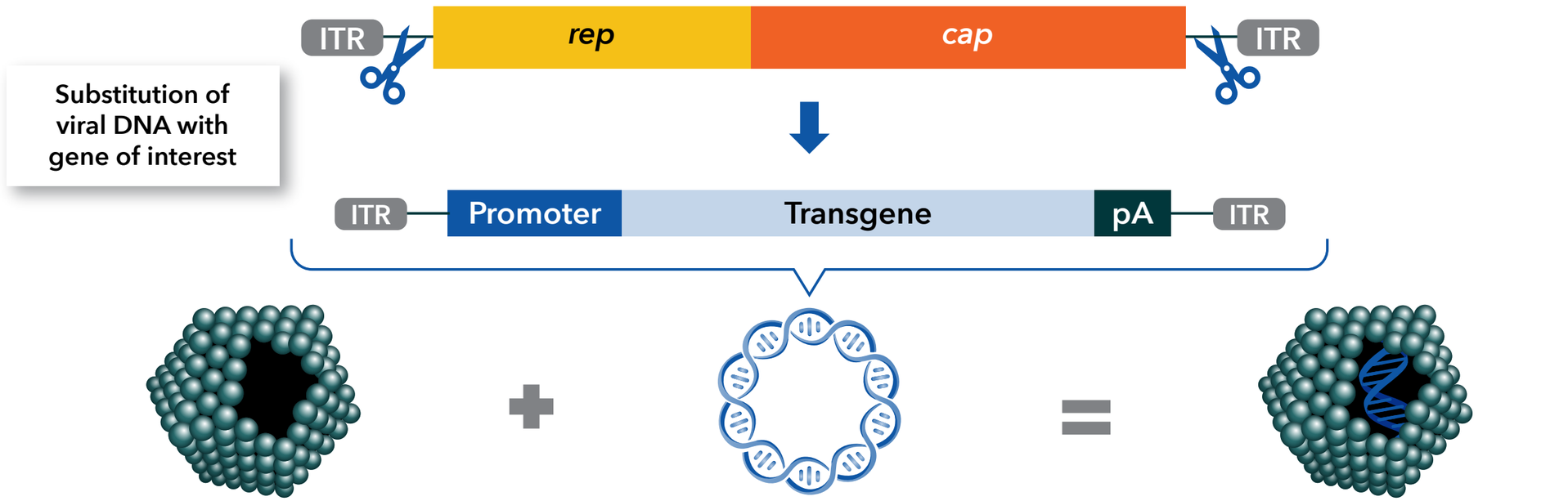
Virus

- Nonpathogenic and not associated with any disease
- Cannot replicate without a helper virus

Vector

- Small packaging capacity
- Less immunogenic and less vector-related toxicity
- Persists in non-dividing tissues, allowing for long-term expression of the transgene

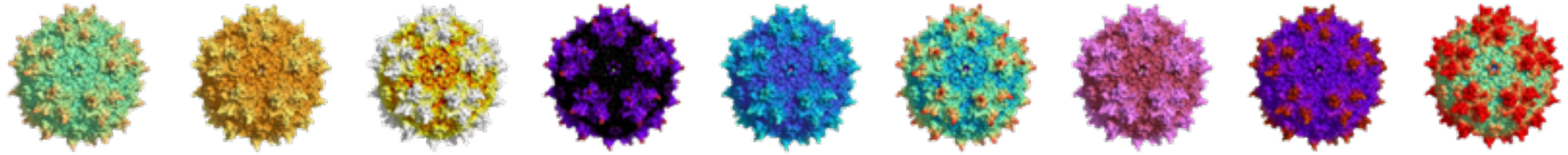
Figure 3. Anatomy of an AAV vector[12,18,19]



The *rep* genes code for viral DNA replication and packaging proteins, while the *cap* genes code for viral capsid proteins.
pA, polyadenylation sequence.

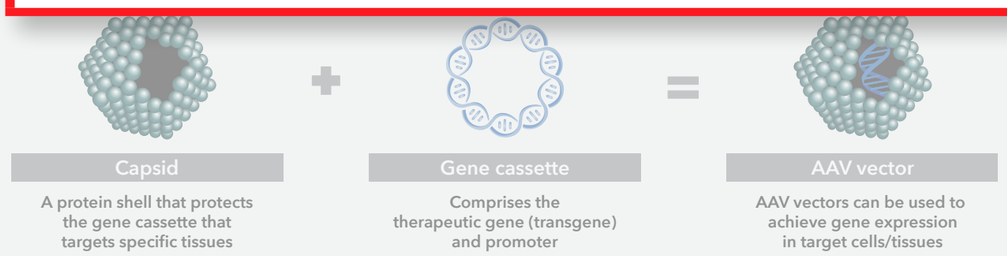
AAV as a Vector for Gene Delivery

Table 2. AAV serotypes[25]



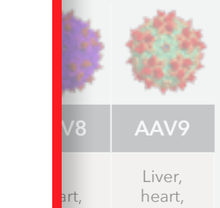
	AAV1	AAV2	AAV3	AAV4	AAV5	AAV6	AAV7	AAV8	AAV9
Bio-distribution (mouse model)	Liver, heart, sk muscle, adipose, CNS	Liver, heart, muscle	Heart, liver	Heart, lung, liver	Liver	Liver, heart, sk muscle	Liver, sk muscle	Heart, liver, CNS, muscle	Liver, heart, CNS, lung, sk muscle
Large animal model	Heart, CNS, sk muscle	CNS, eye		Eye	Liver, CNS	Heart, CNS, sk muscle		Liver, eye, CNS	Heart, CNS, sk muscle

CNS, central nervous system. SK, skeletal muscle.



AAV serotypes

AAV vector-promoter combination results in efficient, tissue-specific[25]



	AAV8	AAV9
	art, CNS, cle	Liver, heart, CNS, lung, sk muscle
	eye, NS	Heart, CNS, sk muscle

- Transduction into a range of tissues
- Long-term gene expression
- Poor integration into the host genome
- Low pathogenicity
- Low immunogenicity

es[26,27]

- Gradual loss of transgene expression
- Preexisting humoral immunity to WT AAV

Baseline characteristics

Table 3. Baseline characteristics[28,36]

Variable
Age, y
Weight, kg
FIX use[a] Prophylaxis, Annualized
Mean no. of b Spontaneou Traumatic Unknown
Hemophilia J
HIV-positive s
Prior hepatitis
AAV5 NAb+, I

Values are mec calculations. [b]C bleed data mis Haemophilia Jo

Long-ter

- Reporte
- Three **tre events (S** 3.5 mont
- Three **tre** also repo
- **No partic** inhibitors

[a]Treatment-rela fever in first 24 hours post AMT-060 (1 participant) and mild, asymptomatic elevations in liver enzymes (2 participants; 1 in each cohort). [b]Treatment-unrelated SAEs included ureteral calculi and renal colic (1 participant), myelopathy (1 participant), and death due to natural causes after 5-year visit (1 participant).

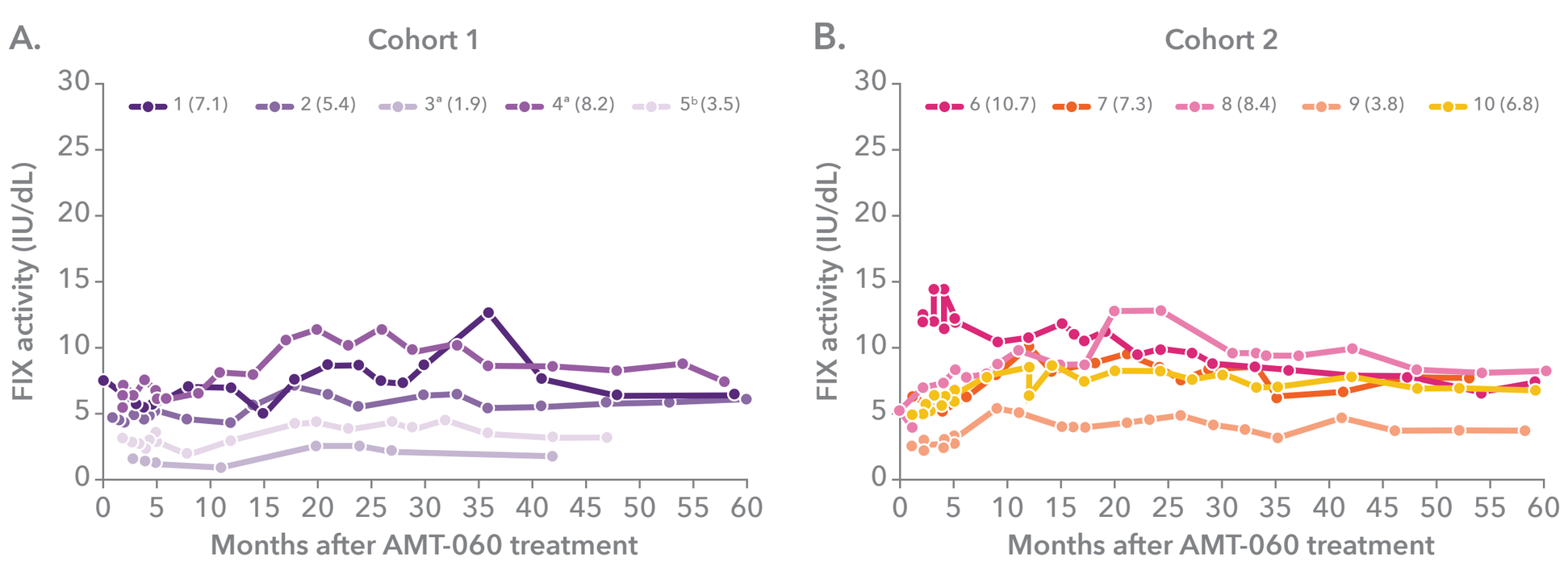
Rash	0	1 (1)

[a]TRAE reported as possibly/probably related to treatment by the investigator. [b]Two events reported in the same participant. [c]This TRAE occurred in year ~3 post-AMT-060.
n, number of participants with events; E, number of events.

FIX activity for up to 5 years in all participants

Cohort 1 Cohort 2

Figure 6. FIX activity for up to 5 years[36]



Values in parentheses represent mean FIX activity over time. Only values at least 10 days after last FIX concentrate administration are included.
FIX prophylaxis was continued after AMT-060 and tapered between weeks 6 and 12. [a]Patients 3, 4, and 5 retrospectively tested positive for AAV5 neutralizing antibodies using the luciferase-based assay. [b]Patient 5 was unable to attend 4.5-year follow-up visit because of COVID-19, and the 5-year follow-up blood sample was obtained within 10 days of exogenous FIX use for bleed and therefore excluded per protocol.

Haemophilia Joint Health Score
decreased in both cohorts[36]

Baseline characteristics

Table 3. Baseline characteristics[28,36]

Variable
Age, y
Weight, kg
FIX use[a]
Prophylaxis,
Annualized
Mean no. of b
Spontaneou
Traumatic
Unknown
Hemophilia J
HIV-positive s
Prior hepatitis
AAV5 NAb+, l

Values are mec
calculations. [b]C
bleed data mis
Haemophilia Jo

Long-ter

- Reported
- Three tre
events (S
3.5 mont
- Three tre
also repo
- No partic
inhibitors

[a]Treatment-related SAEs included short, self-limiting fever in first 24 hours post-AMT-060 (1 participant) and mild, asymptomatic elevations in liver enzymes (2 participants; 1 in each cohort). [b]Treatment-unrelated SAEs included ureteral calculi and renal colic (1 participant), myelopathy (1 participant), and death due to natural causes after 5-year visit (1 participant).

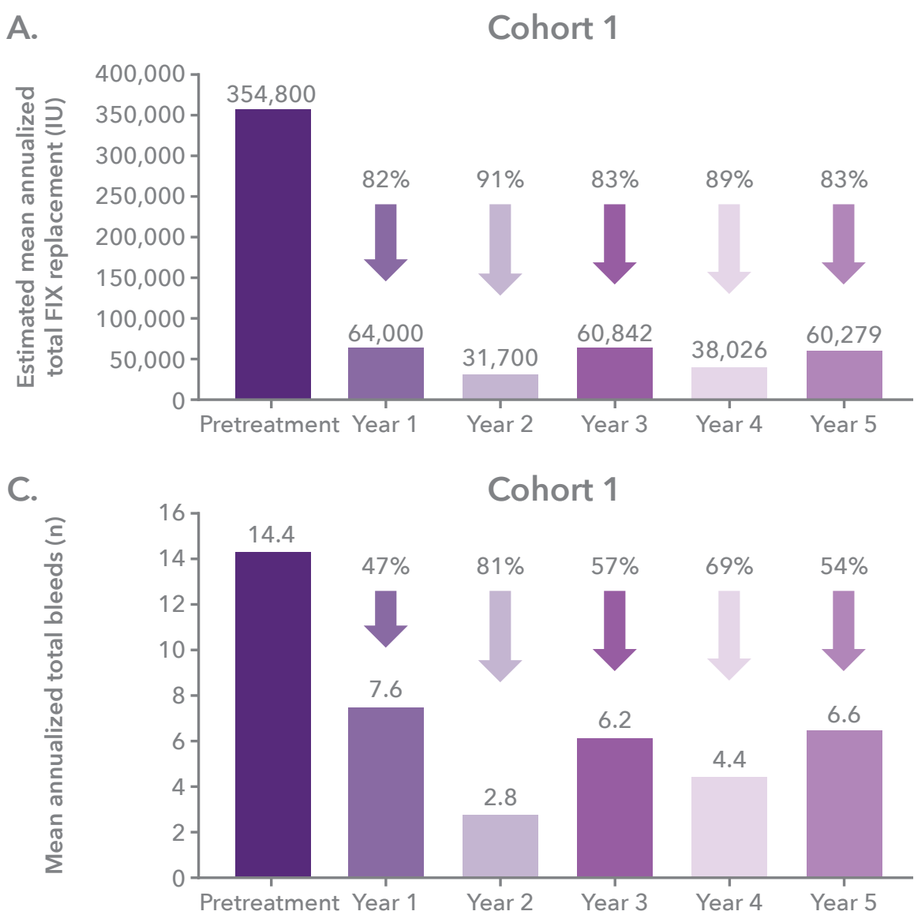
Headache	0	1 (1)
Prostatitis	0	1 (1)
Rash	0	1 (1)

[a]TRAE reported as possibly/probably related to treatment by the investigator. [b]Two events reported in the same participant. [c]This TRAE occurred in year ~3 post-AMT-060.
n, number of participants with events; E, number of events.

FIX activity for up to 5 years in all participants

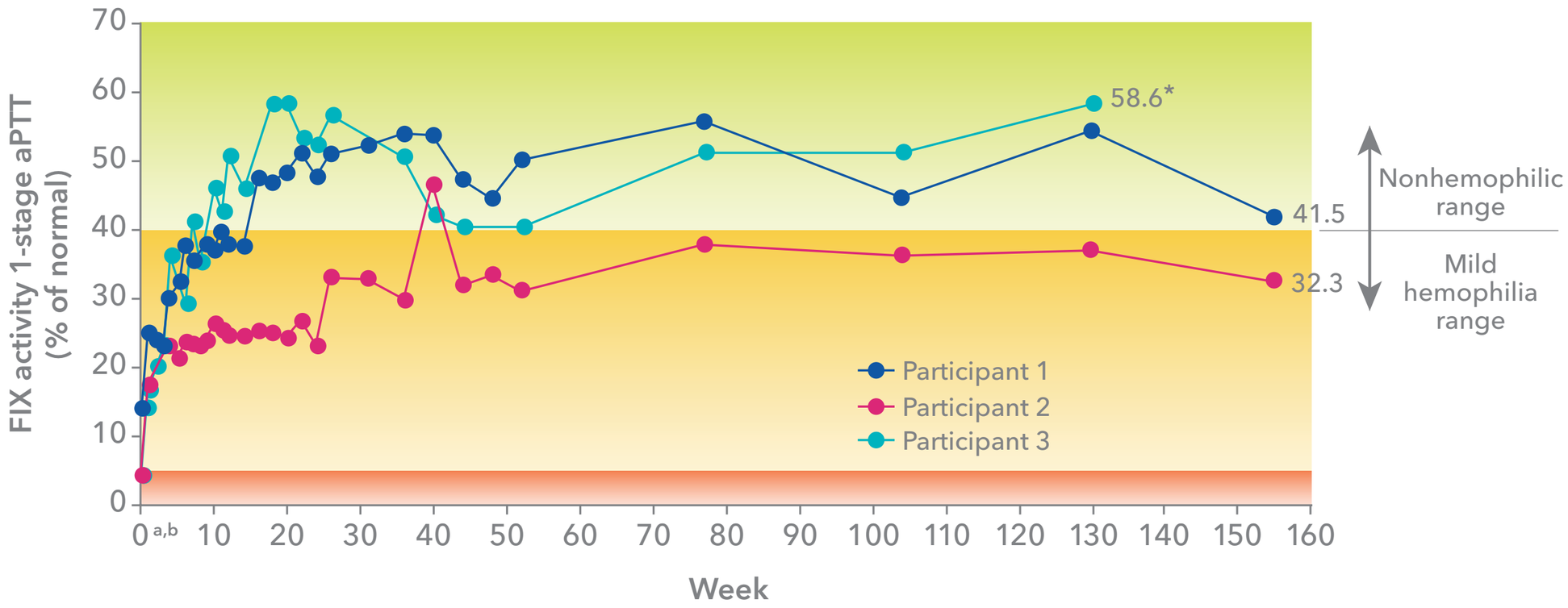
Cohort 1 Cohort 2

Figure 7. FIX use (A, B) and bleeds (C, D) for up to 5 years[36]



Haemophilia Joint Health Score
decreased in both cohorts[36]

Figure 9. FIX activity during 3 years after etranacogene dezaparvovec-drlb treatment[40]



[a]Samples at baseline and week 1 may have included activity from exogenous FIX replacement.
[b]Week 0 reflects FIX activity before etranacogene dezaparvovec-drlb treatment.
*Measured at the last time point of uncontaminated sample for participant 3 (2.5 years). Uncontaminated FIX activity measured by using a one-stage aPTT assay

Etranacogene dezaparvovec-drlb HOPE-B Overview

HOPE-B Phase 3 Study

Health outcomes with Padua gene: Evaluation in hemophilia B (HOPE-B)

Phase 3, open-label, single-dose, multicenter, multinational trial investigating the efficacy and safety of etranacogene dezaparvovec-drlb in patients with severe or moderately severe HB (NCT03569891)[30,41]

Study endpoints

Primary endpoint[30]

- ABR (all bleeds) comparison of etranacogene dezaparvovec-drlb and prophylaxis for noninferiority between the lead-in phase and the 52 weeks following stable FIX expression (months 7-18 post-treatment)

Secondary endpoints[30]

- FIX activity (1-stage assay) at 6, 12, and 18 months
- FIX consumption
- AsBR and AjBR
- FIX activity correlated to pre-existing AAV5 NAb titers
- Non disease specific patient-reported outcomes

Exploratory endpoint[30]

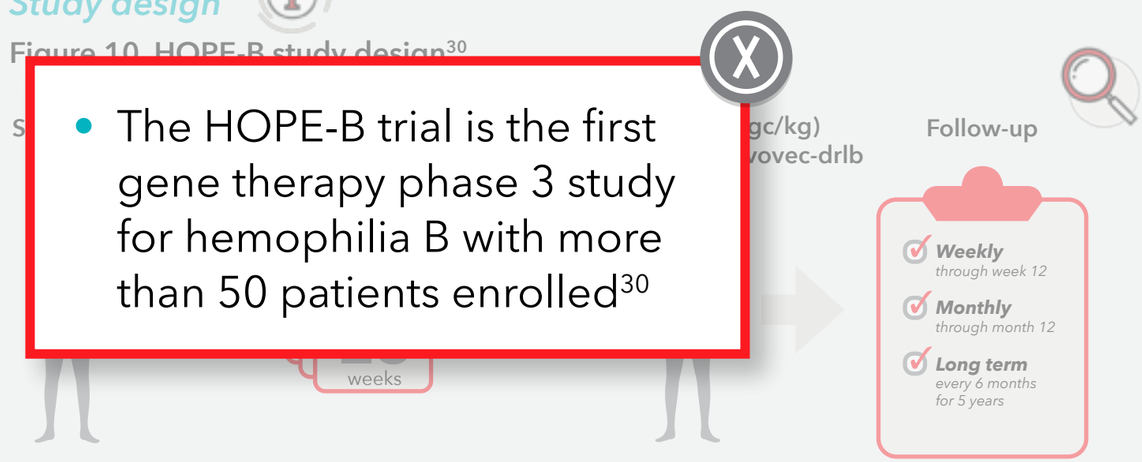
- Quality of life and patient-reported outcomes
- Hemophilia-specific patient reported outcomes

HOPE-B continues to evaluate the efficacy and safety of a single dose of etranacogene dezaparvovec-drlb (2×10^{13} gc/kg) for a follow-up period of 5 years[30,41]

AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate.

Study design

Figure 10. HOPE-B study design[30]



- The HOPE-B trial is the first gene therapy phase 3 study for hemophilia B with more than 50 patients enrolled[30]

Pre-existing NAbs allowed. No prophylactic immunosuppression was required.

Key inclusion criteria[30]

- Male aged ≥18 years
- Diagnosed with severe or moderately severe congenital HB
- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months
- >150 exposure days of treatment with factor IX

Key exclusion criteria[30]

- History of FIX inhibitors
- Positive FIX inhibitor test at screening
- Positive HIV test, not controlled with antivirals
- Active infection with hepatitis B or C virus
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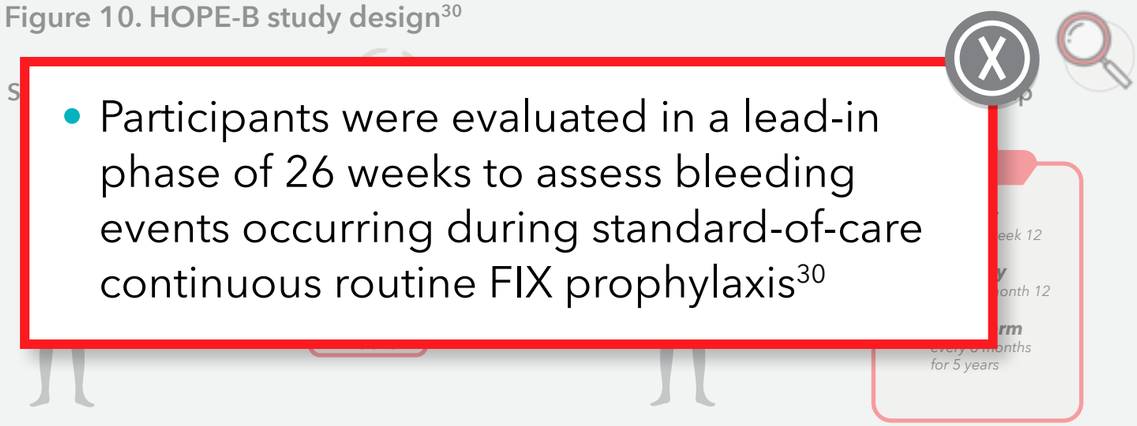

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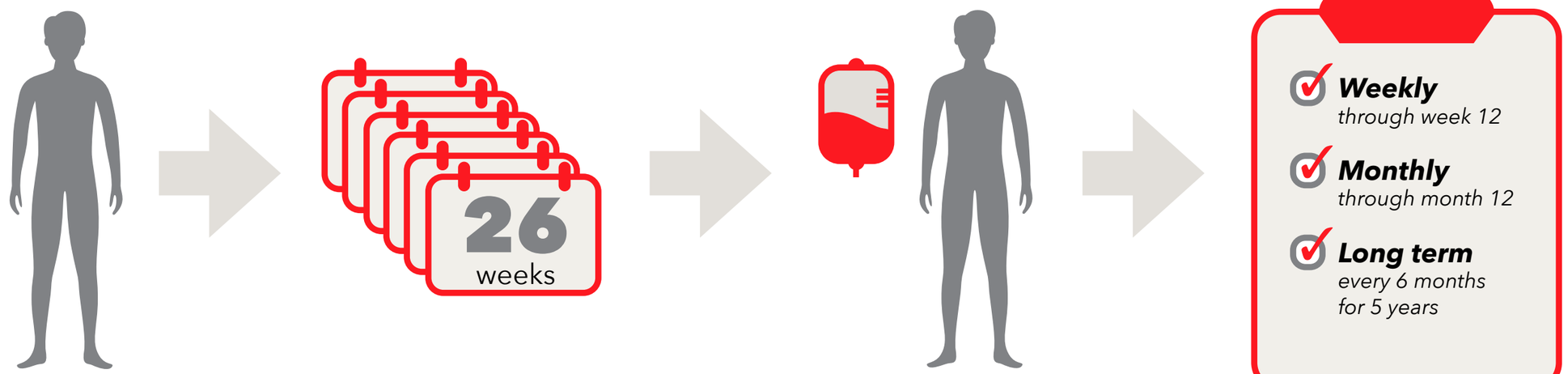

Pre-existing NAbs allowed. No prophylactic immunosuppression was required.

(months 7-18 post-treatment)

Exploratory endpoint[30]

- Quality of life and patient-reported outcomes
- Hemophilia-specific patient reported outcomes

- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months
- >150 exposure days of treatment with factor IX

- Positive HIV test, not controlled with antivirals
- Active infection with hepatitis B or C virus
- Evidence of advanced liver disease

HOPE-B continues to evaluate the efficacy and safety of a single dose of etranacogene dezaparvovec-drlb (2 × 10[13] gc/kg) for a follow-up period of 5 years[30,41]

AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate.

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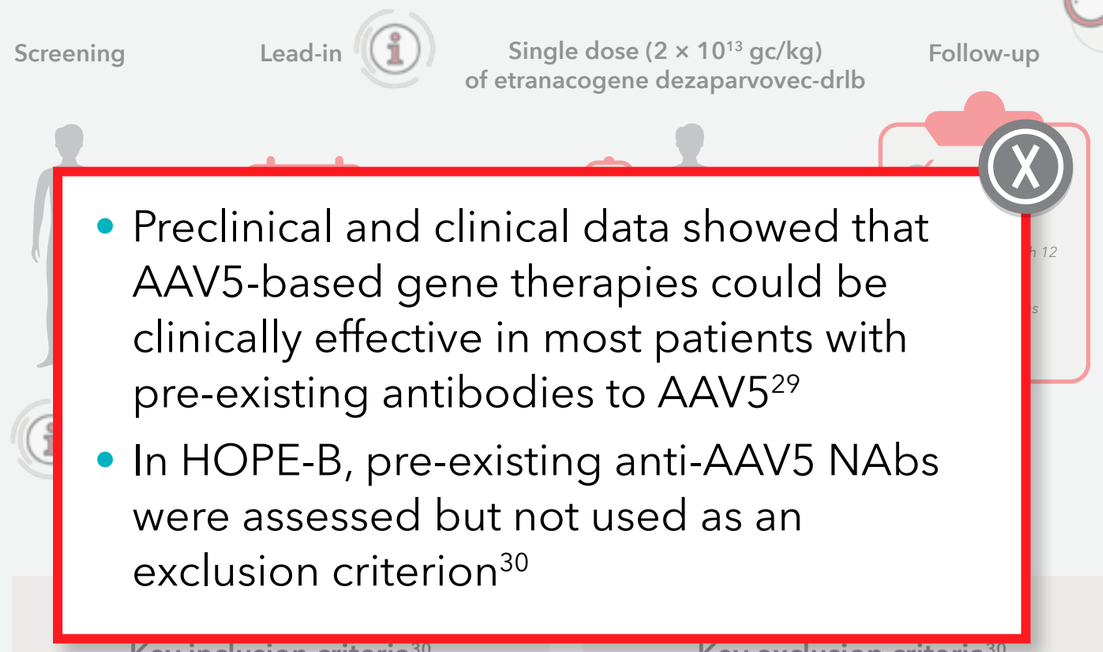
- Quality of life and patient-reported outcomes
- Hemophilia-specific patient reported outcomes

HOPE-B continues to evaluate the efficacy and safety of a single dose of etranacogene dezaparvovec-drlb (2 × 10^{13} gc/kg) for a follow-up period of 5 years[30,41]

AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate.

Study design

Figure 10. HOPE-B study design[30]



- Preclinical and clinical data showed that AAV5-based gene therapies could be clinically effective in most patients with pre-existing antibodies to AAV5[29]
- In HOPE-B, pre-existing anti-AAV5 NAbs were assessed but not used as an exclusion criterion[30]

Key inclusion criteria[30]

- Male aged ≥18 years
- Diagnosed with severe or moderately severe congenital HB
- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months
- >150 exposure days of treatment with factor IX

Key exclusion criteria[30]

- History of FIX inhibitors
- Positive FIX inhibitor test at screening
- Positive HIV test, not controlled with antivirals
- Active infection with hepatitis B or C virus
- Evidence of advanced liver disease

Table 8. TRAEs[30,42]

- Most TEAEs were mild (76%; moderate, 21%; severe, 3.2%)
- 93 TEAEs in 38 of 54 participants were TRAEs
  - 1 TRAE occurred during months 18-24
- 11 participants had elevations in ALT levels reported as adverse events
  - 9 were treated per protocol with corticosteroids
  - Mean duration of corticosteroids was 79.8 days

Most frequent TRAEs	Participants with post-treatment events, n (%) N = 54
ALT[a]	9 (17)
Headache	8 (15)
Influenza-like illness	7 (13)
Infusion-related reaction	7 (13)
AST[a]	5 (9)
Blood CPK increased	4 (7)
Dizziness	4 (7)
Fatigue	4 (7)
Nausea	4 (7)
Arthralgia	3 (6)

[a]As measured by central laboratory.
CPK, creatine phosphokinase.

Safety

Most common Treatment Related Adverse Events[30]
- Transient transaminitis
- Headaches
- Infusion-related reactions
- Influenza-like illness

- One death reported; unrelated to study treatment[30]
- One case of hepatocellular carcinoma; unrelated to study treatment[30]

Year 2

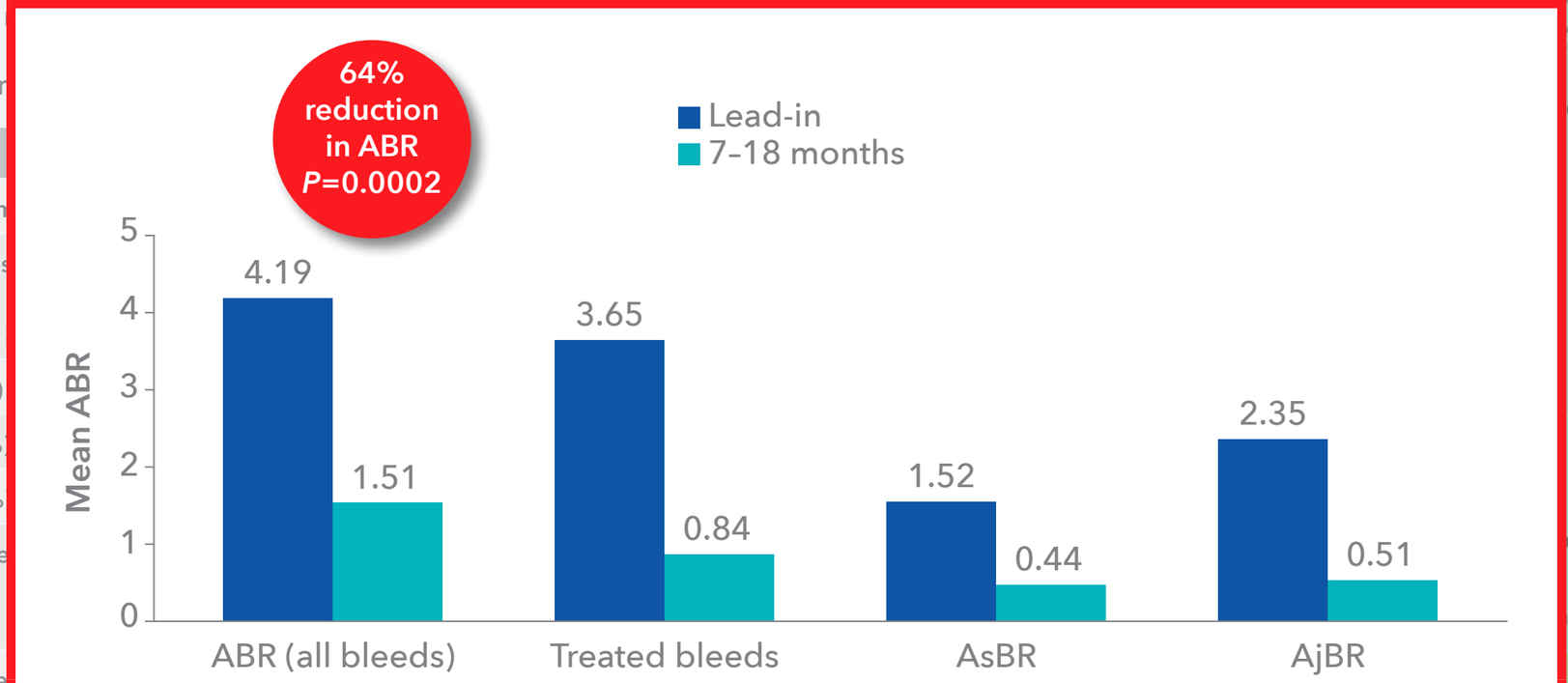
[a]Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.

[b]Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.

aPTT=activated partial thromboplastin time; CRF=case report form; FIX=factor IX; M=Month; W=Week

Etranacogene dezaparvovec-drlb HOPE-B Results

Figure 12. Primary endpoint: ABR at 18 months post-treatment[30]



One-sided *P* value of ≤0.025 for post-treatment/lead-in <1 is regarded as statistically significant.

Patient disposition

54 patients dosed; 53 pati
52 patients completed 24

Table 7. Baseline character

Age, mean (SD; minimun	
Severity of HB at diagnos	
Severe, FIX <1%	
Moderately severe, FIX	
Positive HIV status, n (%)	
Prior HBV infection, n (%)	
Prior HCV infection, n (%	
Prescreening FIX treatme	
Extended half-life	
Standard half-life	
Detectable NAbs at base	
Participants with zero ble	

Safety

General safety

Most common Treatment Related Adverse Events[30]

- Transient transaminitis
- Headaches
- Infusion-related reactions
- Influenza-like illness

Serious Adverse Events

- One death reported; unrelated to study treatment[30]
- One case of hepatocellular carcinoma; unrelated to study treatment[30]

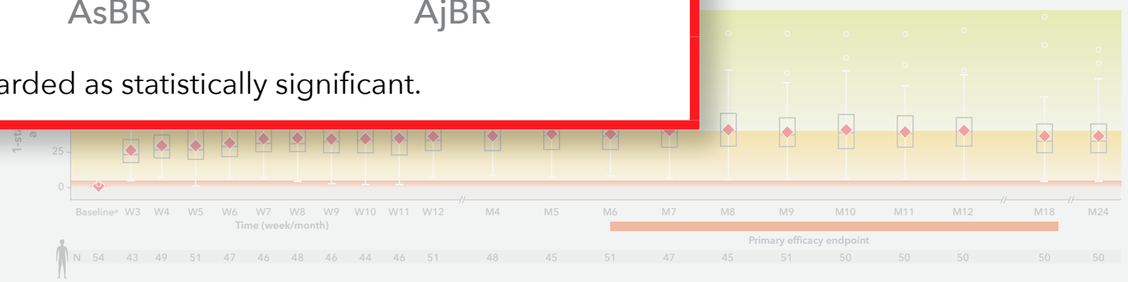
e score

Exploratory endpoint: Quality-of-life score[30]

- Improvement in Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) score

.0; 4.7–99.2) at Year 2

ent period[30]



[a]Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.

[b]Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.

aPTT=activated partial thromboplastin time; CRF=case report form; FIX=factor IX; M=Month; W=Week

Figure 13. FIX replacement use[42]

- **96.3%** of participants **(52/54)** were able to stop prophylactic FIX infusions
- **None** of the 52 returned to prophylaxis during the study period
- Two nonresponders
  - One participant with AAV5 NAb titre of 3212
  - One participant who received a partial dose of ~10% of planned dose

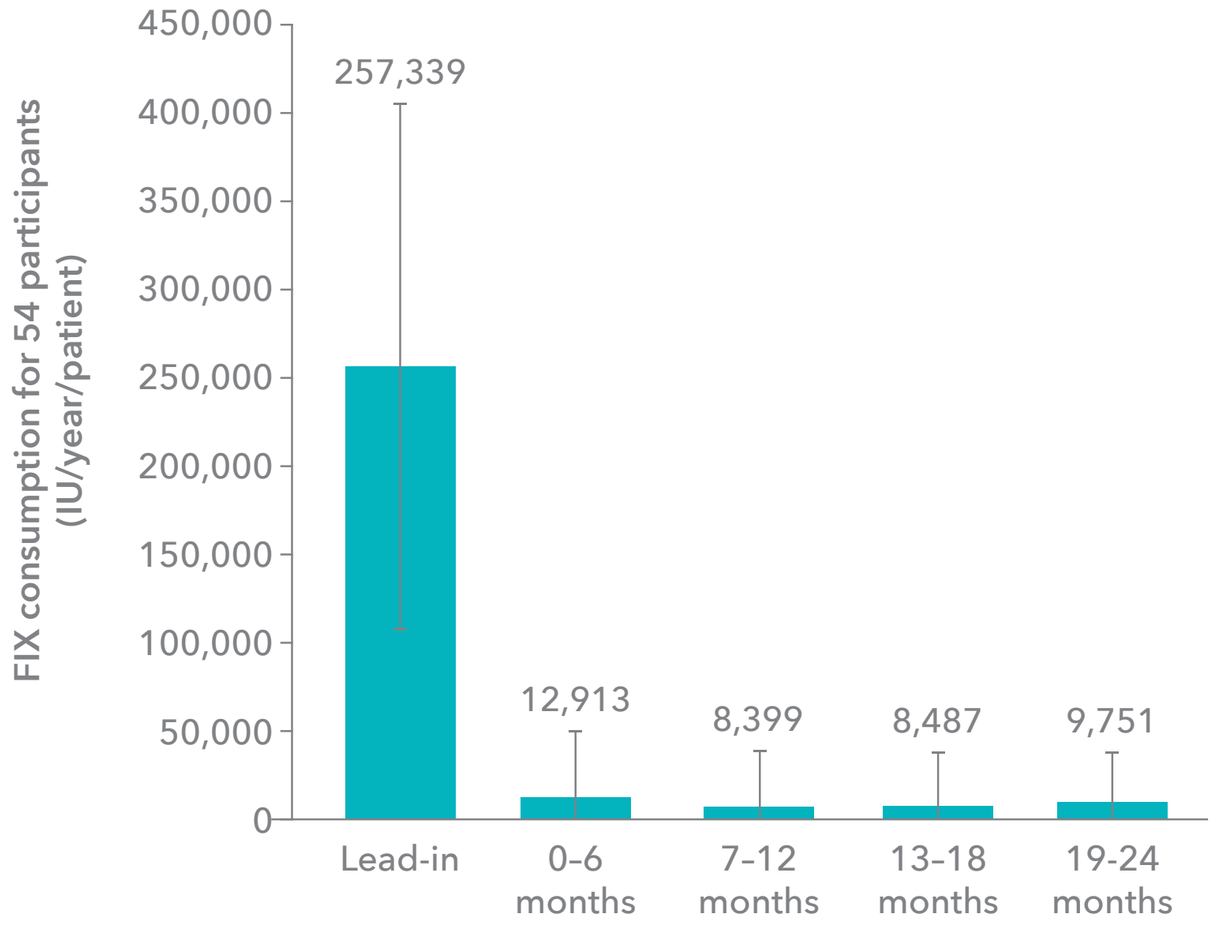


Table 9. Quality-of-life score[44,45]

Domain	Mean in lead-in period (SE)[a]	Mean in post-treatment period (SE)[a]	Mean difference between treatment periods (SE)[b]	95% CI	Percentage improvement
Total	25.56 (2.072)	20.06 (2.054)	–5.50 (0.972)	-7.42, -3.58	21.5%
Feelings[c]	20.61 (2.838)	11.19 (2.790)	–9.42 (1.938)	-13.26, -5.59	45.7%
Treatment[d]	25.24 (1.857)	10.36 (1.804)	–14.88 (1.789)	-18.42, -11.34	59.0%
Work/school[e]	17.34 (2.555)	12.35 (2.534)	–4.99 (1.825)	- 8.61, -1.38	28.8%
Future[f]	30.94 (2.753)	25.92 (2.712)	–5.02 (1.736)	- 8.45, -1.58	16.2%

[a] Scores range from 0 to 100; higher scores indicate lower quality of life.
[b] LS mean difference from lead-in to month 12 post-treatment.
[c] 'Feelings' reflected current emotions associated with having hemophilia B.
[d] 'Treatment' reflected how burdened individuals were by the treatments.
[e] 'Work/school' refleced how well individuals thought they performed work/school-related responsibilities.
[f] 'Future' reflected concerns about how hemophilia B would affect life plans.
CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
SE, standard error.

Patient d

54 patient
52 patient

Table 7. Ba

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Year 2

M12 M18 M24
50 50 50

Safety

Most common Treatment Related Adverse Events[30]

- Transient transaminitis
- Headaches
- Infusion-related reactions
- Influenza-like illness

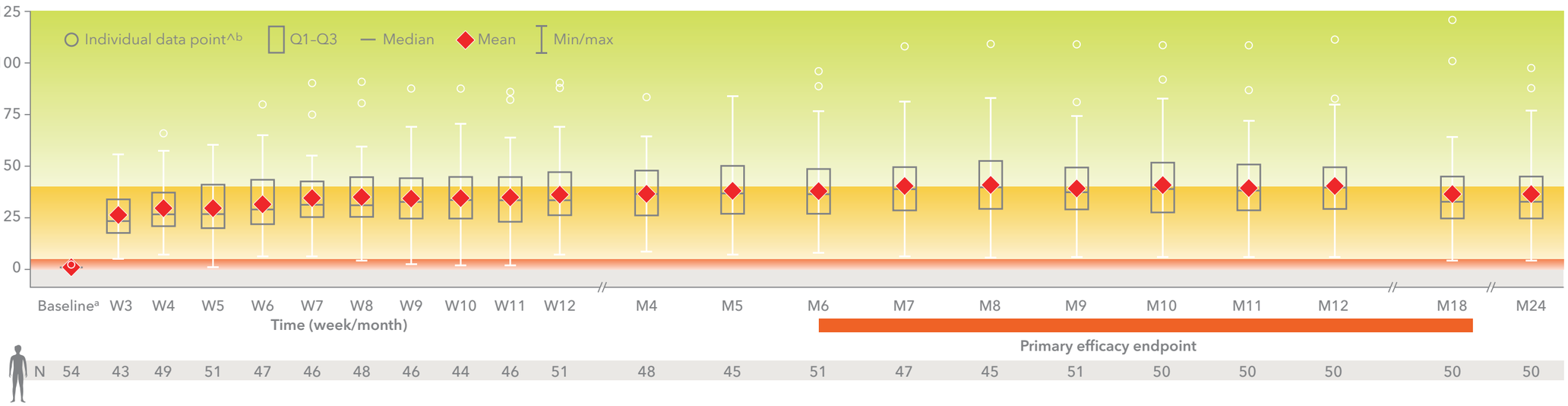
- One death reported; unrelated to study treatment[30]
- One case of hepatocellular carcinoma; unrelated to study treatment[30]

[a]Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.

[b]Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.

aPTT=activated partial thromboplastin time; CRF=case report form; FIX=factor IX; M=Month; W=Week

Figure 11. FIX activity during 24-month post-treatment period[30,42]



Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the week 3 assessment were used in the analysis. Subjects with no uncontaminated central laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their postbaseline value set equal to their baseline value. Baseline FIX was imputed based on patient's historical hemophilia B severity documented on the case record form. If the patient had documented severe FIX deficiency (FIX plasma level <1%), their baseline FIX activity level was imputed as 1%. If the subject had documented moderately severe FIX deficiency (FIX plasma level ≥1% and ≤2%), their baseline FIX activity level was imputed as 2%.

M, month; W, week.

[a]Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.

[b]Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.

aPTT=activated partial thromboplastin time; CRF=case report form; FIX=factor IX; M=Month; W=Week