WFH COMPREHENSIVE CARE SUMMIT

Efficacy and safety of valoctocogene roxaparvovec for severe hemophilia A 5 years after gene transfer in GENEr8-1

SPEAKER

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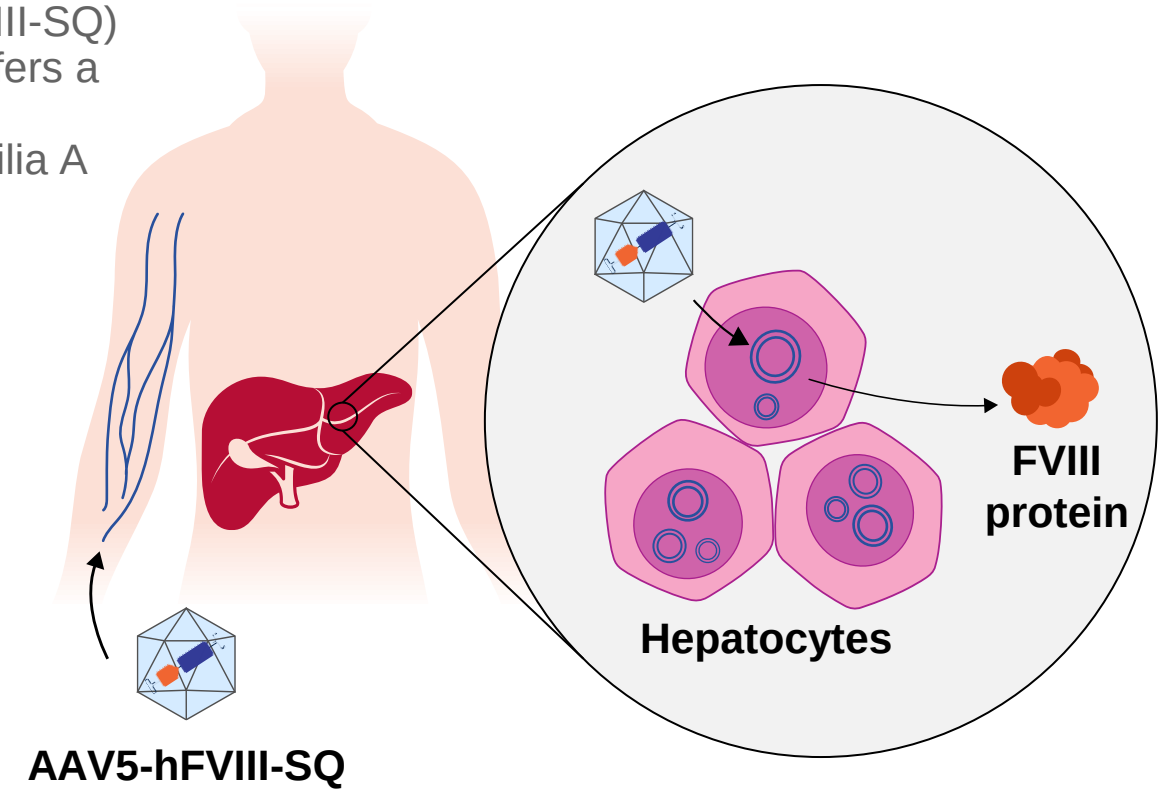
Valoctocogene roxaparvovec for severe hemophilia A

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a FVIII coding sequence to enable FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1-4]

As previously shown, participants who received $6x10^{13}$ vg/kg valoctocogene roxaparvovec had improved protection from bleeds compared with regular FVIII prophylaxis over 4 years[1-4]

Here, we present the final outcomes of the phase 3 GENEr8-1 trial 5 years after gene transfer



1. Ozelo M, et al. *N Engl J Med.* 2022;386(11):1013-25. 2. Mahlangu J, et al. *N Engl J Med.* 2023;388:694-705. 3. Madan B, et al. *J Thromb Haemost*. 2024;22:1880-93. 4. Leavitt A, et al. *Res Pract Thromb Haemost*. 2024;8:e102615.
FVIII, factor VIII.

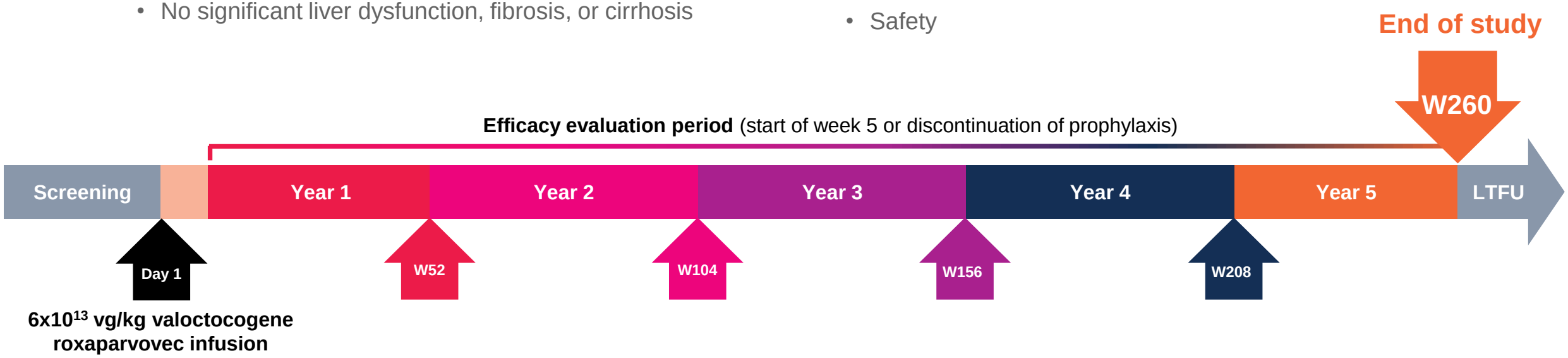
Study design

Eligibility

- Adult men with severe hemophilia A (FVIII ≤1 IU/dL)
- Previously receiving FVIII prophylaxis
- No history of FVIII inhibitors or anti-AAV5 antibodies
- No significant liver dysfunction, fibrosis, or cirrhosis

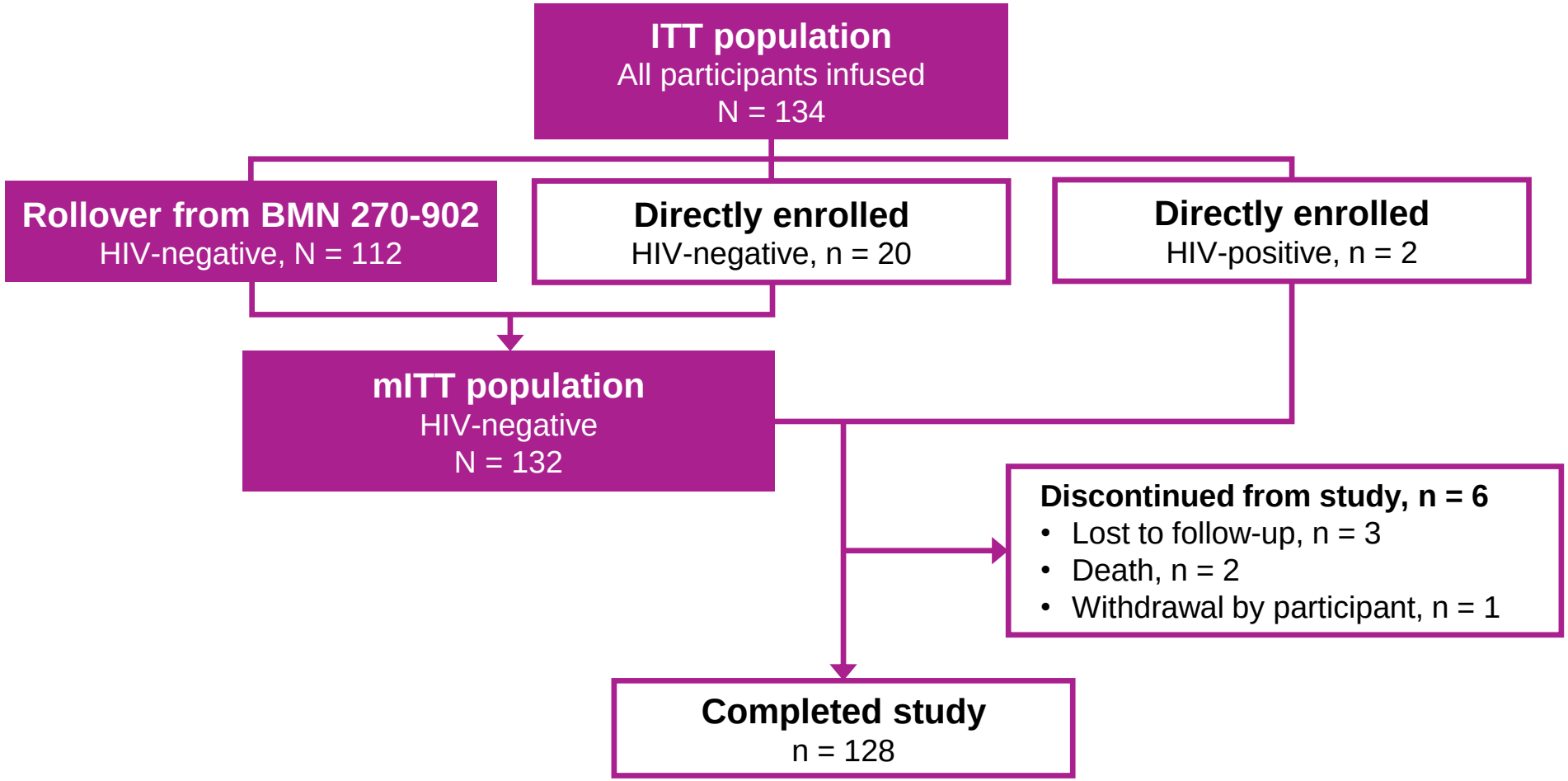
Endpoints

- FVIII activity
- Change from baseline
  - Annualized bleeding rate
  - Annualized FVIII infusion rate
- Safety



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; LTFU, long-term follow-up; W, week.

Participant disposition



HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified ITT.

Baseline characteristics

Baseline characteristics	Rollover population N = 112	mITT N = 132	ITT N = 134
Age, years, mean (range)	31.8 (19–70)	31.4 (18–70)	31.7 (18–70)
Race, n (%)			
White	78 (69.6)	94 (71.2)	96 (71.6)
Asian	17 (15.2)	19 (14.4)	19 (14.2)
Black or African American	14 (12.5)	15 (11.4)	15 (11.2)
Hawaiian or Pacific Islander	1 (0.9)	1 (0.8)	1 (0.7)
Not provided	2 (1.8)	3 (2.3)	3 (2.2)
Hispanic or Latino ethnicity, n (%)	5 (4.5)	7 (5.3)	7 (5.2)
BMI, kg/m^2, mean ± SD	25.2 ± 4.7	25.3 ± 4.6	25.3 ± 4.6
Medical history, n (%)			
Hepatitis B	17 (15.2)	18 (13.6)	20 (14.9)
Hepatitis C	33 (29.5)	39 (29.5)	41 (30.6)
HIV	0	0	2 (1.5)
Number of problem joints,[a] n (%)			
0	82 (73.2)	95 (72.0)	97 (72.4)
1	13 (11.6)	17 (12.9)	17 (12.7)
2	9 (8.0)	9 (6.8)	9 (6.7)
3	6 (5.4)	8 (6.1)	8 (6.0)
>3	2 (1.8)	3 (2.3)	3 (2.2)

[a]Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.
BMI, body mass index; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified ITT; SD, standard deviation.

No new safety signals in year 5

ITT population (N = 134)

In year 5

- No new safety signals
- No grade 3 or higher ALT elevations occurred
- No treatment-related SAEs occurred

Across the trial

- No treatment-related malignancies
- No participants experienced thromboembolic events or developed FVIII inhibitors

AEs in year 5		Participants, n (%) ITT (N = 129)
AEs		102 (79.1)
SAEs		4 (3.1)
Treatment-related AEs[a]		5 (3.9)
Treatment-related SAEs		0 (0.0)
AEs grade ≥3		6 (4.7)
Glucocorticoid-related AEs[a]		0 (0.0)
AEs of special interest	ALT elevation	52 (40.3)
	ALT elevation grade ≥3	0 (0.0)
	Potential Hy's law case	0 (0.0)
	Infusion-related reactions[b]	0 (0.0)
	Systemic hypersensitivity	0 (0.0)
	Anaphylactic or anaphylactoid reactions	0 (0.0)
	Thromboembolic events	0 (0.0)
	Anti-FVIII neutralizing antibodies	0 (0.0)
	Malignancy (except non-melanoma skin cancer)	0 (0.0)

[a]Treatment-related and glucocorticoid-related AEs were assessed by the investigator.
[b]Infusion-related reactions were defined as AEs occurring during valoctocogene roxaparvovec infusion or within 6 hours post-infusion.
AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; ITT, intention-to-treat; SAE, serious AE.

ALT elevation and glucocorticoid use

ITT population (N = 134)

In year 5

- 63 (48.8%) participants had an ALT elevation >1.5x baseline
- 23 (17.8%) participants had an ALT elevation >ULN
- No participants used glucocorticoids to manage ALT elevations

Glucocorticoid use in previous years

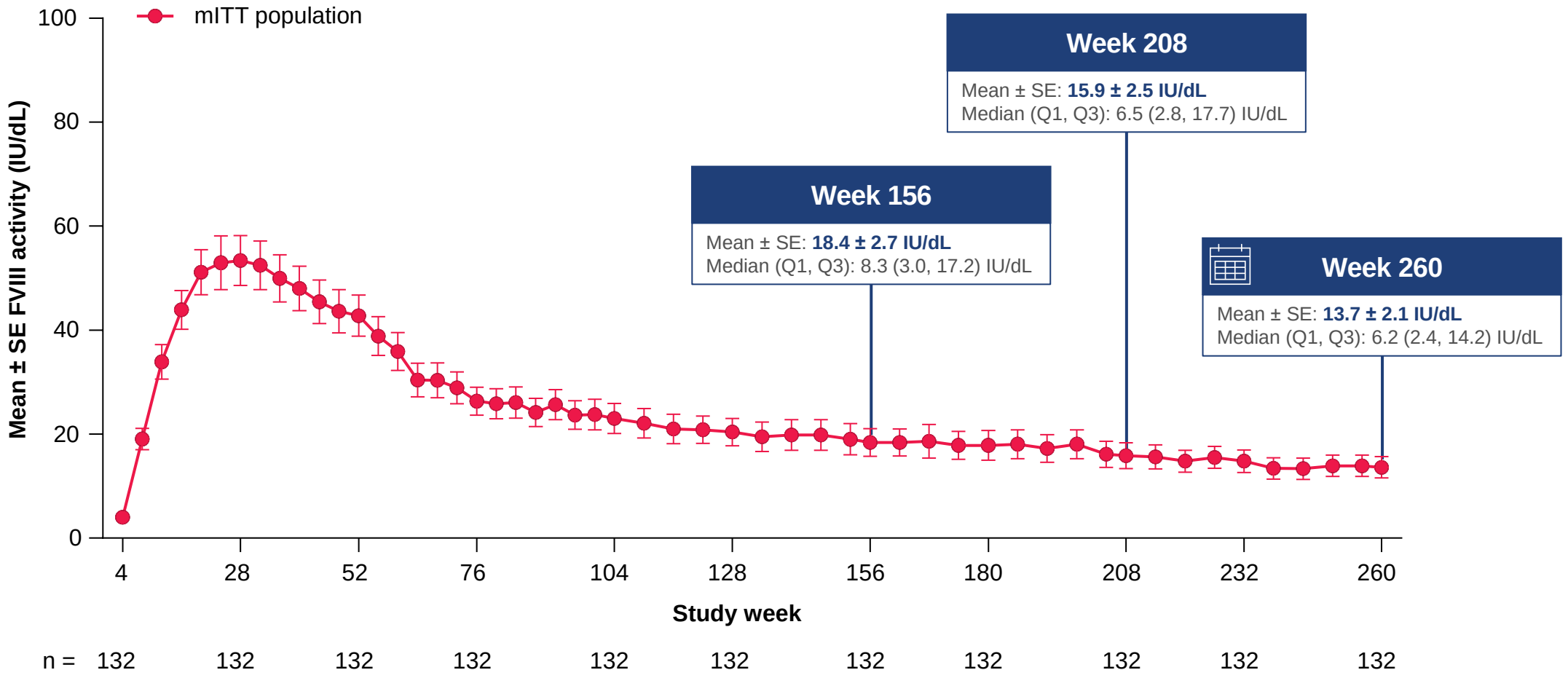
- Since year 2, glucocorticoids have not been used to manage ALT elevations
- Since year 1, glucocorticoids have not been initiated to manage ALT elevations

Events in year 5	Participants, n (%) (N = 129)
ALT elevation >ULN, n (%)	23 (17.8)
ALT elevation >1.5x baseline, n (%)	63 (48.8)
Used corticosteroids for any purpose, n (%)	2 (1.6)
Total duration, weeks, median (min, max)	0.8 (0.7, 0.9)
Total dose, mg, median (min, max)	70.0 (20.0, 120.0)
Used corticosteroids for ALT elevation, n (%)	0 (0.0)

AE, adverse event; ALT, alanine aminotransferase; ITT, intention-to-treat; max, maximum; min, minimum; ULN, upper limit of normal.

FVIII activity across the trial (CSA)

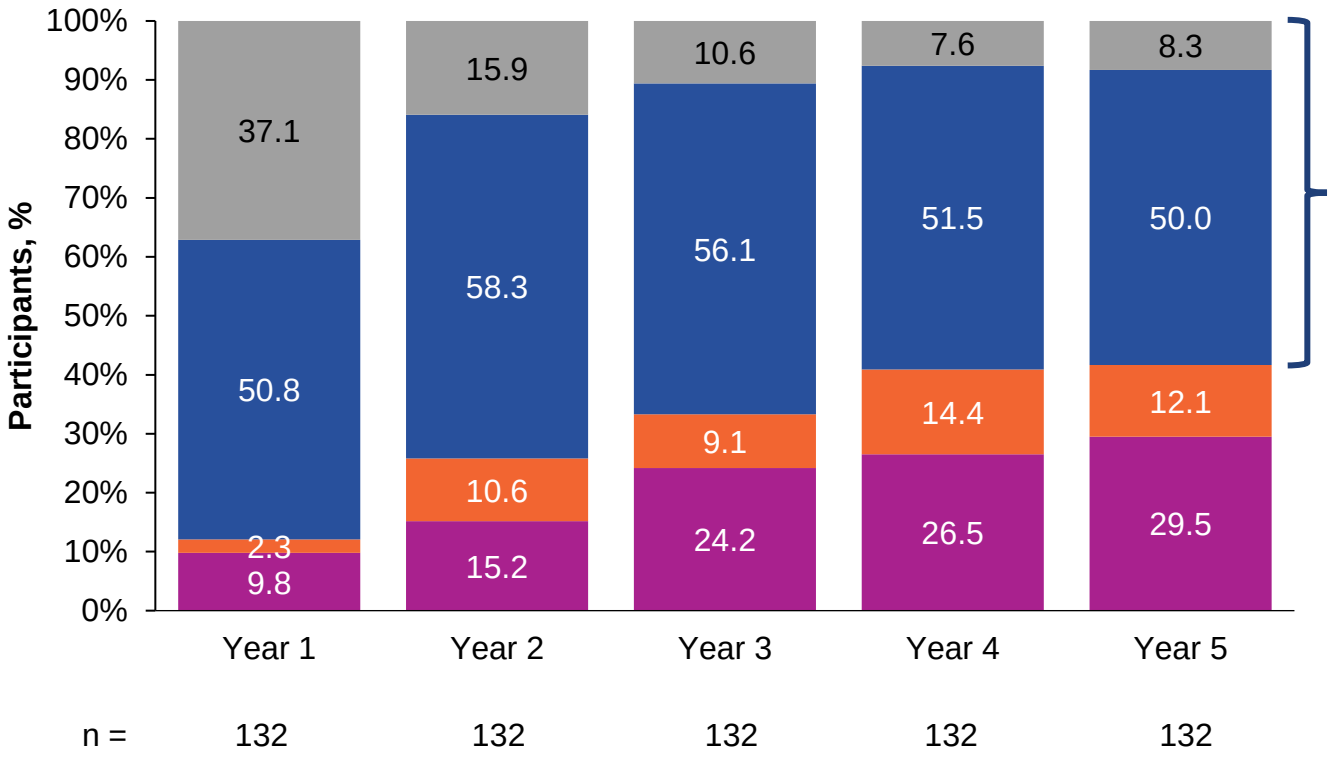
mITT population (N = 132)



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

FVIII activity (CSA) at the end of year 5

mITT population (N = 132)



58.3% of participants remain in the mild to non-hemophilic range

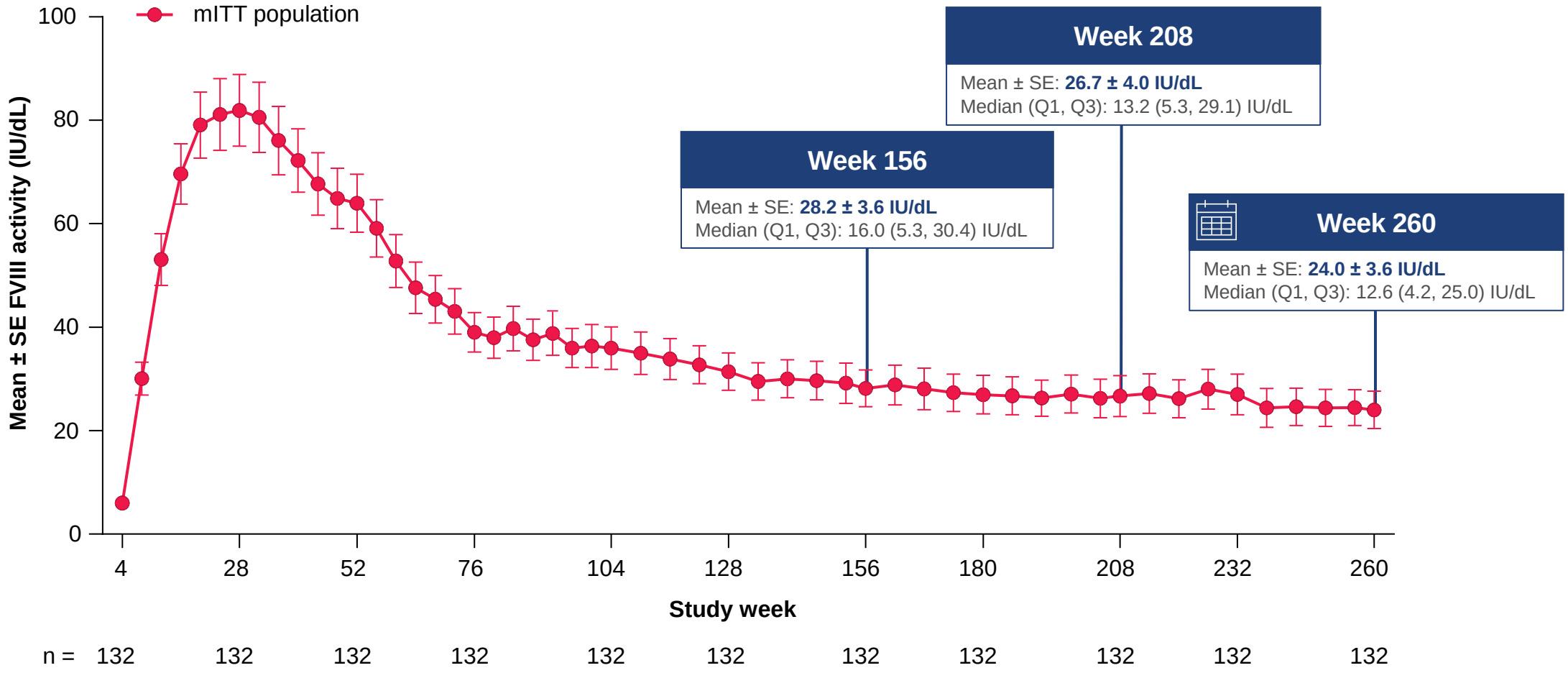
Median FVIII activity per CSA

- ≥40 IU/dL
- ≥5 to <40 IU/dL
- ≥3 to <5 IU/dL
- <3 IU/dL (LLOQ)

For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intention-to-treat.

FVIII activity across the trial (OSA)

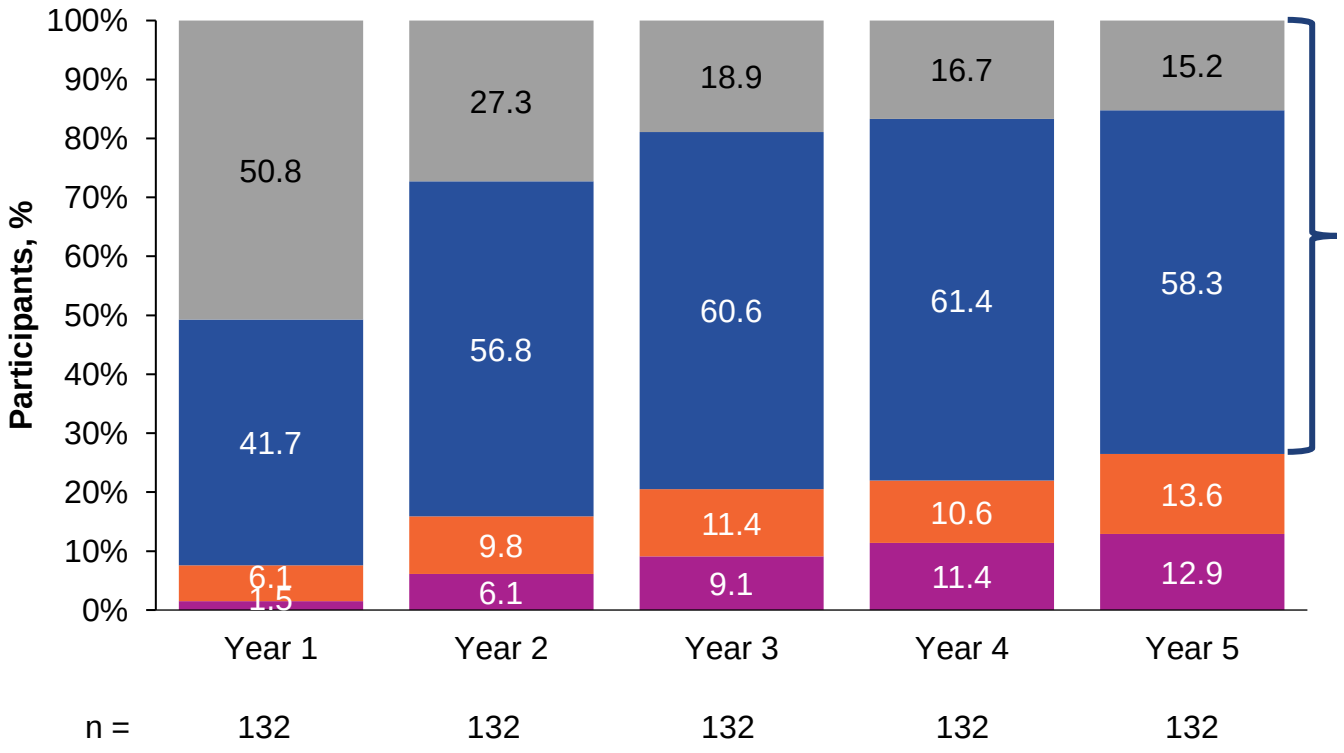
mITT population (N = 132)



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

FVIII activity (OSA) at the end of year 5

mITT population (N = 132)



73.5% of participants remain in the mild to non-hemophilic range

Median FVIII activity per OSA

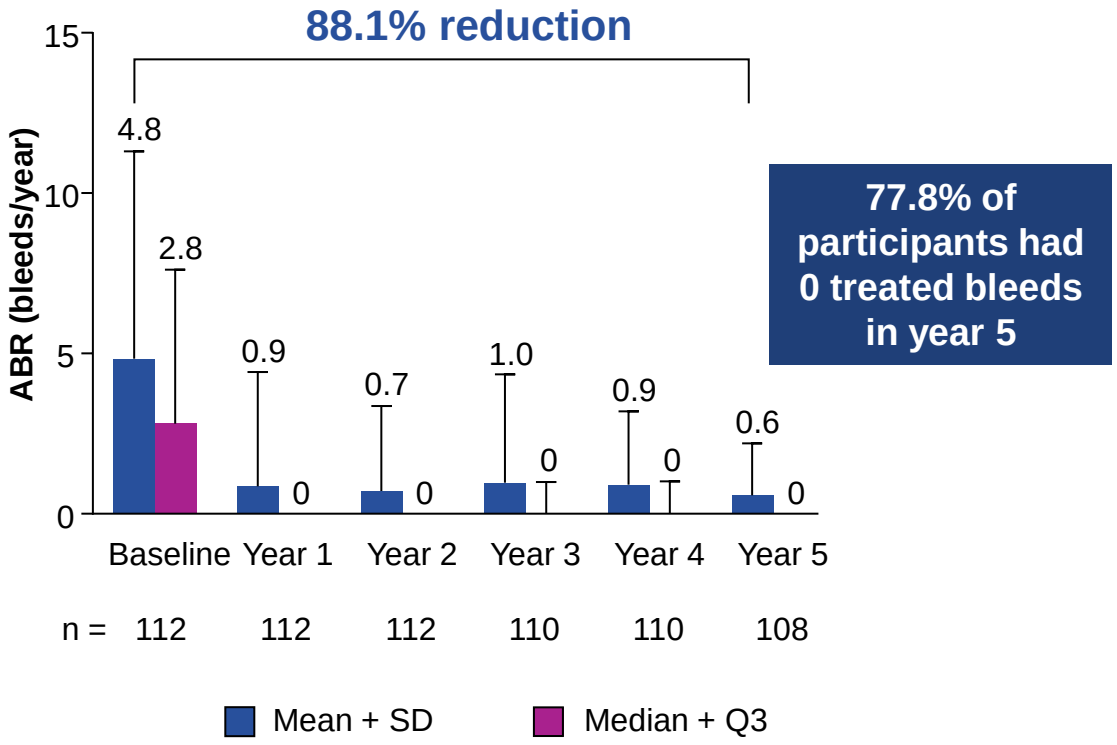
- ≥40 IU/dL
- ≥5 to <40 IU/dL
- ≥1 to <5 IU/dL
- <1 IU/dL (LLOQ)

For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intention-to-treat; OSA, one-stage assay.

Durable hemostatic efficacy across 5 years

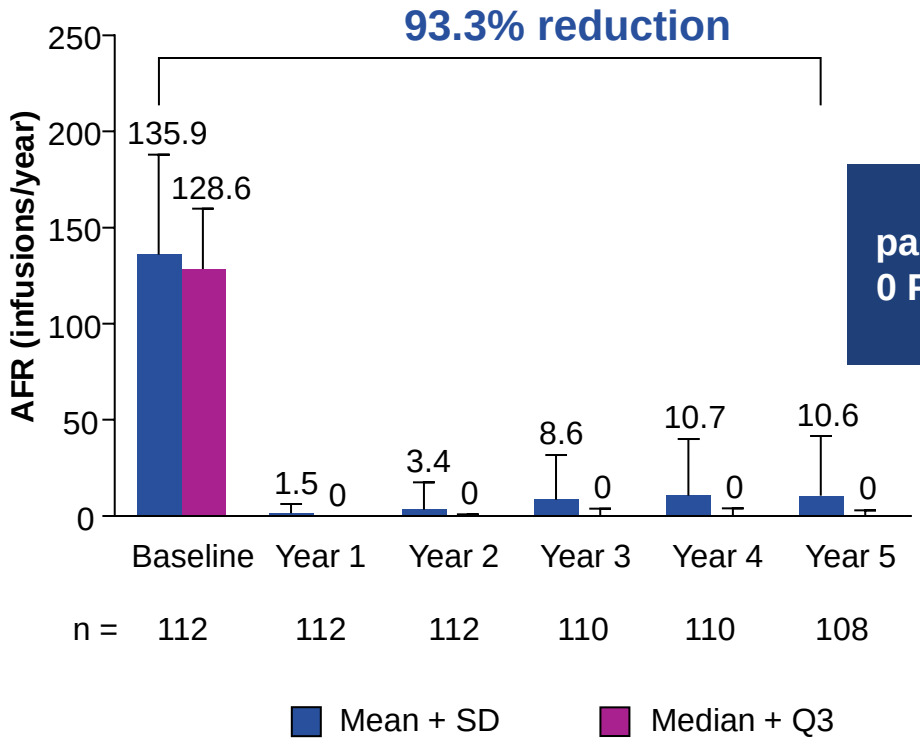
Rollover population (N = 112)

ABR for treated bleeds decreased >80% from baseline during the post-prophylaxis period



77.8% of participants had 0 treated bleeds in year 5

Annualized FVIII infusion rate decreased >90% from baseline during the post-prophylaxis period



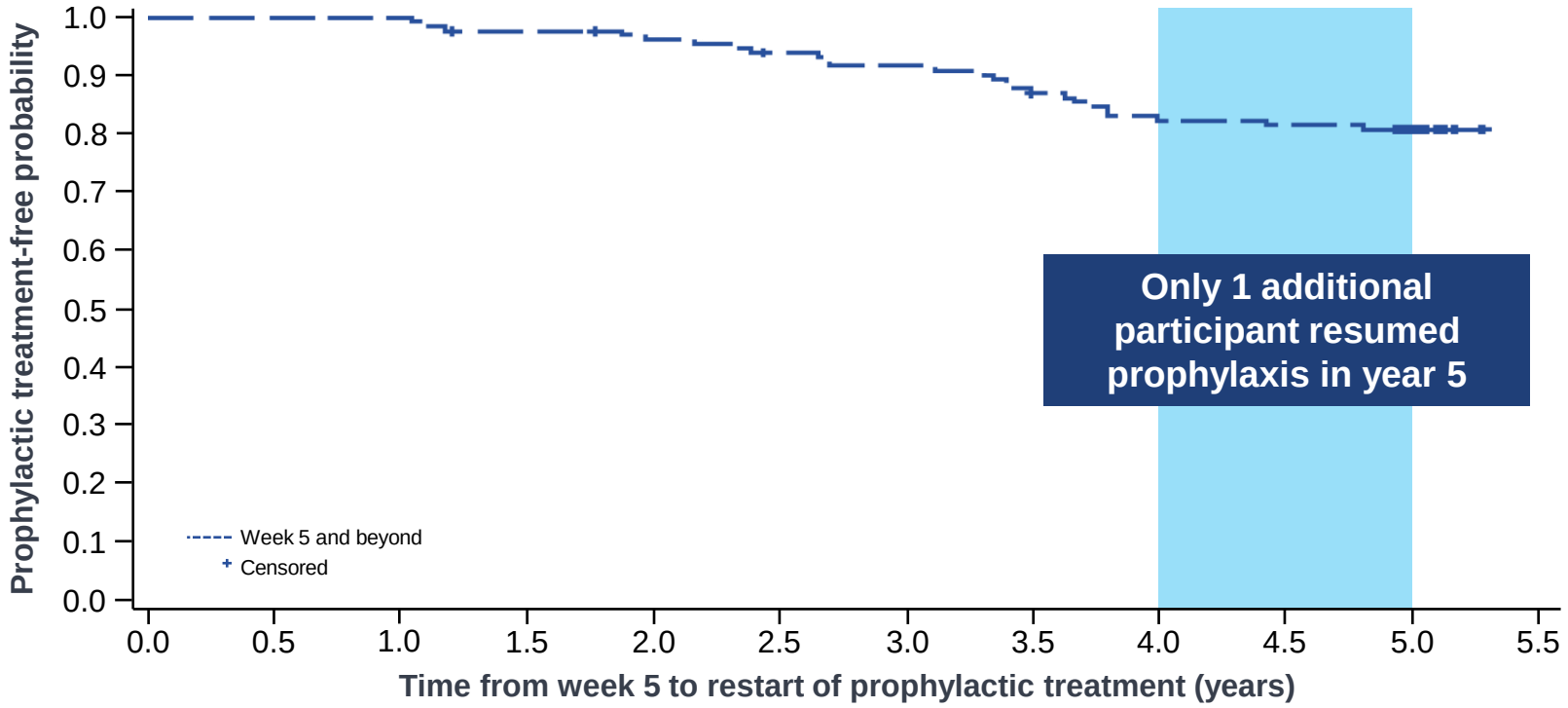
58.3% of participants had 0 FVIII infusions in year 5

Missing data were not imputed.
ABR, annualized bleeding rate; AFR, annualized FVIII infusion rate; FVIII, factor VIII; Q, quartile; SD, standard deviation.

Most participants continue to remain off prophylaxis at year 5

ITT population (N = 134)

81.3% of participants remain off prophylaxis at the end of year 5 (25/134 have resumed)



Missing data were not imputed.
ITT, intention-to-treat.

Conclusions

Valoctocogene roxaparvovec provided stable, durable, and clinically significant efficacy with a reassuring clinical safety profile at 5 years

Durable hemostatic efficacy

- The rate of treated bleeds and FVIII infusions was reduced compared with FVIII prophylaxis 5 years after infusion, consistent with durable hemostatic efficacy

FVIII activity was maintained

- After 5 years, mean FVIII activity was in the mild hemophilia range (CSA, 13.7 IU/dL; OSA, 24.0 IU/dL)

Most (81.3%) participants continue to remain off prophylaxis and experience a favorable impact on hemophilia treatment burden 5 years after infusion

- Since the last data cut, only one additional participant resumed prophylaxis in year 5

No new safety signals

- Across the trial, the most common AE was mild, transient ALT elevation

An ongoing long-term follow-up study will further characterize the long-term efficacy and safety of valoctocogene roxaparvovec

AE, adverse event; ALT, alanine aminotransferase; CSA, chromogenic substrate assay; FVIII, factor VIII; OSA, one-stage assay.

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