

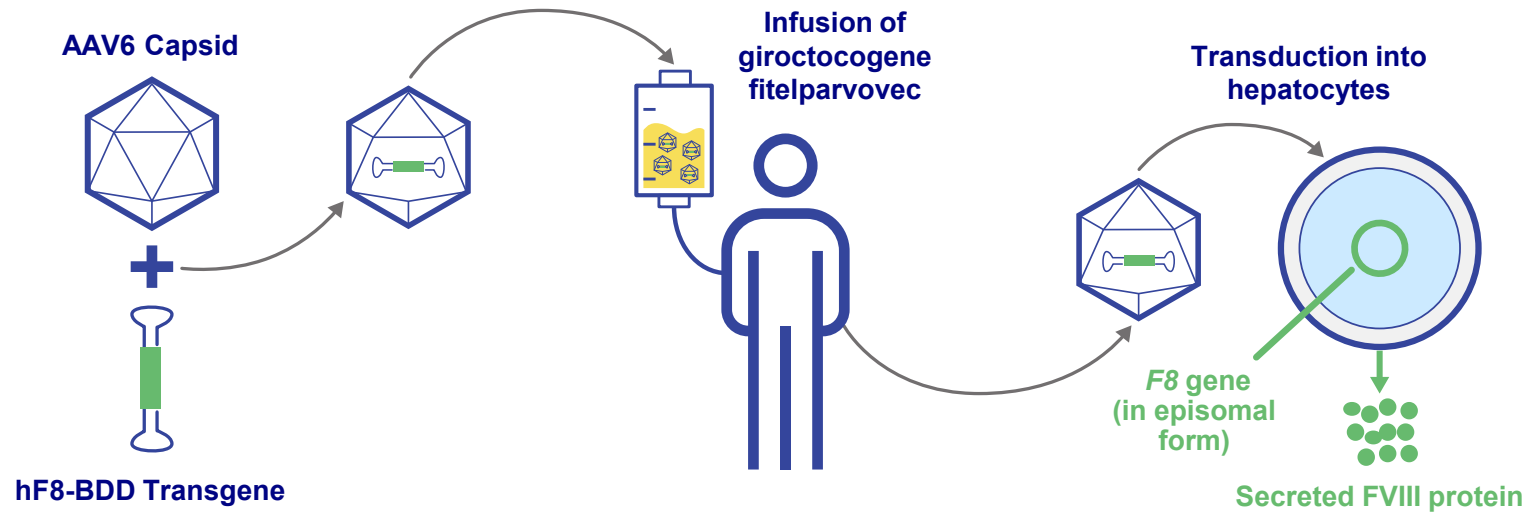
Efficacy and Safety of Giroctocogene Fitelparvovec in Adults With Moderately Severe to Severe Hemophilia A: Primary Analysis Results From the Phase 3 AFFINE Gene Therapy Trial

Andrew D Leavitt¹, Kaan Kavakli², Laurent Frenzel³, Ali Bülent Antmen⁴, Margareth Ozelo⁵, Davide Martino^{6,7}, Hazza Alzahrani⁸, Barbara A Konkle⁹, Steven W Pipe¹⁰, Jerome M Teitel¹¹, Li-Jung Tseng¹², Annie F Fang¹², Florence Ganne¹³, Gregory DiRusso¹⁴, Jeremy Rupon¹⁴, Pascal Klaus¹⁵, Jasmine Healy¹⁶, Delphine Agathon¹³, Francesca Biondo¹⁷, Frank Plonski¹⁴, on behalf of the AFFINE Investigators

¹University of California San Francisco, San Francisco, CA, USA; ²Ege University Faculty of Medicine, Izmir, Turkey; ³Hemophilia Care and Research, Necker Hospital, Institut Imagine, Paris, France; ⁴Acibadem Adana Hospital, Adana, Turkey; ⁵Hemocentro UNICAMP, School of Medical Sciences, University of Campinas, Campinas, Brazil; ⁶Thrombosis and Atherosclerosis Research Institute (TaARI), McMaster University, Hamilton, ON, Canada; ⁷McMaster University, Hamilton, ON, Canada; ⁸King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; ⁹Washington Center for Bleeding Disorders and the University of Washington, Seattle, WA, USA; ¹⁰University of Michigan, Ann Arbor, MI, USA; ¹¹St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; ¹²Pfizer Inc, New York, NY, USA; ¹³Pfizer Inc, Paris, France; ¹⁴Pfizer Inc, Collegeville, PA, USA; ¹⁵Pfizer Pharma GmbH, Berlin, Germany; ¹⁶Pfizer Canada ULC, Kirkland, QC, Canada; ¹⁷Pfizer Srl, Rome, Italy

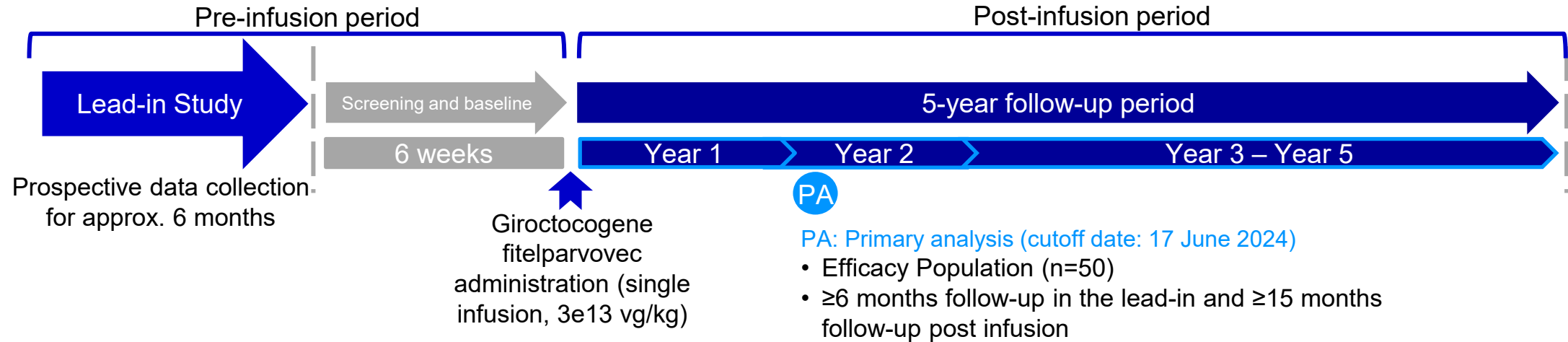
Giroctocogene fitelparvovec for hemophilia A

- 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

AFFINE study design



Key eligibility criteria

- Adult males with moderately severe to severe hemophilia A (FVIII activity level $\leq 1\%$)
- 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

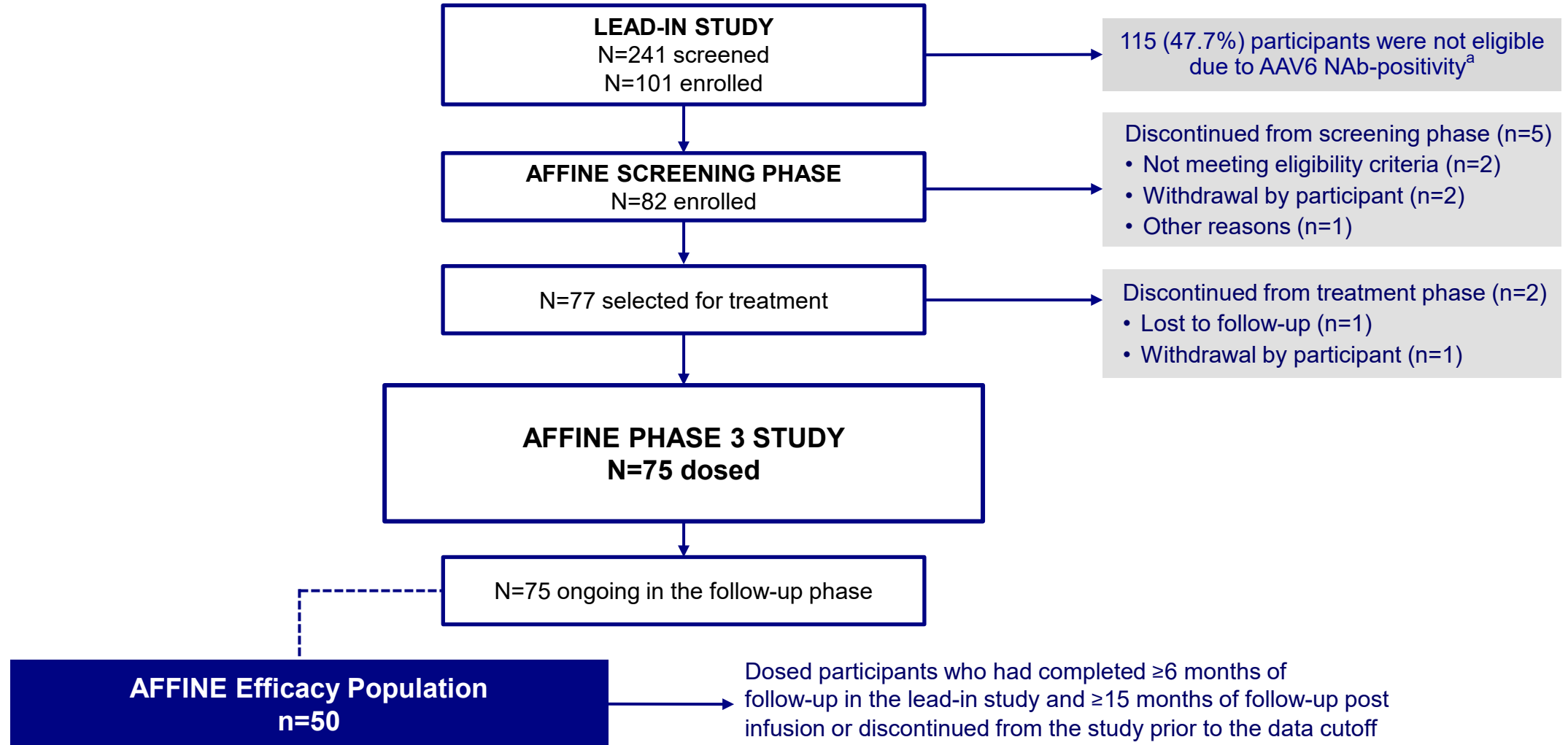
Key secondary endpoints

- 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

Participant disposition



^a anti-AAV-6 NAb titer ≥1:4.

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

Baseline demographics and characteristics

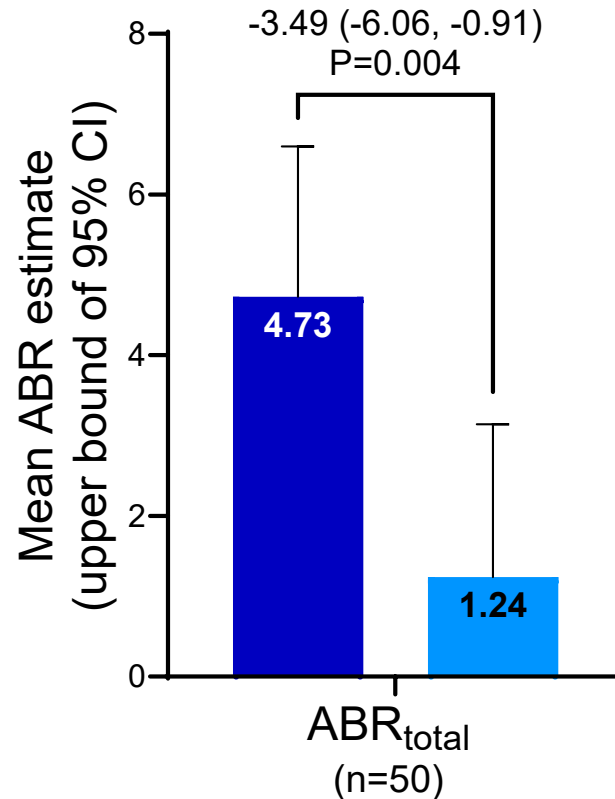
n (%) ^a	N=75
Age (range), y	32.3 (19–59)
BMI ± SD, kg/m ²	26.1 ± 5.1
Male	75 (100)
Race	
White	56 (74.7)
Asian	14 (18.7)
Black	5 (6.7)
Ethnicity	
Non-Hispanic	59 (78.7)
Hispanic	3 (4.0)
Not reported	13 (17.3)

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



- Pre infusion (FVIII prophylaxis)
- Post infusion (Week 12 through ≥15 months)

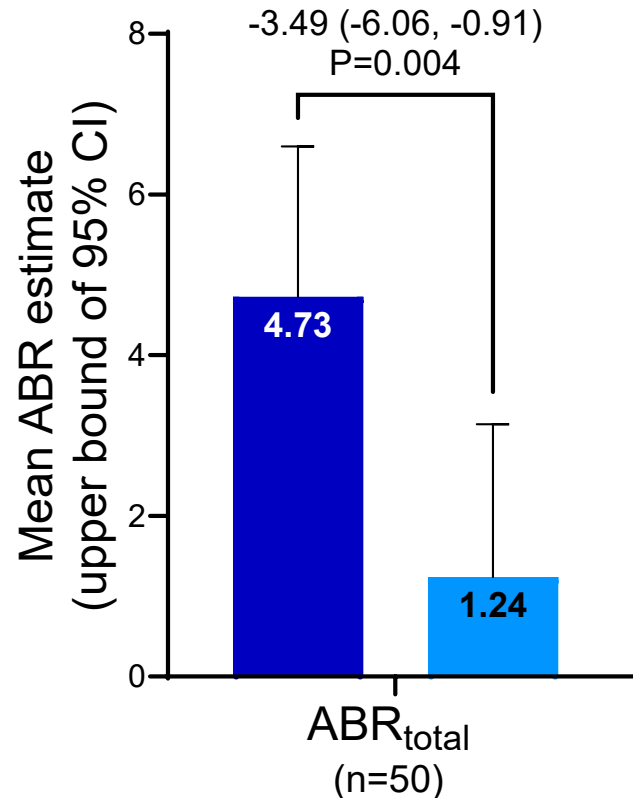
Superiority demonstrated vs FVIII prophylaxis (Efficacy Population, n=50)

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



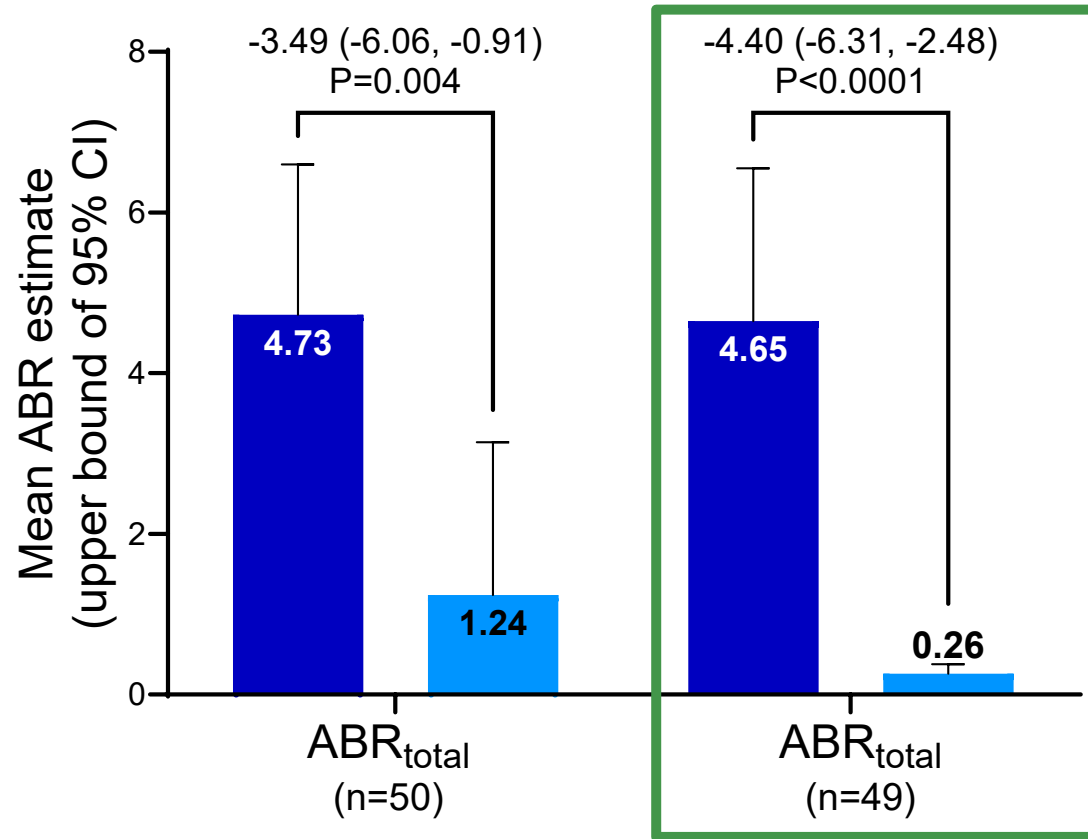
- Pre infusion (FVIII prophylaxis)
- Post infusion (Week 12 through ≥15 months)

- 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

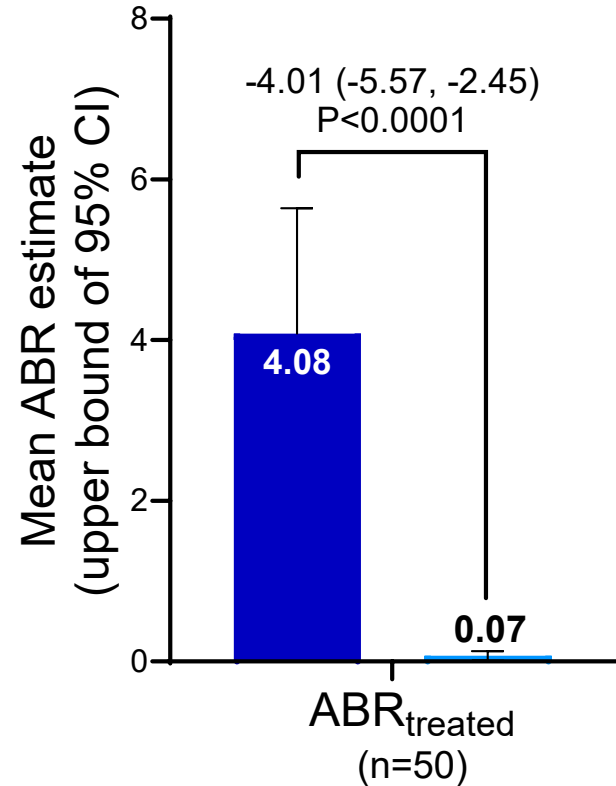


- Pre infusion (FVIII prophylaxis)
- Post infusion (Week 12 through ≥15 months)

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



- Pre infusion (FVIII prophylaxis)
- Post infusion (Week 12 through ≥15 months)

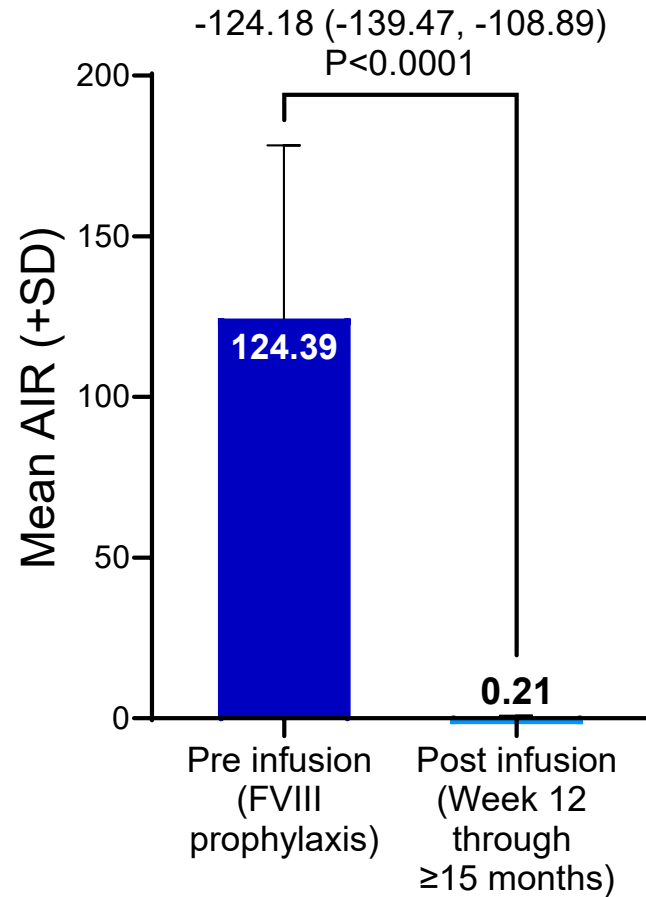
Superiority demonstrated vs FVIII prophylaxis (Efficacy Population, n=50)

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

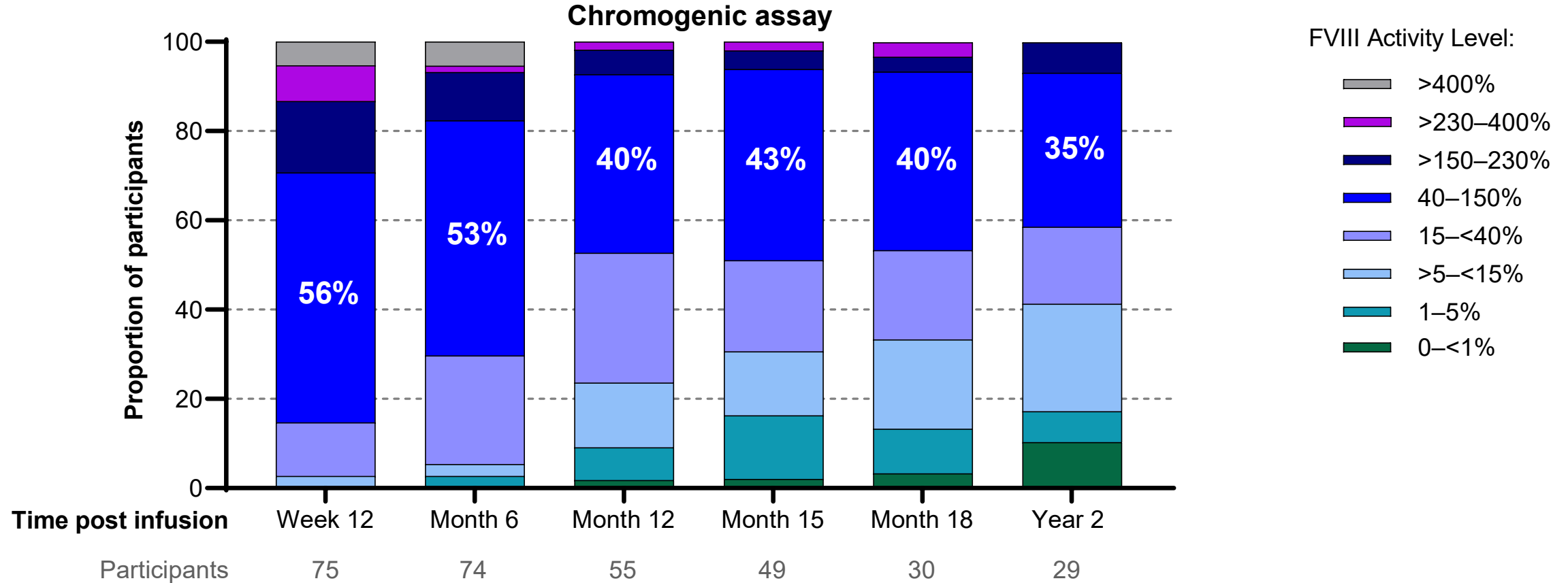


Superiority demonstrated vs FVIII prophylaxis (Efficacy Population, n=50)

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

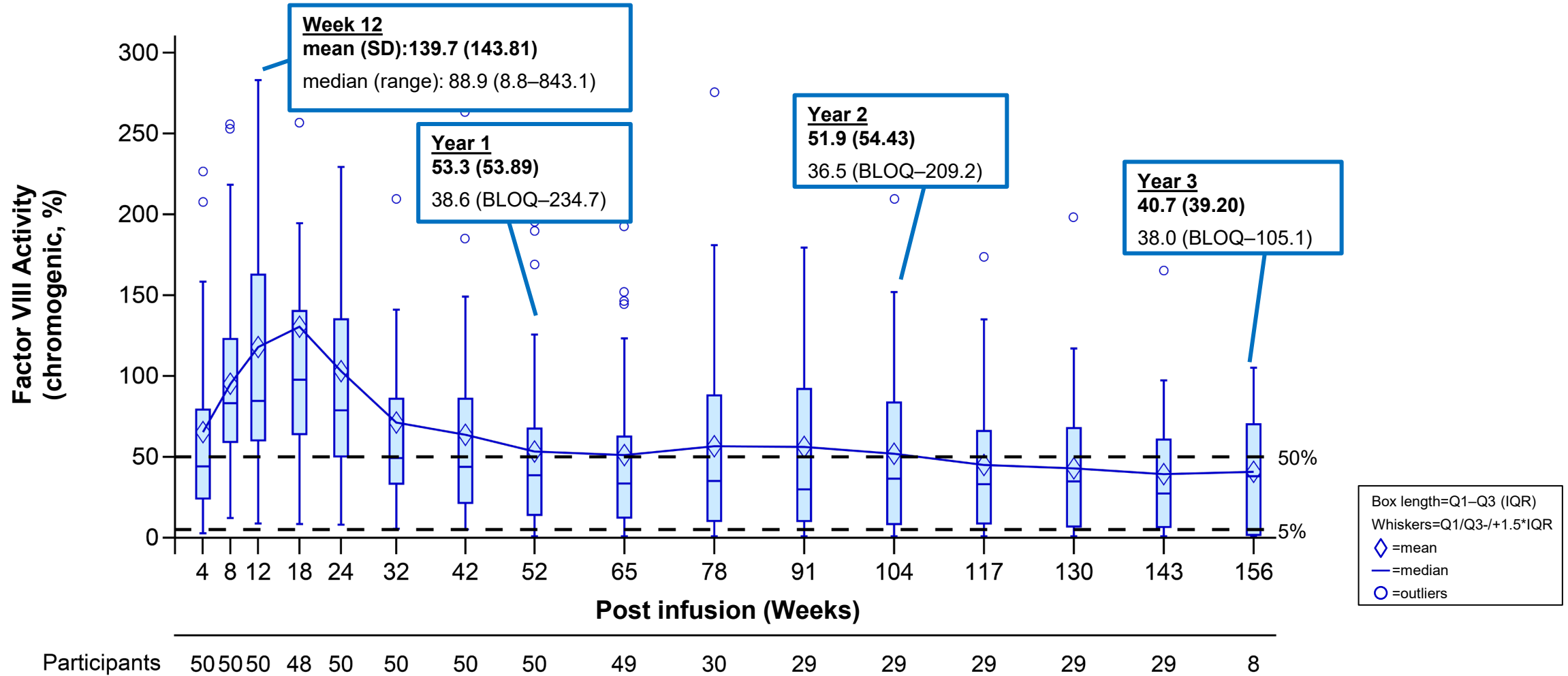
FVIII activity levels post infusion



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)

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)

Summary: Efficacy and safety of giroctocogene fitelparvovec

- A single IV infusion of 3×10^{13} 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

Acknowledgments

- We thank
 - All the AFFINE study participants
 - The AFFINE investigators and site staff:
 - Sheng-Chieh Chou, Elena M Fernandez Fontecha, Ali Bulent Antmen, Huyen Tran, Andrew D Leavitt, Effrosyni Nomikou, Tadashi Matsushita, Margareth C Ozelo, Yoshitaka Miyakawa, Laurent Frenzel, Jan SP Astermark, Gerard Dolan, Caroline Berube, Hazzaa Alzahrani, Fahri Sahin, Ramazan K Kavakli, Barbara A Konkle, Young Shil Park, Robert Klamroth, Davide Matino, Vahap Okan
- This study was funded by Pfizer
- Medical writing support was provided by Courtney Cameron, PhD, of Engage Scientific Solutions and funded by Pfizer



Plain Language Study (PLS)

Please scan this QR code with your smartphone app to view or obtain a copy of the PLS for this poster. If you don't have a smartphone, access the poster via the internet at:

<https://scientificpubs.congressposter.com/pls/fgm1s88xfssnn9ly>

Plain Language Study Results Summaries are descriptions in everyday language of the design and results of clinical studies. These summaries (also called layperson summaries, plain language summaries, lay language summaries, simple summaries, and trial results summaries) are intended to make the clinical results of these studies understandable and accessible to patients, healthcare providers, caregivers, researchers, and a general audience.