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Efficacy and Safety of Giroctocogene Fitelparvovec in Adults With Moderately Severe to Severe Hemophilia A: Primary Analysis Results From the Phase 3 AFFINE Gene Therapy Trial

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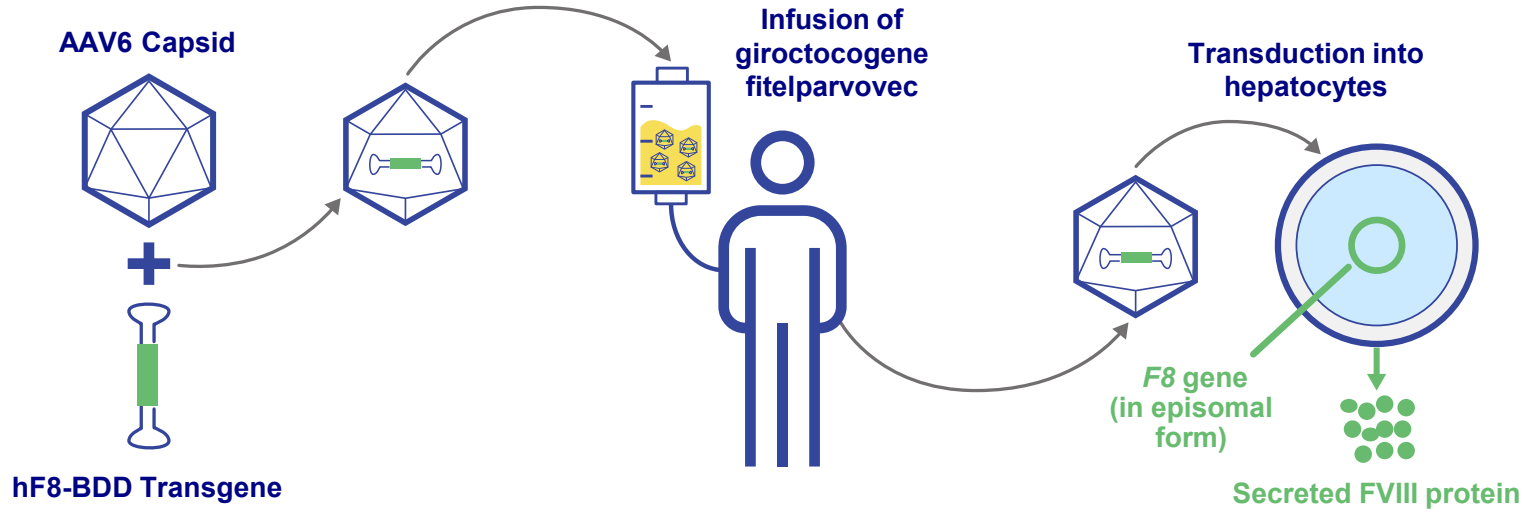
Giroctocogene fitelparvovec for hemophilia A

- Liver-tropic recombinant AAV serotype 6 (rAAV6) vector carrying B-domain–deleted human *F8* transgene enabling endogenous FVIII expression in individuals with severe to moderately severe hemophilia A

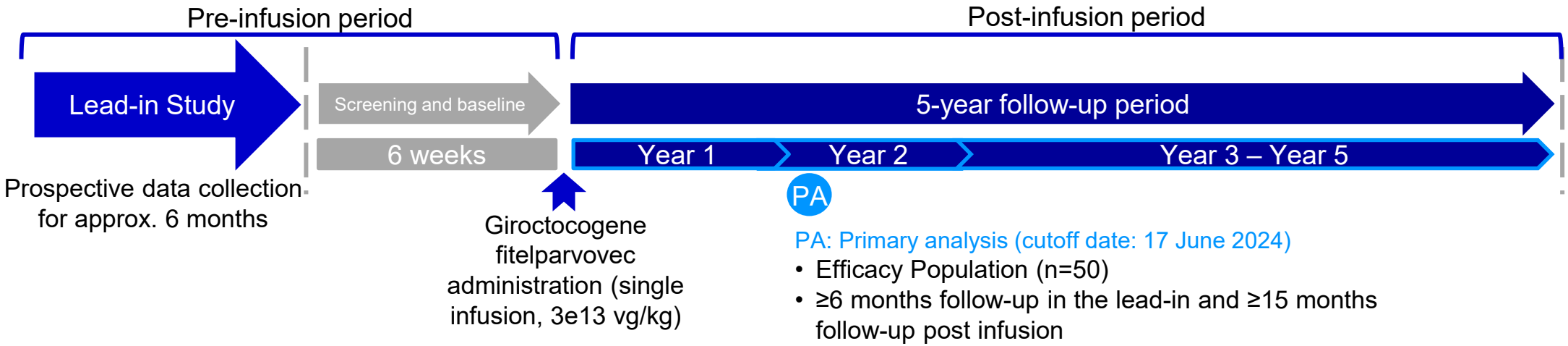


- The completed Alta phase 1/2 dose-ranging study[1,2] (up to 5 years) demonstrated a single infusion of giroctocogene fitelparvovec in the 3e13 vg/kg cohort (n=5) was well tolerated and resulted in:
  - Sustained FVIII activity levels in the moderate-to-normal range in most participants, no bleeds in the first year post infusion in all participants, and low bleeding rates through follow-up in 4 of 5 participants

AAV=adeno-associated virus; BDD=B-domain–deleted; FVIII=factor VIII; hF8=human factor 8; vg=vector genome

1. Harrington TJ, et al. Blood 2023;142(suppl 1):1054. **2.** Leavitt AD, et al. Blood 2024;143(9):796–806.

AFFINE study design



PA: Primary analysis (cutoff date: 17 June 2024)

- Efficacy Population (n=50)
- ≥6 months follow-up in the lead-in and ≥15 months follow-up post infusion

Key eligibility criteria

- Adult males with moderately severe to severe hemophilia A (FVIII activity level ≤1%)
- No anti-AAV6 NAbs or prior history FVIII inhibitors
- No significant liver dysfunction or fibrosis
- No active Hepatitis B or C, well controlled HIV
- No history of thrombotic events or major thromboembolic risk

Primary endpoint

- ABR for total bleeds (treated and untreated) from Week 12 through ≥15 months

Key secondary endpoints

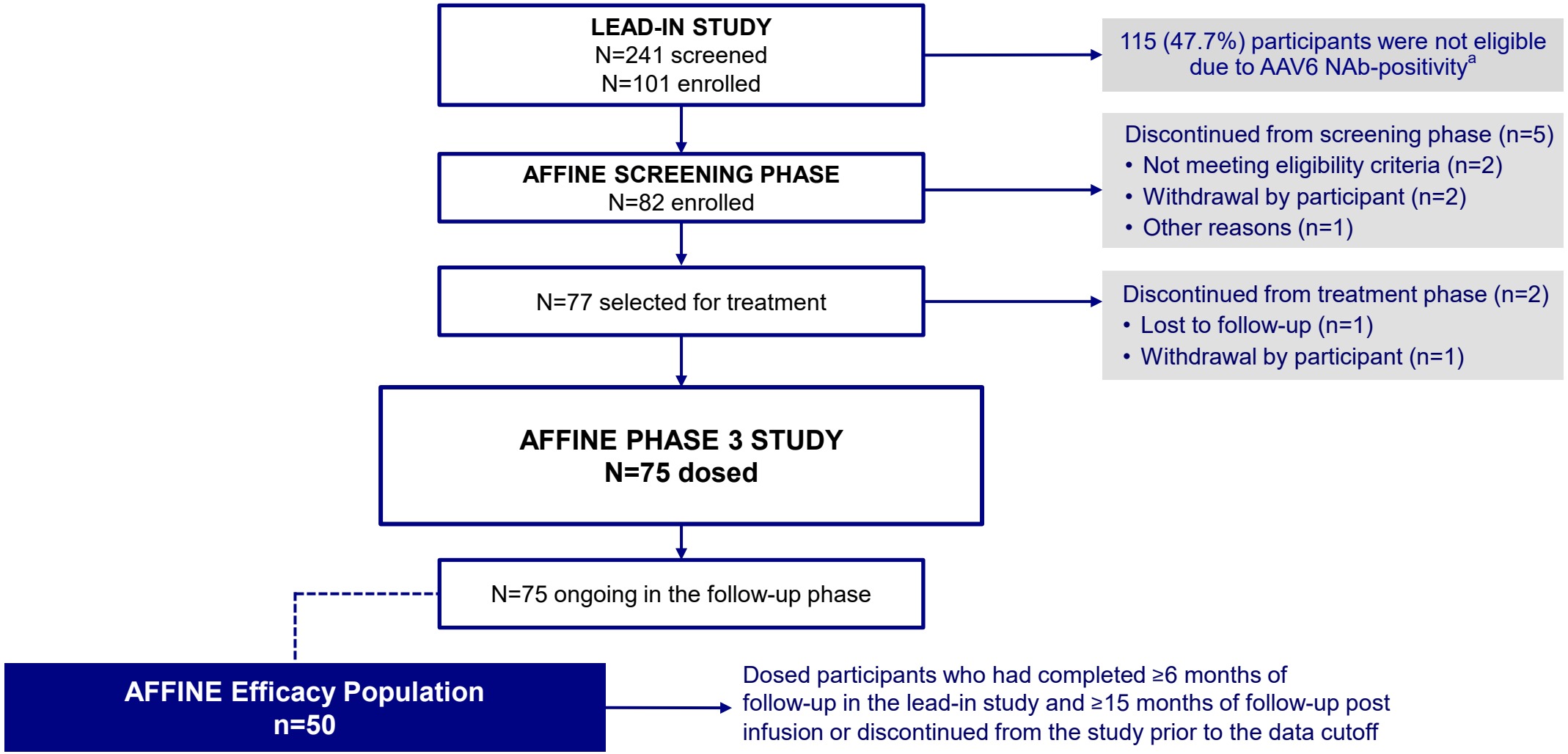
- Percentage of participants with FVIII activity level >5% at Month 15
- ABR for treated bleeds from Week 12 through ≥15 months

Secondary endpoint

- AIR of exogenous FVIII from Week 12 through ≥15 months

AAV-6=adeno-associated virus serotype 6; ABR=annualized bleeding rate; AIR=annualized infusion rate; FVIII=factor VIII; NAb=neutralizing antibody; vg=vector genome

Participant disposition



[a] anti-AAV-6 NAb titer ≥1:4.

AAV-6=adeno-associated virus serotype 6; NAb=neutralizing antibody

Baseline demographics and characteristics

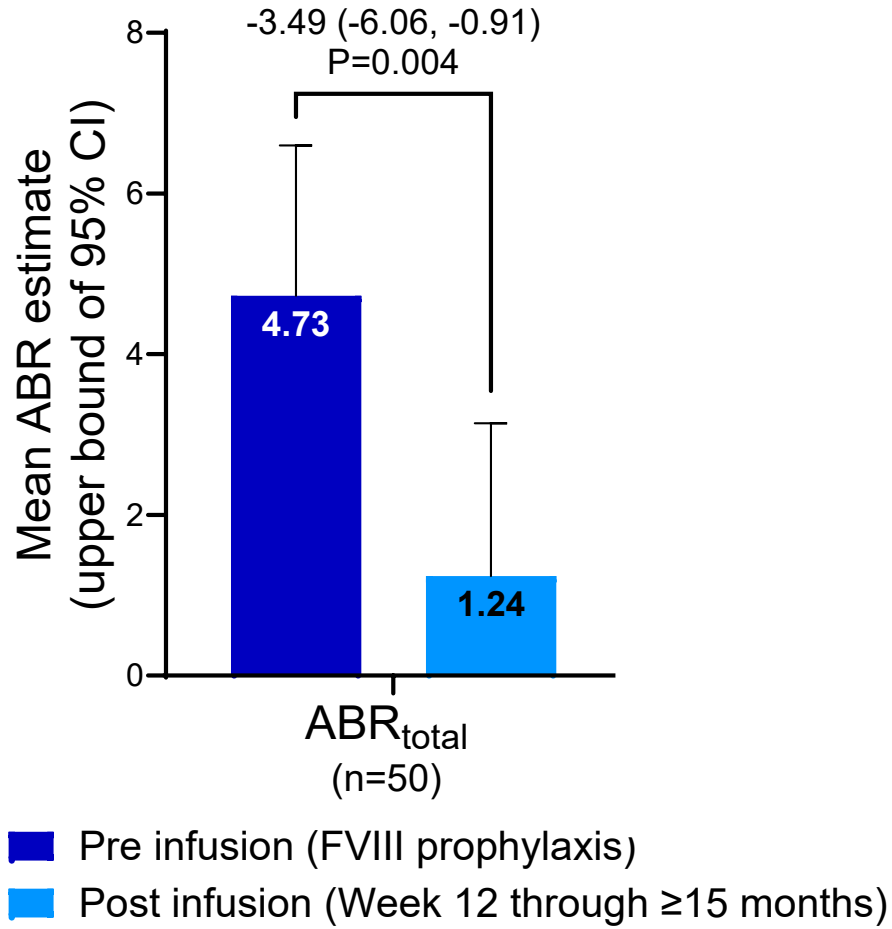
n (%)[a]	N=75
Age (range), y	32.3 (19–59)
BMI ± SD, kg/m^2	26.1 ± 5.1
Male	75 (100)
Race	
White	56 (74.7)
Asian	14 (18.7)
Black	5 (6.7)
Ethnicity	
Non-Hispanic	59 (78.7)
Hispanic	3 (4.0)
Not reported	13 (17.3)

n (%)[a]	N=75
Region	
North America	12 (16.0)
Europe	19 (25.3)
Middle East	30 (40.0)
Asia Pacific	10 (13.3)
South America	3 (4.0)
Australia	1 (1.3)
Ongoing controlled HIV	6 (8.0)
History of hepatitis B	11 (14.7)
History of hepatitis C	19 (25.3)
Target joints at baseline	25 (33.3)

[a] n (%) unless otherwise noted.

BMI=body mass index

Annualized bleeding rate: Total (treated and untreated) bleeds

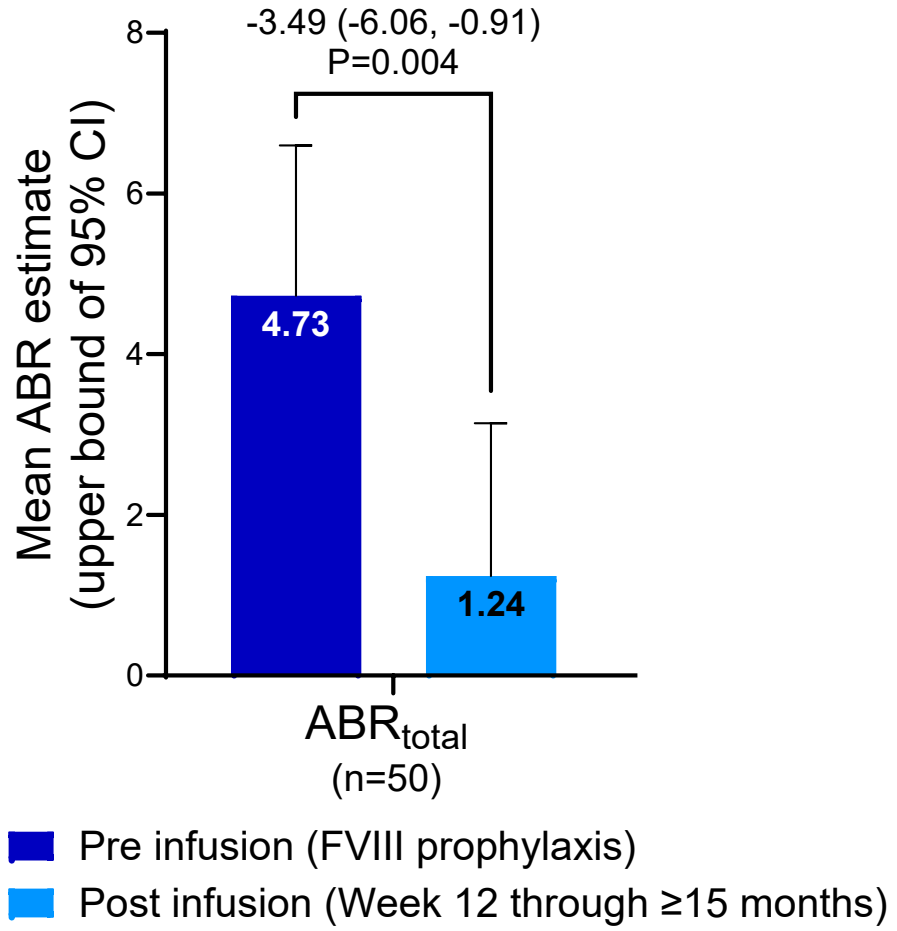


Superiority demonstrated vs FVIII prophylaxis
(Efficacy Population, n=50)

64.0% (32/50) of participants had no bleeding events
(median duration of follow-up, 33.6 months [range 14.5–44.4])

Numbers above graph represent treatment difference and 95% CI. Estimates and 1-sided P-value were obtained from a repeated measures generalized linear model with negative binomial distribution and identity link function with participant as a random effect and treatment and duration of follow-up (in years) as fixed effects.
ABR_{total}=annualized bleeding rate for total (treated and untreated) bleeds; CI=confidence interval; FVIII=factor VIII

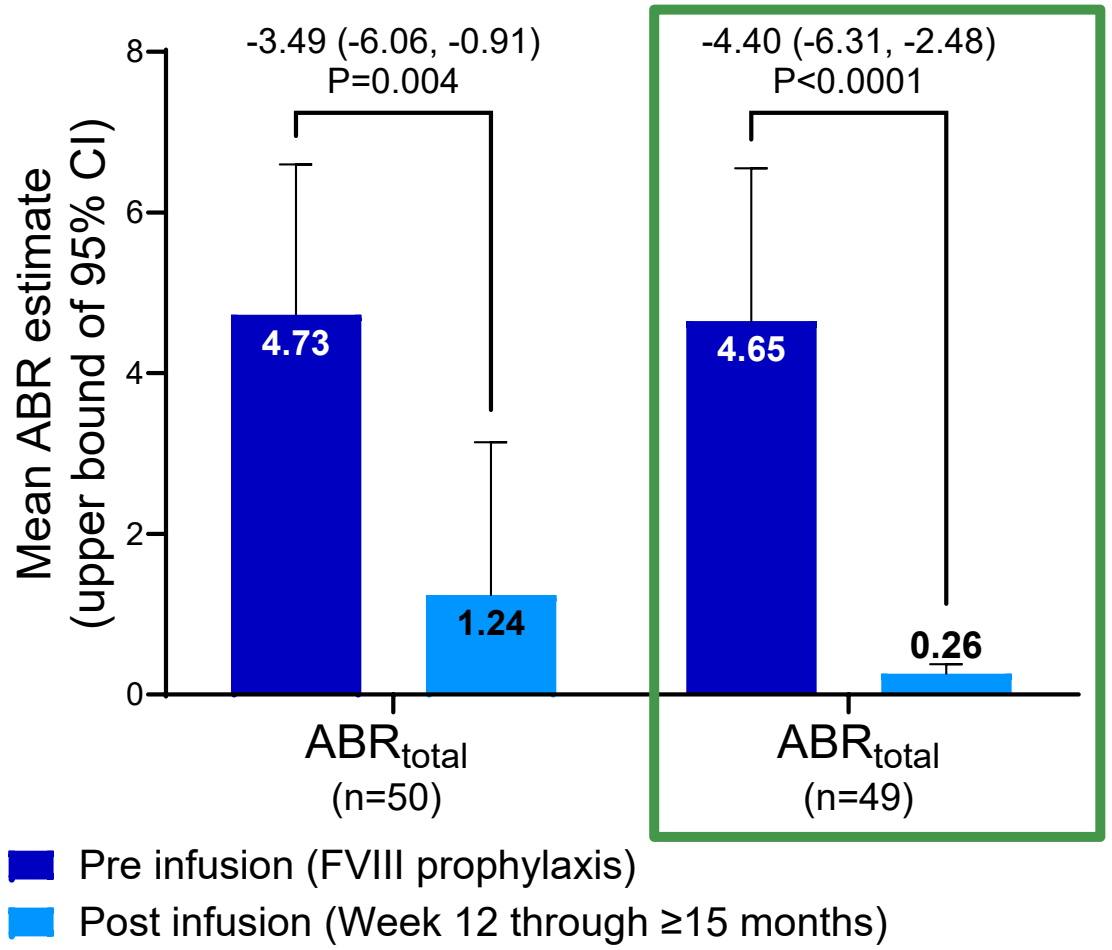
Annualized bleeding rate: Total (treated and untreated) bleeds



- 1 participant had inconsistencies in bleed reporting
  - High number of bleeds (126, total ABR = 47.4) starting at Month 18 post infusion
  - Maintained FVIII activity levels >150% (via CA) through data cutoff
- Median (min, max) bleeds excluding participant: 0.0 (0, 5)

Numbers above graph represent treatment difference and 95% CI. Estimates and 1-sided P-value were obtained from a repeated measures generalized linear model with negative binomial distribution and identity link function with participant as a random effect and treatment and duration of follow-up (in years) as fixed effects.
ABR_{total}=annualized bleeding rate for total (treated and untreated) bleeds; CA=chromogenic assay; CI=confidence interval; FVIII=factor VIII; max=maximum; min=minimum

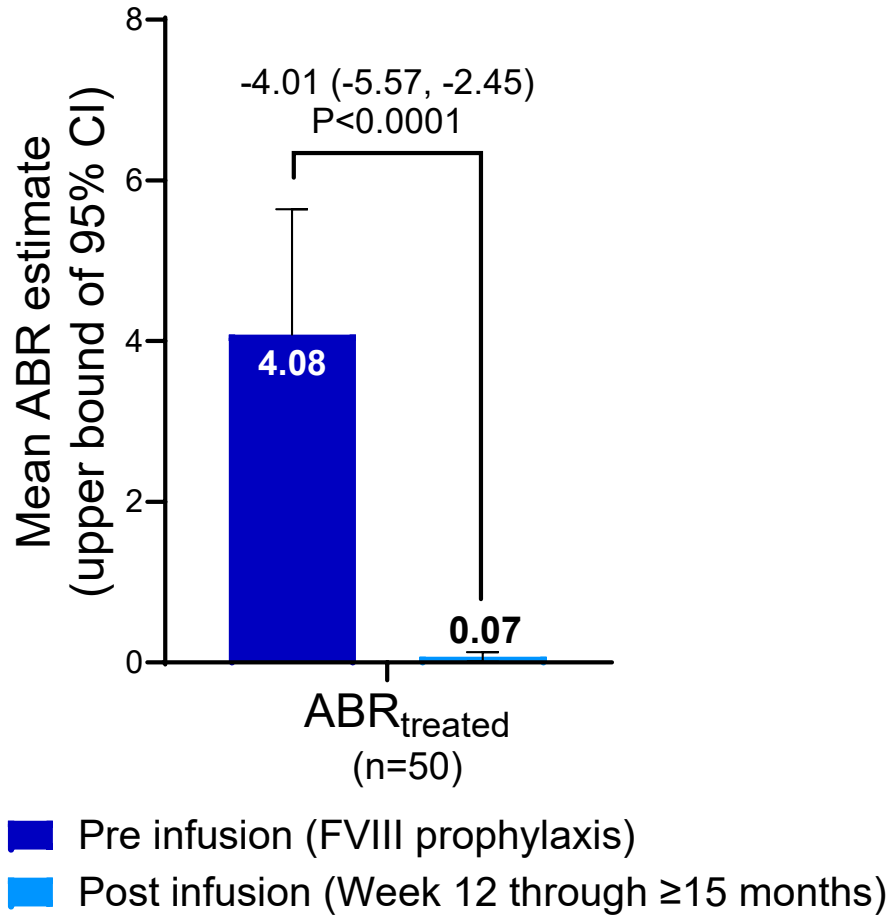
Annualized bleeding rate: Total (treated and untreated) bleeds



Post hoc sensitivity analysis excluding 1 participant (n=49) demonstrated superiority vs FVIII prophylaxis

Numbers above graph represent treatment difference and 95% CI. Estimates and 1-sided P-value were obtained from a repeated measures generalized linear model with negative binomial distribution and identity link function with participant as a random effect and treatment and duration of follow-up (in years) as fixed effects.
ABR_{total}=annualized bleeding rate for total (treated and untreated) bleeds; CI=confidence interval; FVIII=factor VIII

Annualized bleeding rate: Treated bleeds

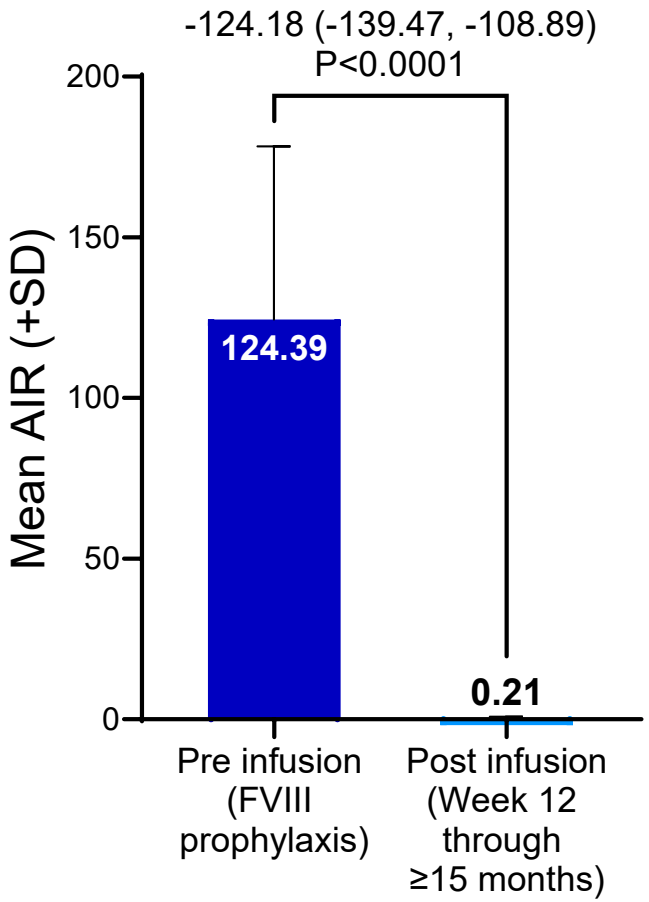


Superiority demonstrated vs FVIII prophylaxis
(Efficacy Population, n=50)

88.0% (44/50) of participants had no treated bleeds
(median duration of follow-up, 33.6 months [range 14.5–44.4])

Numbers above graph represent treatment difference and 95% CI. Estimates and 1-sided P-value were obtained from a repeated measures generalized linear model with negative binomial distribution and identity link function with participant as a random effect and treatment and duration of follow-up (in years) as fixed effects.
$ABR_{treated}$=annualized bleeding rate for treated bleeds; CI=confidence interval; FVIII=factor VIII

Annualized infusion rate of exogenous FVIII

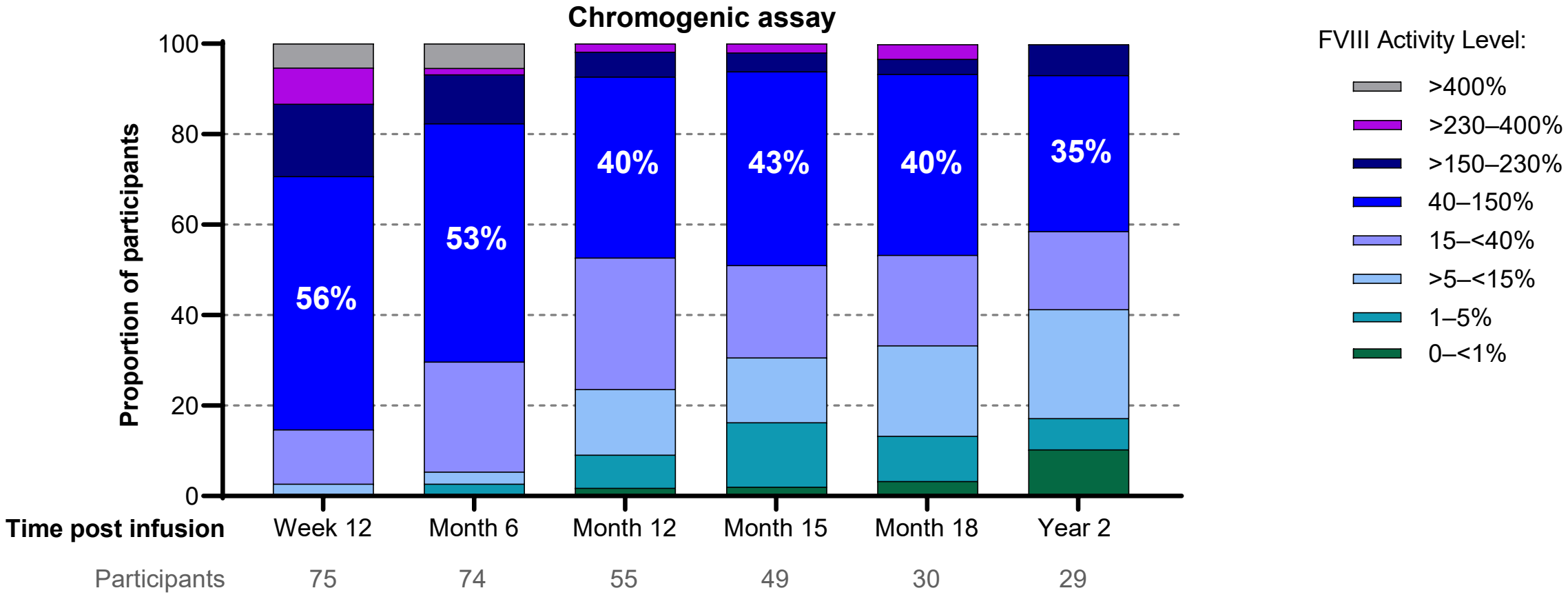


Superiority demonstrated vs FVIII prophylaxis
(Efficacy Population, n=50)

1 of 75 dosed participants resumed FVIII prophylaxis (time to resumption, 16.07 months)

The mean difference (95% CI) and 1-sided P-value were obtained from paired *t*-test.
AIR=annualized infusion rate; FVIII=factor VIII; SD=standard deviation

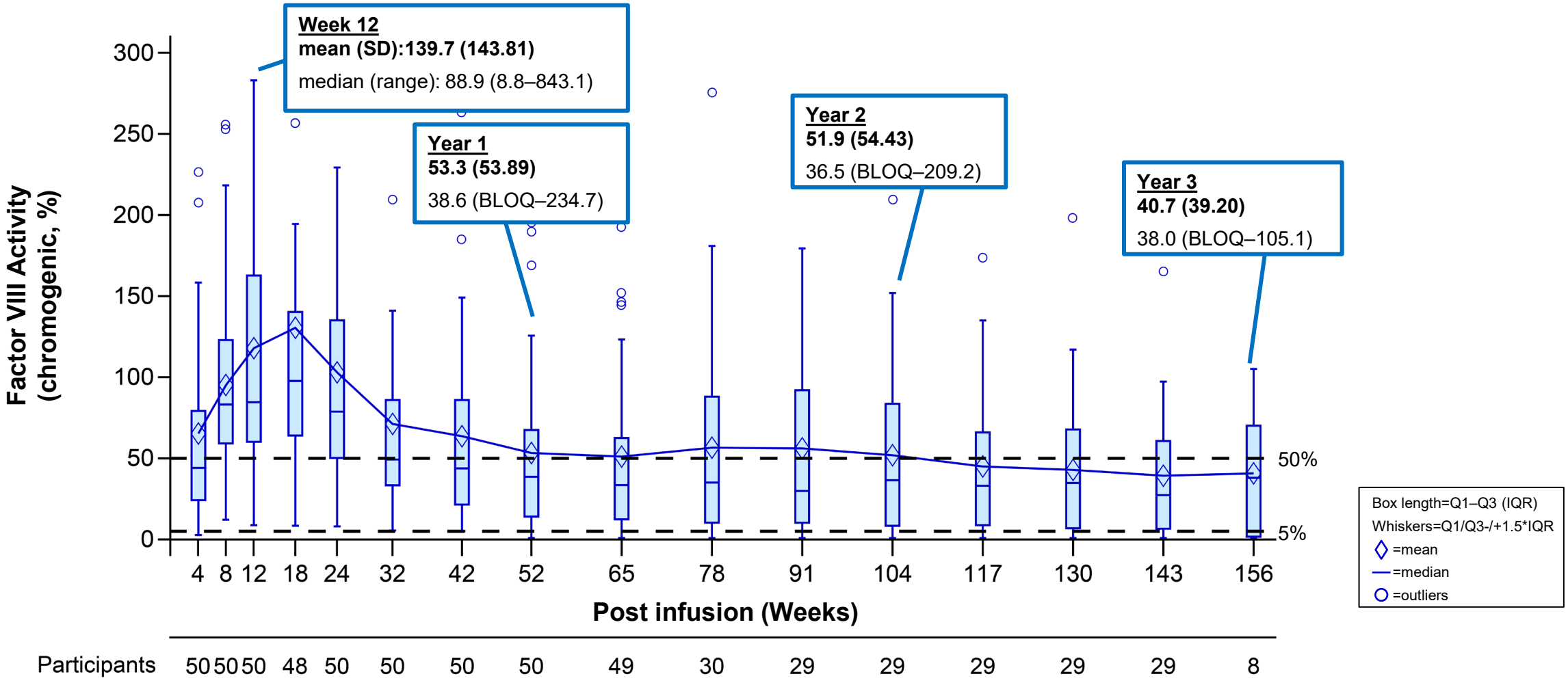
FVIII activity levels post infusion



At Month 15, 84% (95% CI 70.9, 92.8) of participants in the Efficacy Population (n=50) had FVIII activity levels >5% (via CA); 1-sided P=0.0086 vs null hypothesis of ≤68%

CA=chromogenic assay; FVIII=factor VIII; LLOQ=lower limit of quantification

FVIII activity levels through Year 3



Values >300% not shown.
CA=chromogenic assay; BLOQ=below lower limit of quantification; FVIII=factor VIII; IQR=interquartile range; max=maximum; min=minimum; Q=quartile

Safety overview

- No infusion interruptions or rate slowing
- Infusion-related reactions (events occurring within 2 days post infusion) in 58 (77.3%) participants
  - Mostly mild (n=39/58; 67.2%) with resolution within 2 days
- At data cutoff (mean [range] follow-up, 21.88 [7.8-44.4] months):
  - No FVIII inhibitors
  - No malignancies related to study drug
  - One thrombotic event in a participant with major protocol deviation (prior history of DVT and PE) and multiple thrombotic risk factors

Participants with AEs, n (%) and number of events (when specified)	Dosed Population N=75
AEs	74 (98.7)
Number of events	740
Discontinued due to AEs	0 (0)
SAEs	15 (20.0)
Number of events	26
Treatment-related AEs	68 (90.7)
Selected treatment-related AESIs	
Hepatotoxicity (transaminase increased)	47 (62.7)
Infusion-related reactions	55 (73.3)
Pyrexia	38 (50.7)
Headache	23 (30.7)
Chills	14 (18.7)
Deep vein thrombosis	1 (1.3)

AE=adverse event; AESI=adverse event of special interest; DVT=deep vein thrombosis; FVIII=factor VIII; PE=pulmonary embolism; SAE=serious adverse event

ALT elevations and corticosteroid use

- ALT elevations were mild and manageable
  - ALT elevations resolved within a median of 28.0 days
- Overall, corticosteroids were well tolerated, with corticosteroid-related AEs reported in 19 (25.3%) participants
- At the time of the data cutoff, no participants in the Efficacy Population remained on corticosteroids
- 5 (6.7%) participants received alternative immunosuppressive therapies following corticosteroid treatment, including MMF in 4 participants, and azathioprine in 1 participant

ALT and corticosteroid use	N=75
Treatment-related AEs related to hepatotoxicity (transaminase increased), n (%)	47 (62.7)
SAEs related to transaminase increased, n (%)	2 (2.7)
Participants with ALT increase >ULN, n (%)	46 (61.3)
ALT grades (CTCAE grading)[a] among all dosed participants, n (%)	
Normal	30 (40.0)
Grade 1	40 (53.3)
Grade 2	4 (5.3)
Grade 3	1 (1.3)
Grade 4	0 (0)
Pts with corticosteroid use, n (%)	47 (62.7)
Time to corticosteroid initiation, median (range), days	84 (7–193)
Corticosteroid courses per participant, mean (range), days	2.0 (1–5)
Duration of corticosteroid use, mean (range), days	114.6 (11–296)

[a] The highest CTCAE grade among all post baseline assessments from each participant are reported.
AE=adverse event; ALT=alanine aminotransferase; CTCAE=common terminology criteria for adverse events; MMF=mycophenolate mofetil; pts=participants; SAE=serious adverse event; ULN=upper limit of normal

FVIII activity elevations

- DOACs were well tolerated, with no significant bleeding events while on DOAC
  - In total, 6 participants reported ≥1 bleed while on DOAC, none were treated
- 1 participant (major PD with prior history of DVT and PE and multiple thrombotic risk factors) experienced a thromboembolic event
- No other thromboembolic events were reported

FVIII elevations throughout follow-up	N=75
≥1 FVIII activity level >150% (CA), n (%)	37 (49.3)
Time to first FVIII activity level >150%, mean (range), days	74.7 (15–540)
Days with FVIII >150%, mean (range)	143.8 (4–953)
Received prophylactic DOAC, n (%)	23 (30.7)
Time to DOAC initiation, mean (range), days	86.13 (28–370)
Total duration of DOAC, mean (range), days	166 (7–944)

CA=chromogenic assay; DOAC=direct oral anticoagulant; DVT=deep vein thrombosis; FVIII=factor VIII; OSA=one-stage assay; PD=protocol deviation; PE=pulmonary embolism

Summary: Efficacy and safety of giroctocogene fitelparvovec

- A single IV infusion of 3e13 vg/kg was generally well tolerated and exhibited an acceptable and manageable safety profile
- The study met the primary endpoint with a significantly reduced mean ABR_{total} vs FVIII prophylaxis: 1.24 vs 4.73 (0.26 vs 4.65 in post hoc sensitivity analysis)
- Mean $ABR_{treated}$ was significantly reduced vs FVIII prophylaxis (0.07 vs 4.08)
- Mean AIR was also significantly reduced vs FVIII prophylaxis (0.21 vs 124.39)
- Mean FVIII activity levels >50% of normal (via CA) were achieved and stable up to 2 years post infusion
- At the time of primary analysis, 1 participant returned to prophylaxis at month 16

ABR_{total}=total annualized bleeding rate; $ABR_{treated}$=treated annualized bleeding rate; AIR=annualized infusion rate; CA=chromogenic assay; FVIII=factor VIII; IV=intravenous; vg=vector genome

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Plain Language Study (PLS)

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