

# **Clinical Outcomes in Adults with Hemophilia B With and Without Pre-existing Neutralizing Antibodies to AAV5: 6 Month Data from the Phase 3 Etranacogene Dezaparvovec HOPE-B Gene Therapy Trial**

**Frank W.G. Leebeek**<sup>1</sup>, Wolfgang Miesbach<sup>2</sup>, Michael Recht<sup>3</sup>, Nigel S. Key<sup>4</sup>, Susan Lattimore<sup>3</sup>, Giancarlo Castaman<sup>5</sup>, Eileen K. Sawyer<sup>6</sup>, David Cooper<sup>6</sup>, Valerie Ferreira<sup>6</sup>, Steven W. Pipe<sup>7</sup>, on behalf of the HOPE-B investigators

<sup>1</sup>Erasmus MC, University Medical Center Rotterdam, Netherlands; <sup>2</sup>University Hospital Frankfurt, Frankfurt, Germany; <sup>3</sup>Oregon Health & Science University, Portland, OR, USA <sup>4</sup>University of North Carolina, Chapel Hill, NC, USA; <sup>5</sup>Center for Bleeding Disorders and Coagulation, Careggi University Hospital, Florence, Italy; <sup>6</sup>uniQure BV, Amsterdam, the Netherlands/ uniQure Inc. Lexington, MA, USA; <sup>7</sup>University of Michigan, Ann Arbor, MI, USA

# Disclosures for Frank W.G. Leebeek

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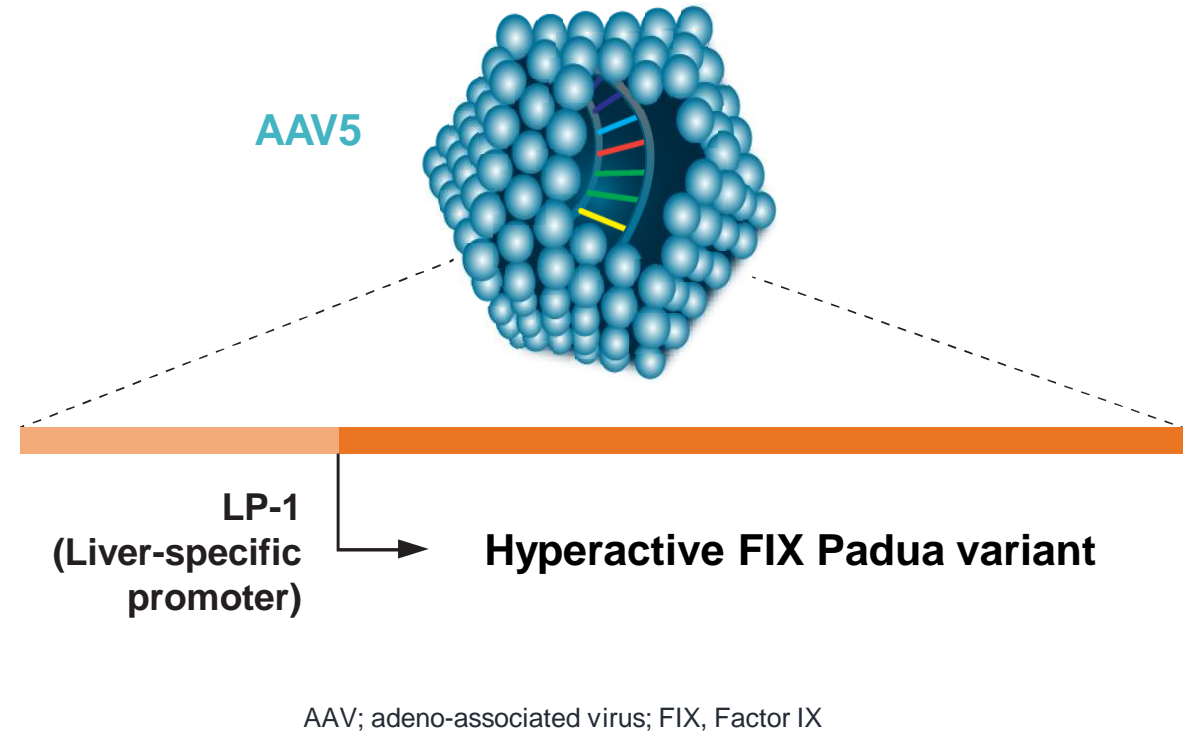
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<b>Research Support/P.I.</b>	<b>Unrestricted research grants from CSL Behring, Takeda, Sobi, UniQure</b>
<b>Employee</b>	<b>No relevant conflicts of interest to declare</b>
<b>Consultant</b>	<b>CSL Behring, UniQure, Biomarin of which fees paid to the university</b>
<b>Major Stockholder</b>	<b>No relevant conflicts of interest to declare</b>
<b>Speakers Bureau</b>	<b>No relevant conflicts of interest to declare</b>
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# HOPE-B: Etranacogene dezaparvovec (AAV5-Padua hFIX)

- Ongoing Phase 3 study in hemophilia B
  - N=54
  - Mean FIX activity increased to near-normal levels at 6 months post-etranacogene dezaparvovec, meeting the first co-primary endpoint<sup>1</sup>
  - Anti-AAV5 neutralizing antibodies (NAbs) are assessed via luciferase assay<sup>2</sup> but are not exclusionary
- **Here we report safety and efficacy outcomes at 6 months post treatment by presence of pre-existing anti-AAV5 NAbs at baseline**

## Etranacogene dezaparvovec: Hyperactive FIX Padua variant



# Rationale for not excluding pre-existing anti-AAV5 NABs

- Pre-existing NABs resulting from previous exposure to AAV may prevent efficient transduction of the therapeutic transgene due to the host's immune response against the vector<sup>1</sup>
- However, prior clinical data have not shown pre-existing anti-AAV5 NABs to have predictive value:
- **Phase I/II (AMT-060): AAV5-WT hFIX (N=10)<sup>2</sup>**
  - Initial NAb analysis (GFP-based) did not detect NABs
    - Retrospective NAb analysis (luciferase-based) found 3/10 NAb positive<sup>3</sup>
    - Subject with highest titer of 340 showed highest circulating FIX activity levels of this cohort<sup>3</sup>
  - Stable FIX activity over 4.5-5 years post dosing<sup>4</sup>
  - No new treatment –related AEs\* observed during the last 12 months of observation post-treatment<sup>4</sup>
- **Ongoing Phase 2b (AMT-061-01): AAV5 with Padua FIX variant (N=3)<sup>5</sup>**
  - All patients NAb positive prior to treatment<sup>5</sup>
    - 2 patients in this trial had been denied another gene therapy trial entry based on pre-existing anti-AAV NABs
  - Mean FIX activity at 2 years was 44.2% with no new treatment-related AEs.<sup>6</sup>

\* Treatment related adverse events; GFP, Green fluorescent protein; NABs, neutralizing antibodies.

1. Boutin S. et al. *Hum Gene Ther.* 2010;21:704-122; 2. Miesbach W, et al. *Blood.* 2018;131:1022-1031; 3. 2 Majowicz A, Nijmeijer B, Lampen MH, et al. Therapeutic hFIX Activity Achieved after Single AAV5-hFIX Treatment in Hemophilia B Patients and NHPs with Pre-existing Anti-AAV5 NABs. *Molecular Therapy - Methods & Clinical Development* 2019;14:27–36 4. Leebeek FWG, et al, ASH 2020; Poster #33724; 5. Von Drygalski A, et al. *Blood Adv.* 2019;3:3241-3247; 6. Von Drygalski A, et al, ASH 2020; Oral presentation #672;

# HOPE-B (AMT-061): study design<sup>1</sup>

## Key inclusion criteria

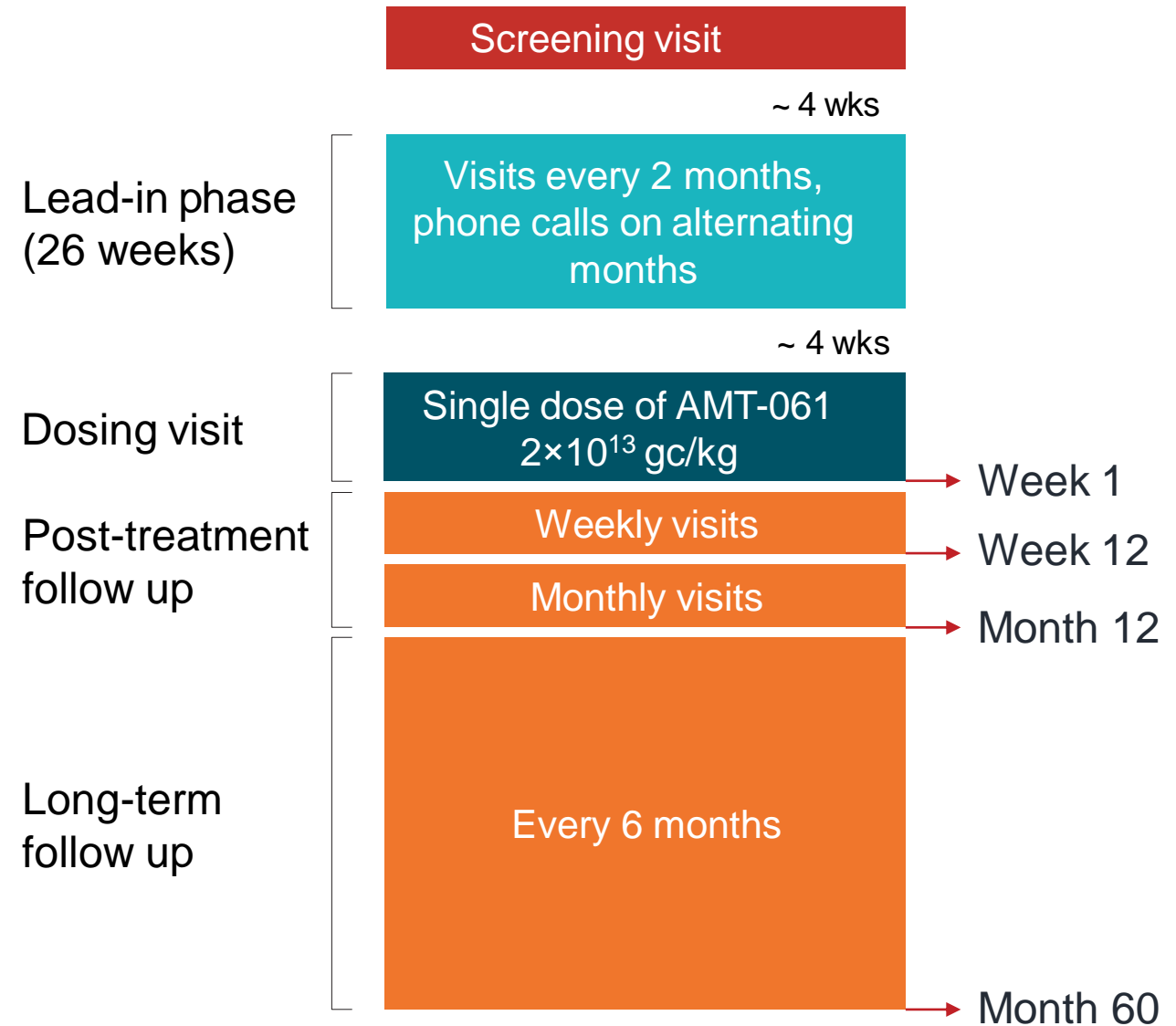
- Male adults  $\geq 18$  years
- FIX activity  $\leq 2\%$  of normal
- Continuous prophylaxis for  $\geq 2$  months

## Key exclusion criteria

- Factors that might affect the evaluation of AMT-061 efficacy or safety, e.g.
  - FIX inhibitors
  - Active hepatitis B/C infection
  - Uncontrolled HIV infection

**Pre-existing anti-NAbs were assessed, but not used as an exclusion criteria**

**No prophylactic immunosuppression**



1. Pipe S, et al. Oral presentation at the 62nd Virtual American Society of Hematology Annual Meeting & Exposition. Dec 5-8, 2020; HIV, human immunodeficiency virus; NAbs, neutralizing antibodies; wks, weeks.

# HOPE-B: study endpoints and analyses<sup>1</sup>

## ■ Primary endpoints

- FIX activity (central one stage aPTT) at 26 weeks after dosing<sup>1</sup>
- FIX activity 52 weeks after dosing\*
- 52-week ABR compared to lead-in\*

## ■ Secondary endpoints

- Rates of total, spontaneous, traumatic, and treated/untreated bleeds
- FIX consumption
- Correlation of FIX activity levels and safety with pre-AMT-061 anti-AAV5 antibody titers over 26 weeks (6 months) follow up
- Safety

## ■ Post-hoc analysis

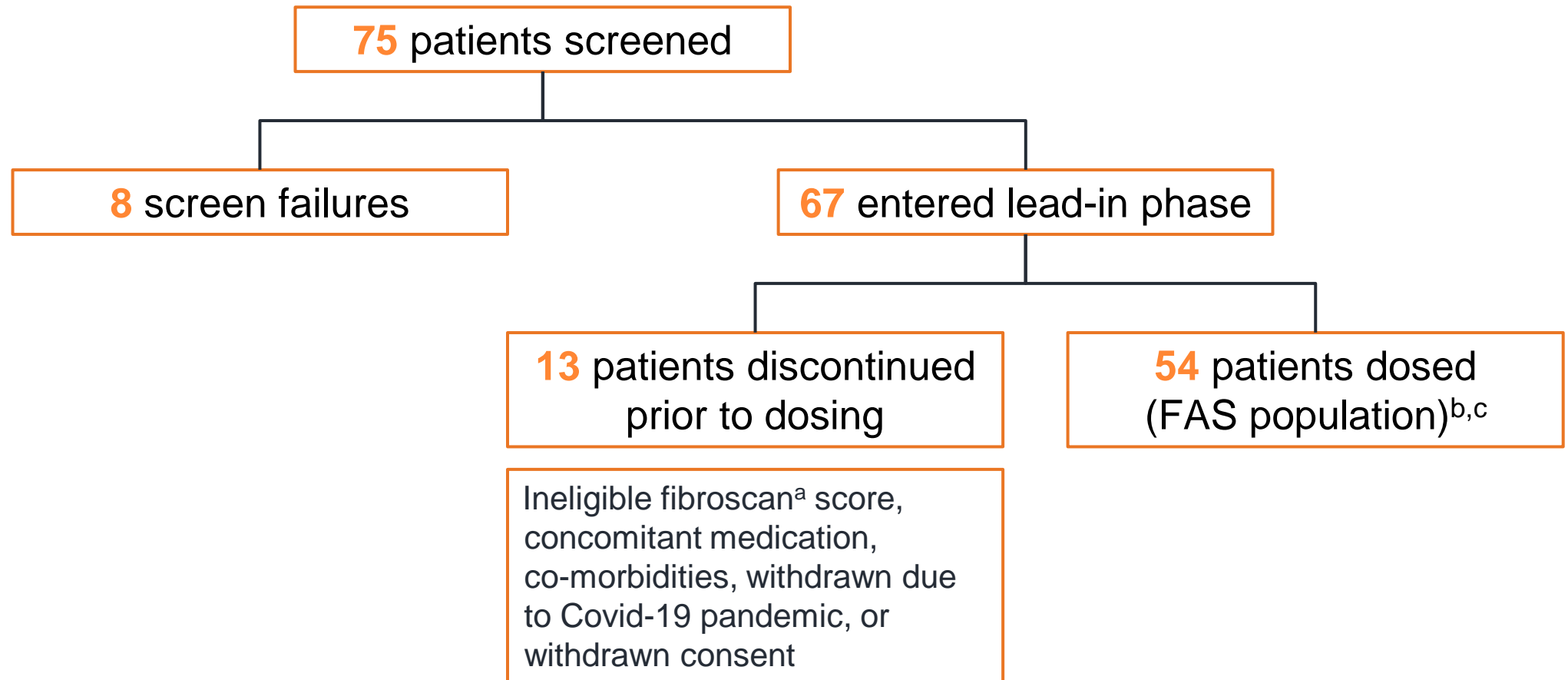
- **FIX activity (central one stage aPTT) and safety at 26 weeks after dosing in participants with and without pre-existing NAbs to AAV5**

1. Pipe S, et al. Oral presentation at the 62<sup>nd</sup> Virtual American Society of Hematology Annual Meeting & Exposition. Dec 5-8, 2020

\*Planned co-primary endpoints; aPTT, activated partial thromboplastin time; ABR, annualized bleeding rate; AAV5, adeno-associated virus; NAbs, neutralizing antibodies.

# HOPE-B: Patient disposition<sup>1</sup>

- 54 patients were dosed and completed 26-weeks of follow up



1. Pipe S, et al. Oral presentation at the 62nd Virtual American Society of Hematology Annual Meeting & Exposition. Dec 5-8, 2020;

<sup>a</sup>Or equivalent scan (magnetic resonance elastography, shear wave elastography). <sup>b</sup>FAS, full analysis set includes subjects who enrolled, entered the lead-in phase, were dosed with AMT-061 and provided  $\geq 1$  efficacy endpoint assessment. <sup>c</sup>Per-Protocol population (N = 53), which included all subjects from the FAS who adhered to a stable and adequate prophylaxis use during the lead-in phase, completed assessments through the 6-month visit, and had no major protocol deviations that impacted the interpretation of efficacy

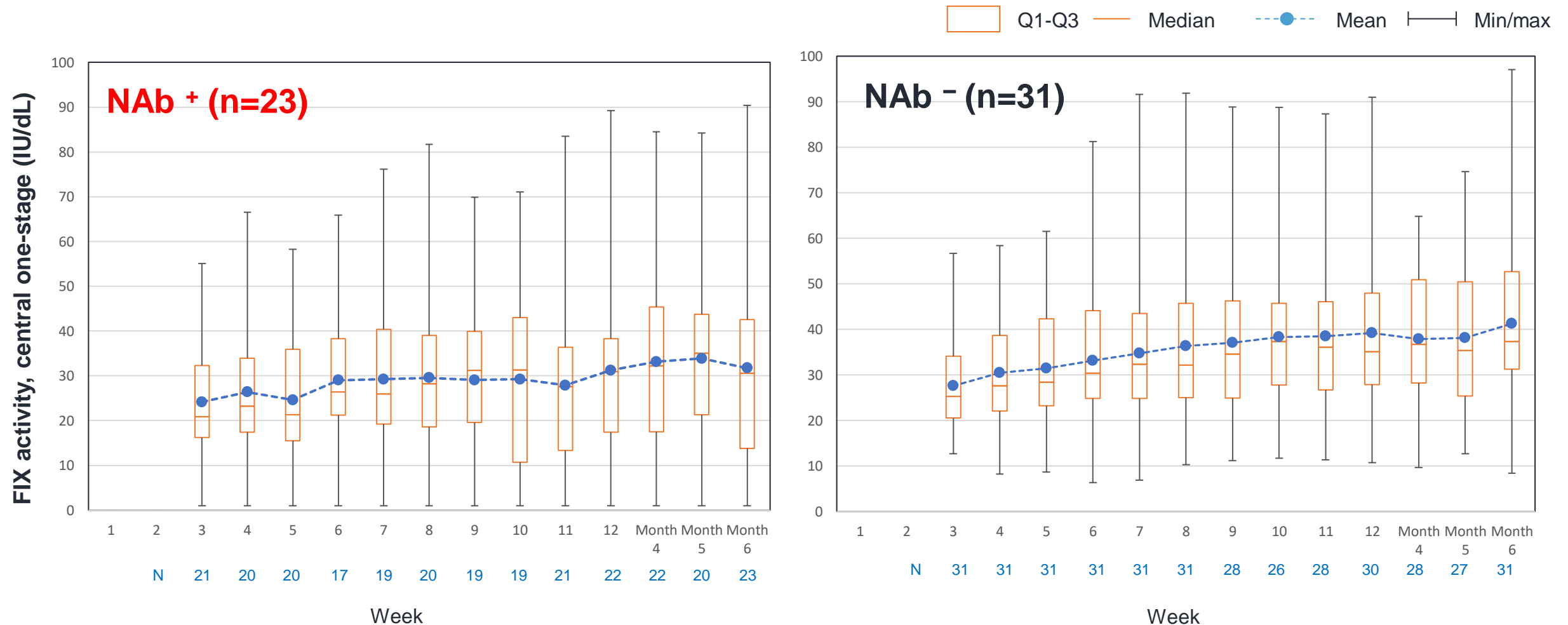
# HOPE-B: Baseline demographics

	Full analysis set (n=54)	antiAAV5 NAb +ve (n=23)	antiAAV5 NAb -ve (n=31)
Age, mean (SD, min-max), years	41.5 (15.8, 19-75)	43.1 (17.4, 19-75)	40.3 (14.6, 21-73)
Severity of hemophilia B at time of diagnosis, n (%)			
Severe (FIX <1%)	44 (81.5)	17 (73.9)	27 (87.1)
Moderately severe (FIX ≥1% and ≤2%)	10 (18.5)	6 (26.1)	4 (12.9)
Positive HIV status, n (%)	3 (5.6)	1 (4.3)	2 (6.5)
Prior hepatitis B infection, n (%)	3 (5.6)	2 (8.7)	1 (3.2)
Prior hepatitis C infection, n (%)	31 (57.4)	15 (65.2)	16 (51.6)
Pre-screening FIX treatment (n, %)			
Extended half-life	31 (57.4)	15 (65.2)	16 (51.6)
Standard half-life	23 (42.6)	8 (34.8)	15 (48.4)
<b>Detectable NAbs at baseline, n (%)</b>	<b>23 (42.6)</b>		
Maximum titer		3212.3	-
Median titer (1 <sup>st</sup> quartile, 3 <sup>rd</sup> quartile)		56.9 (23.8, 282.5)	-



# HOPE-B: FIX activity by BL NAb status: Up to 26 weeks

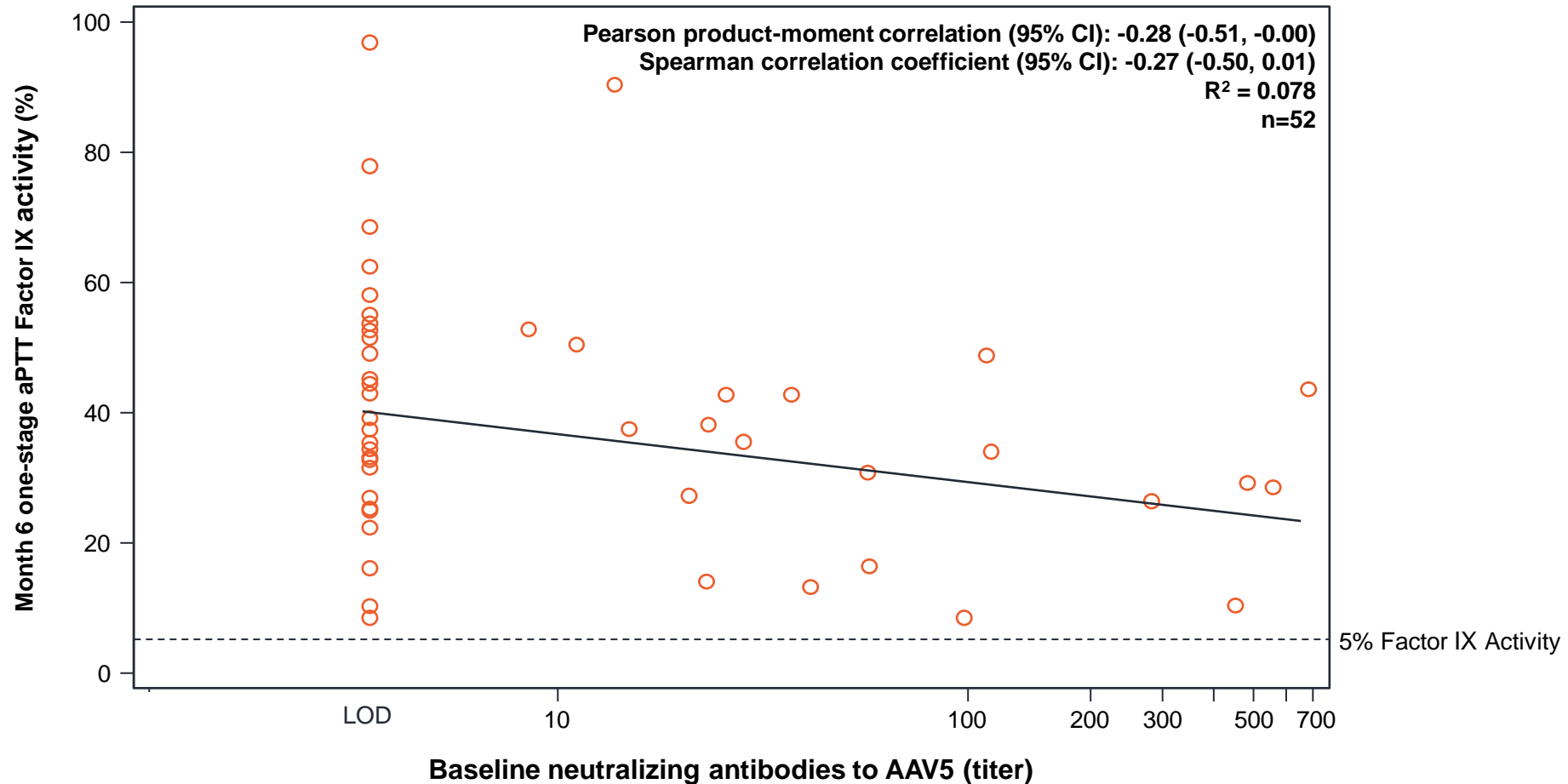
- Mean FIX activity at 26 weeks was 41.3 IU/dL in participants without NAb and 32.7 IU/dL in those with NAb



<sup>a</sup>Uncontaminated central laboratory data (the visit did not occur within 10 days of exogenous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. BL, baseline; Nabs, neutralizing antibodies.

# HOPE-B: Pre-existing NAb titers vs week 26 FIX activity

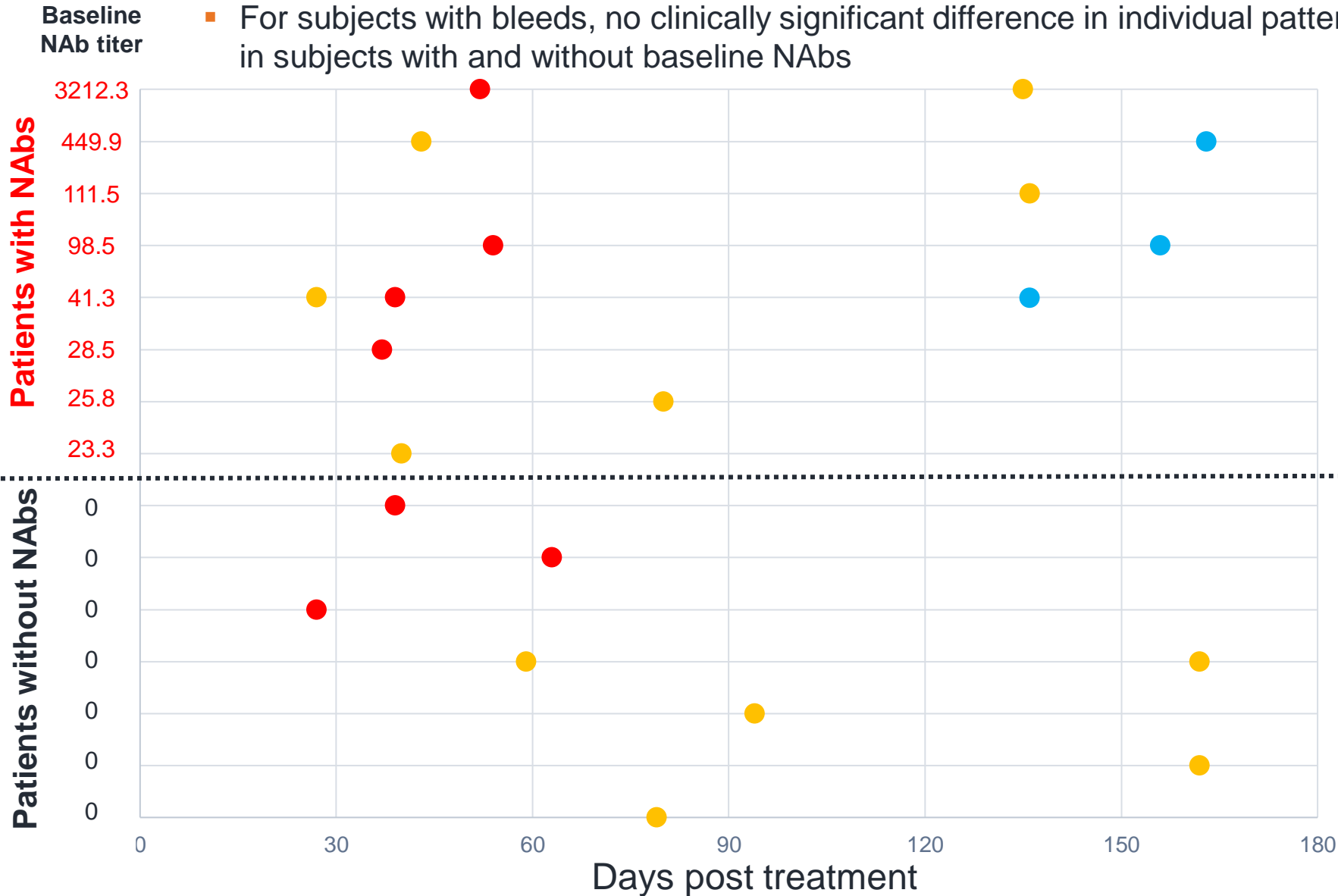
- No clinically significant correlation of pre-existing NABs with FIX activity identified up to a titer of 678
- One patient with a titer of 3212.3 did not respond (data not shown)



Per-protocol population (N = 53), which included all subjects from the full analysis set who adhered to a stable and adequate prophylaxis use during the lead-in phase, completed assessments through the 6-month visit, and had no major protocol deviations that impacted the interpretation of efficacy. One participant who had a baseline titer of >3200 was not included in this analysis. Patients with undetectable NABs were plotted at 7 on the horizontal axis which was the limit of detection (LOD) of this assay. NAB, neutralizing antibody.

# HOPE-B: Post-treatment bleeds by NAb baseline

- For subjects with bleeds, no clinically significant difference in individual patterns of post-treatment bleeds in subjects with and without baseline NAb



NAb +	Type	Treated
13 bleeds in 8/23(35%) subjects	4 Spontaneous	2 (50%)
	6 Traumatic	5 (83%)
	3 Unknown	2 (66%)

NAb -	Type	Treated
8 bleeds in 7/31(23%) subjects	3 Spontaneous	2 (66%)
	5 Traumatic	1 (20%)

# HOPE-B: Most common treatment-related AEs

AE, preferred term	Participants with NAbs N = 23 n (%)	Participants without NAbs N = 31 n (%)
Transient transaminitis, requiring corticosteroids	2 (8.7)	7 (22.6)
Infusion-related reactions	5 (21.7)	2 (6.5)
Headache	2 (8.7)	5 (16.1)
Influenza-like illness	4 (17.4)	3 (9.7)

- No deaths and no inhibitors to FIX were reported
- Post 6-month data cut, an SAE of HCC in a subject with multiple pre-existing risk factors was reported. Integration analyses determined HCC was unlikely to be related to treatment with etranacogene dezaparovec<sup>1</sup>

<sup>1</sup> <https://tools.eurolandir.com/tools/Pressreleases/GetPressRelease/?ID=3890956&lang=en-GB&companycode=nl-qure&v=>  
 AE, adverse event; SAE, serious adverse event; HCC, hepatocellular carcinoma; NAbs, neutralizing antibodies.

# HOPE-B: Conclusions

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- FIX activity was similar in participants without and with pre-existing NAbs to AAV5 up to a titer of 678
- No relationship between AAV5 NAbs and safety was observed
- This study demonstrates for the first time, successful treatment of patients with pre-existing NAbs at generally prevalent levels with an AAV5 construct, supporting broad eligibility for AAV5-based therapies