Clinical Outcomes in Patients With and Without Pre-existing Neutralizing Antibodies to the Vector: 6 Month Data from the Phase 3 HOPE-B Gene Therapy Trial of Etranacogene Dezaparvovec

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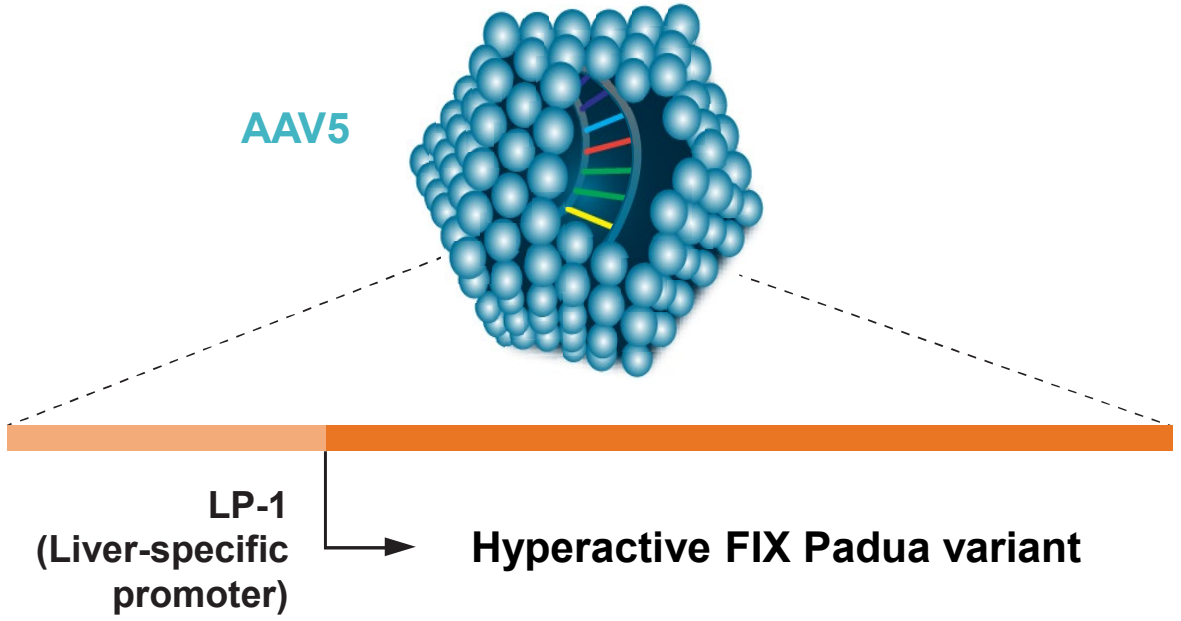
HOPE-B: Etranacogene Dezaparvovec (AAV5-Padua hFIX)

- 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[1]
  - Anti-AAV5 neutralizing antibodies (NAbs) are assessed via luciferase assay[2] 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



AAV; adeno-associated virus; FIX, Factor IX

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

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[1]
- 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)[2]**
  - Initial NAb analysis (GLP based) on screening did not detect NAbs
    - Retrospective NAb analysis (luciferase based) found 3/10 NAb positive[3]
    - Subject with highest titer of 340 showed highest circulating FIX activity levels of this cohort[3]
  - Stable FIX activity over 4.5-5 years post dosing[4]
  - No new treatment –related AEs* observed during the last 12 months of observation post-treatment[4]
- **Ongoing Phase 2b (AMT-061-01): AAV5 with Padua FIX variant (N=3)[5]**
  - All patients NAb positive prior to treatment[5]
    - 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.[6]

* TRAE - treatment related adverse events

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[1]

Key inclusion criteria

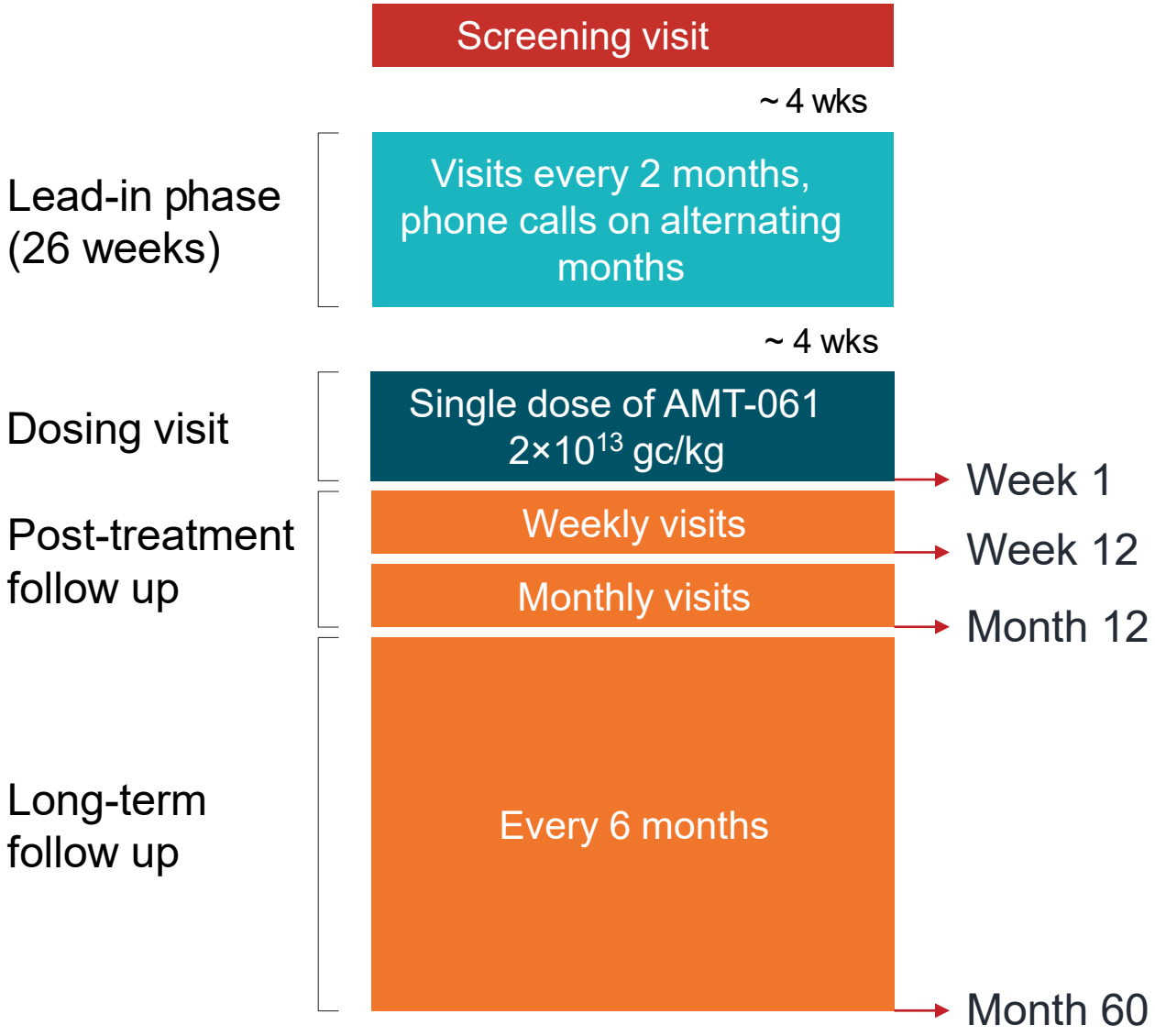
- Male adults ≥18 years
- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months

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[1]

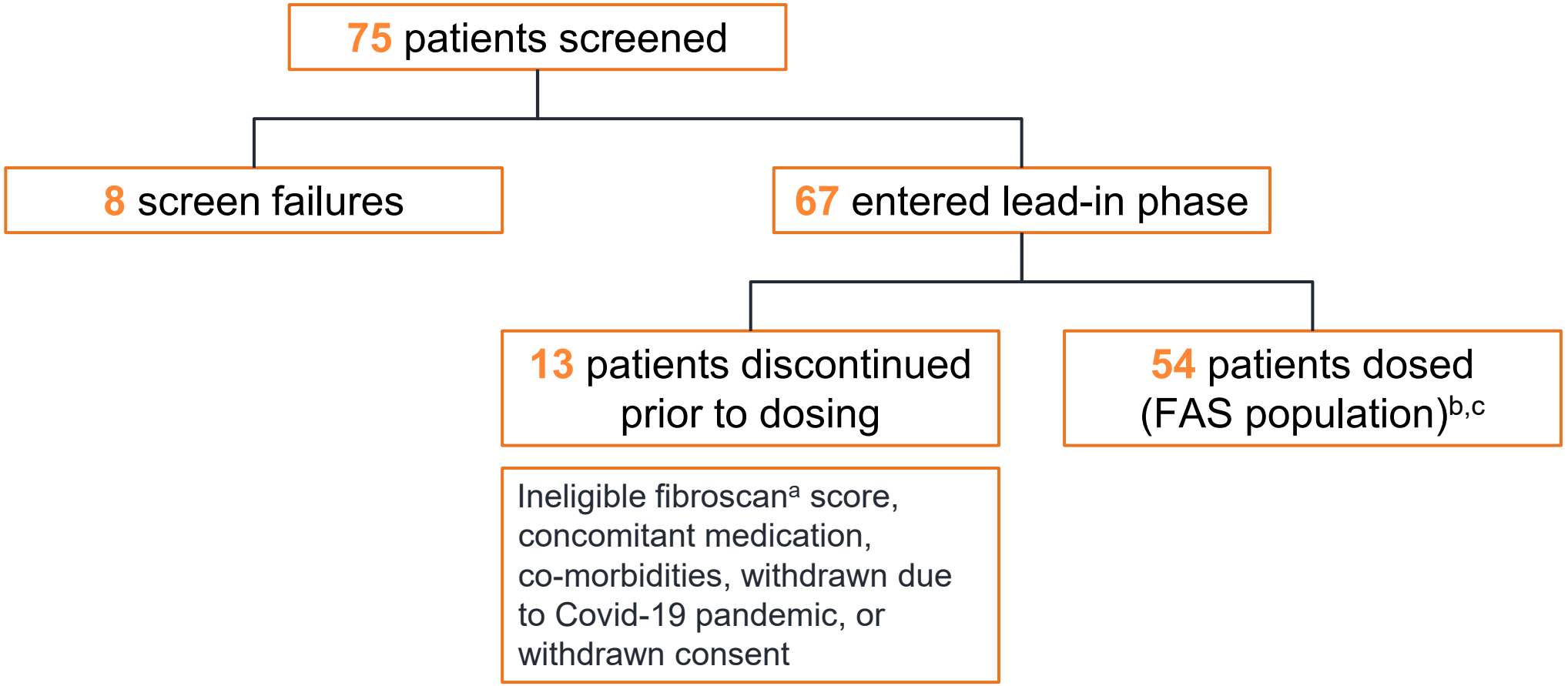
- **Primary endpoints**
  - FIX activity (central one stage aPTT) at 26 weeks after dosing[1]
  - FIX activity 52 weeks after dosing*
  - 52-week ABR compared to lead-in*
- **Secondary endpoints**
  - Rates of total, spontaneous, traumatic, and treated/untreated bleeds
  - FIX consumption
  - Correlation 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 62nd 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[1]

- 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;
[a]Or equivalent scan (magnetic resonance elastography, shear wave elastography). [b]FAS, full analysis set includes subjects who enrolled, entered the lead-in phase, were dosed with AMT-061 and provided ≥1 efficacy endpoint assessment. [c]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

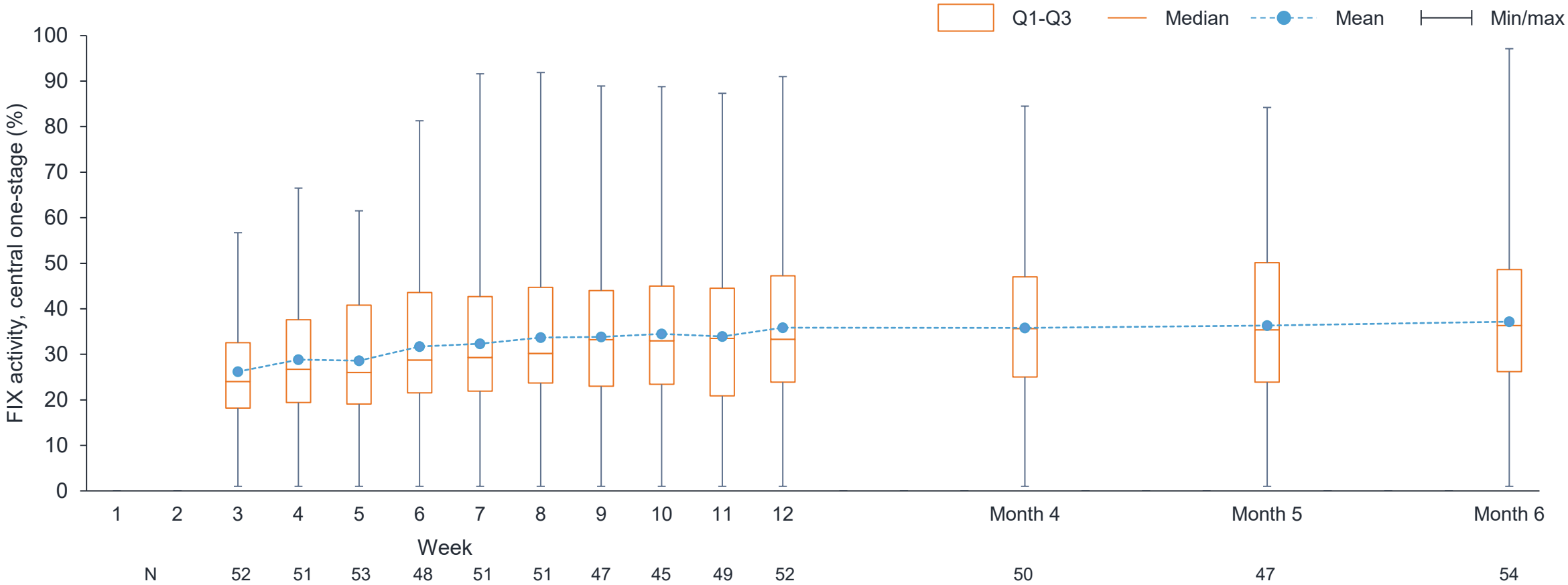
HOPE-B: Baseline demographics

	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%) Moderately severe (FIX ≥1% and ≤2%)	 44 (81.5) 10 (18.5)	 17 (73.9) 6 (26.1)	 27 (87.1) 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 Standard half-life	 31 (57.4) 23 (42.6)	 15 (65.2) 8 (34.8)	 16 (51.6) 15 (48.4)
Detectable NAbs at baseline, n (%)	**23 (42.6)**		
Maximum titer		3212.3	-
Median titer (1st quartile, 3rd quartile)		56.9 (23.8, 282.5)	-

HIV, human immunodeficiency virus; NAb, neutralizing antibody; SD, standard deviation.

HOPE-B: FIX activity[a]: Up to 26 weeks (month 6)[1]

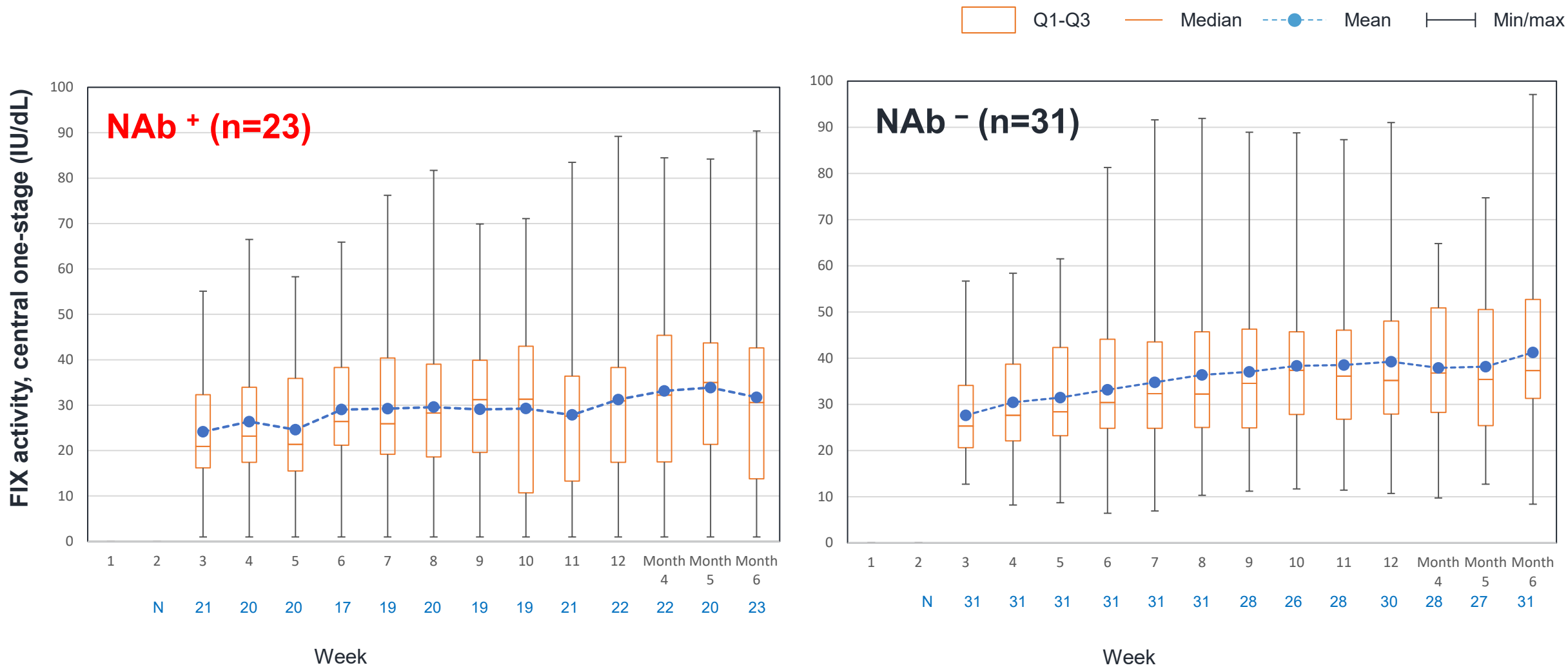
- Mean (SD) FIX activity at Month 6: 37.2% (19.6); change from baseline **+36.01% (19.693), p<0.0001**



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

[a]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 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subject's historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤ 2%), their baseline factor IX activity level was imputed as 2%. SD, standard deviation.

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



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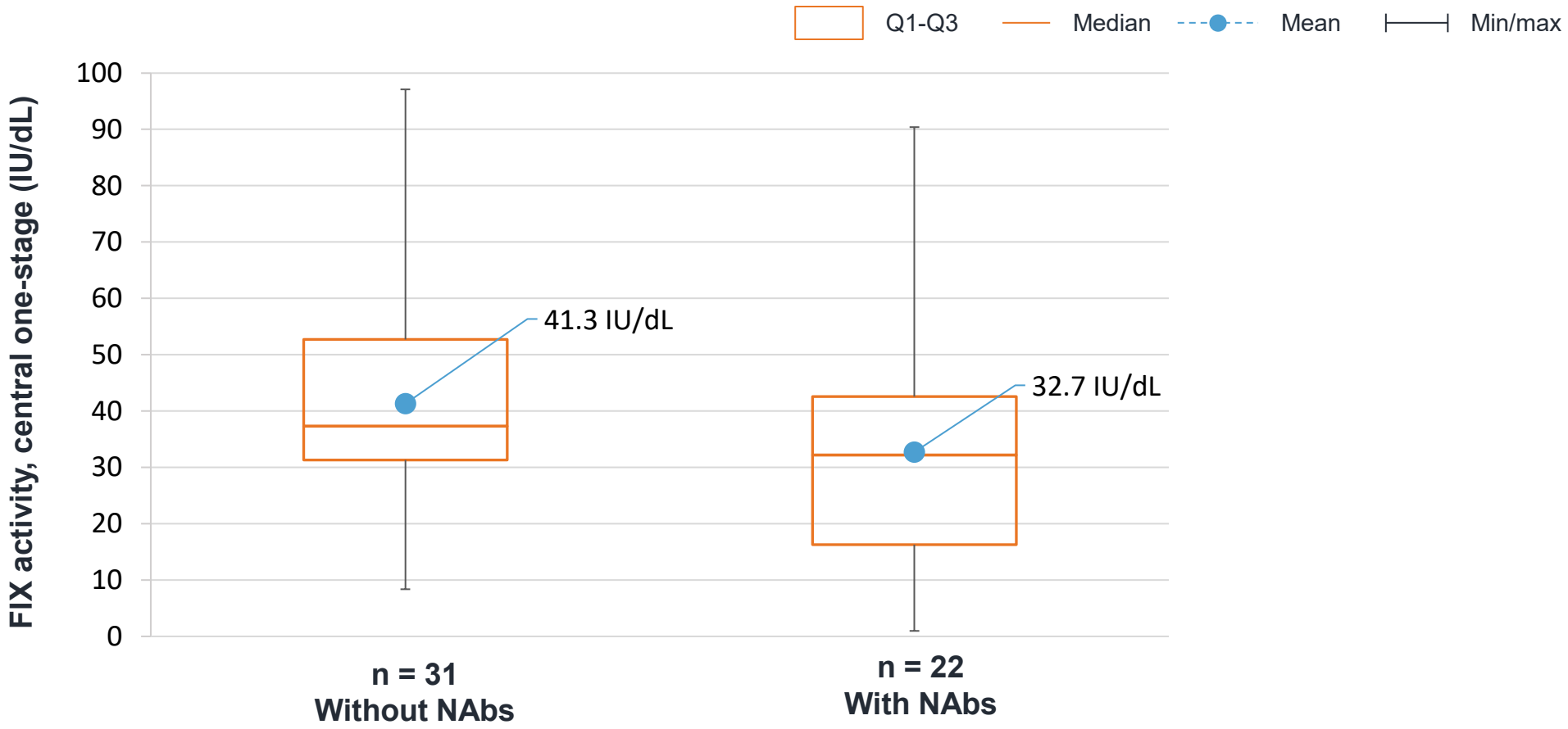
HOPE-B: FIX activity by NAb status[a]: At 26 weeks

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



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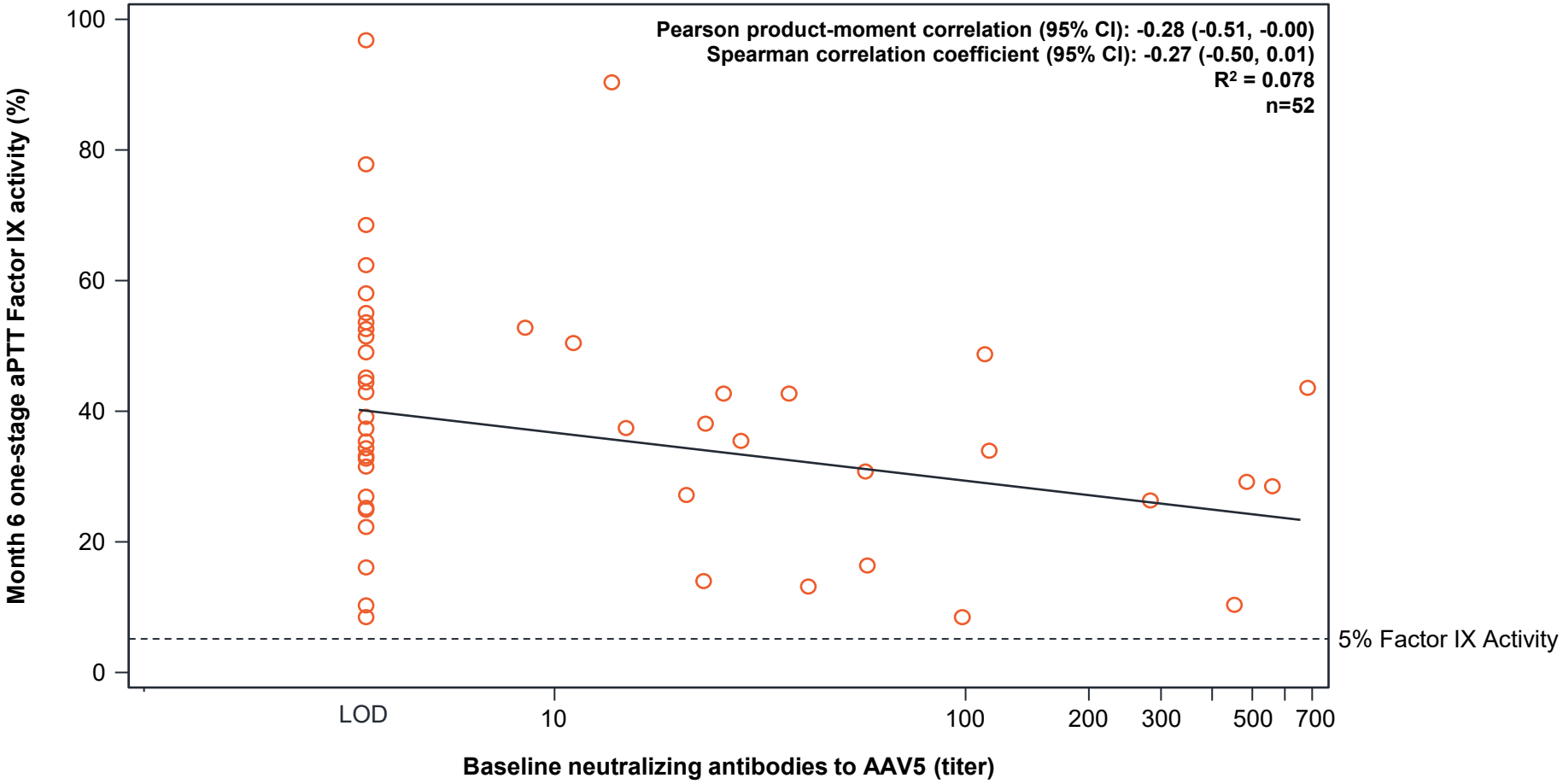
HOPE-B: Pre-existing NAb titers vs week 26 FIX activity

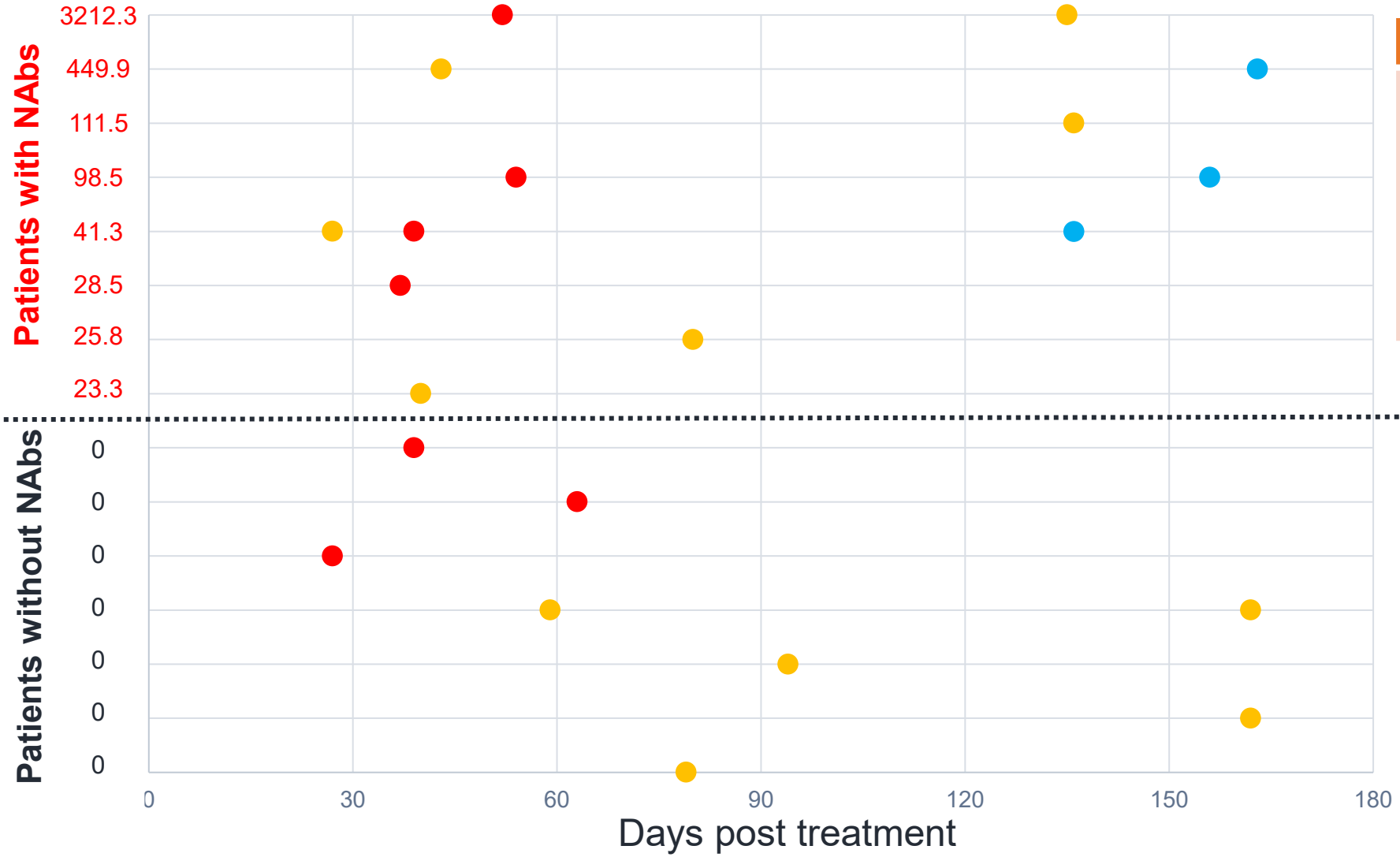
- No clinical significant correlation of pre-existing NABs with FIX activity identified up to a titer of 678
- One patient with a titer of 3212.3 did not respond (data not shown)



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 BL titer of >3200 was not included in this analysis; NAb, neutralizing antibody.
LOD, limit of detection

HOPE-B: Post Treatment Bleeds by NAb BL

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



NAb +	Type	Treated
13 bleeds in 8/23(35%) subjects	4 Spontaneous	2 (50%)
	6 Traumatic	5 (83%)
	3 Unknown	2 (100%)

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[a]	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 dezaparvovec[1]

1 https://tools.eurolandir.com/tools/Pressreleases/GetPressRelease/?ID=3890956&lang=en-GB&companycode=nl-qure&v=

AE, adverse event; LT, alanine aminotransferase; AST, aspartate aminotransferase; IRR, infusion-related reaction SAE serious adverse event; HCC, hepatocellular carcinoma

[a]The set of IRRs here is broader than just the preferred term 'infusion related reactions'.

HOPE-B: Conclusions

- FIX activity was similar in participants without and with pre-existing NAbs to AAV5 up to a titer of 678
- Insufficient data to assess a relationship with higher titer NAbs (n=1, 3213.5)
- 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

NAbs, neutralizing antibodies.