First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing Antibodies

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Goal of gene therapy in hemophilia B: Transformation of disease severity

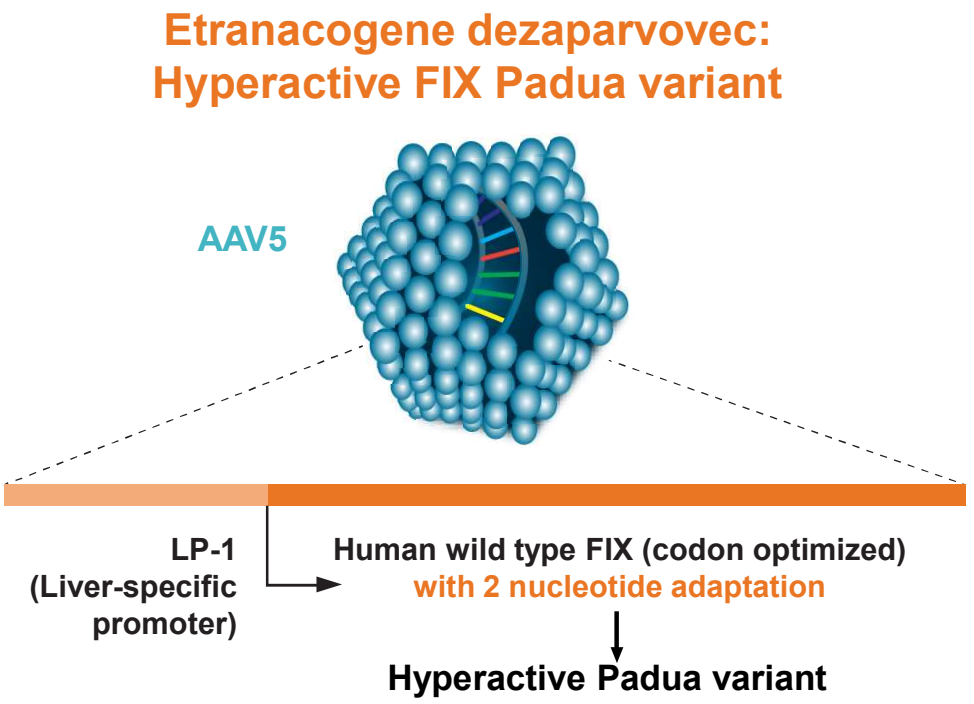
- Establish **long-term benefit with sustained FIX activity** from a one-time procedure
- **Control of bleeding** with effective protection against bleeds
- **Elimination of the requirement** for continuous prophylaxis
- Improvement in **quality of life**

Phenotype	Spontaneous bleeding	Prophylaxis recommended	FIX activity
Severe	frequent	yes	<1%
Moderate	rare	variable	1-5%
Mild	very rare	no	5-40%
Normative	no	no	>40%

Table adapted from Srivasta A, et al. *Hemophilia*. 2020;26:1-158

Etranacogene dezaparvovec

- Etranacogene dezaparvovec (AAV5-Padua hFIX):
  - Developed by combining the AAV5 vector from AMT-060 (AAV5-WT hFIX) with the naturally occurring Padua FIX variant
  - Enhanced version of AMT-060, which demonstrated efficacy and safety in a Phase 1/2 trial (N=10)[1]
    - Stable expression of WT FIX at 4.5-5 years[2]
    - No late-emergent safety signals[2]
- A Phase 2b study long-term follow-up is ongoing[3,4]
  - Mean FIX activity at 2 years was 44.2% with no new treatment-related AEs.
- HOPE-B is the first Phase 3 study in hemophilia B and has the largest gene therapy cohort to date



AAV; adeno-associated virus; FIX, Factor IX; wt, wildtype

AE, adverse event; WT, wild type.

1. Miesbach W, et al. *Blood*. 2018;131:1022-1031.
2. Leebeek FWG, et al, ASH 2020; Poster #33724.
3. Von Drygalski A, et al. *Blood Adv*. 2019;3:3241-3247.
4. Von Drygalski A, et al, ASH 2020; Oral presentation #672.

HOPE-B study design

Key inclusion criteria

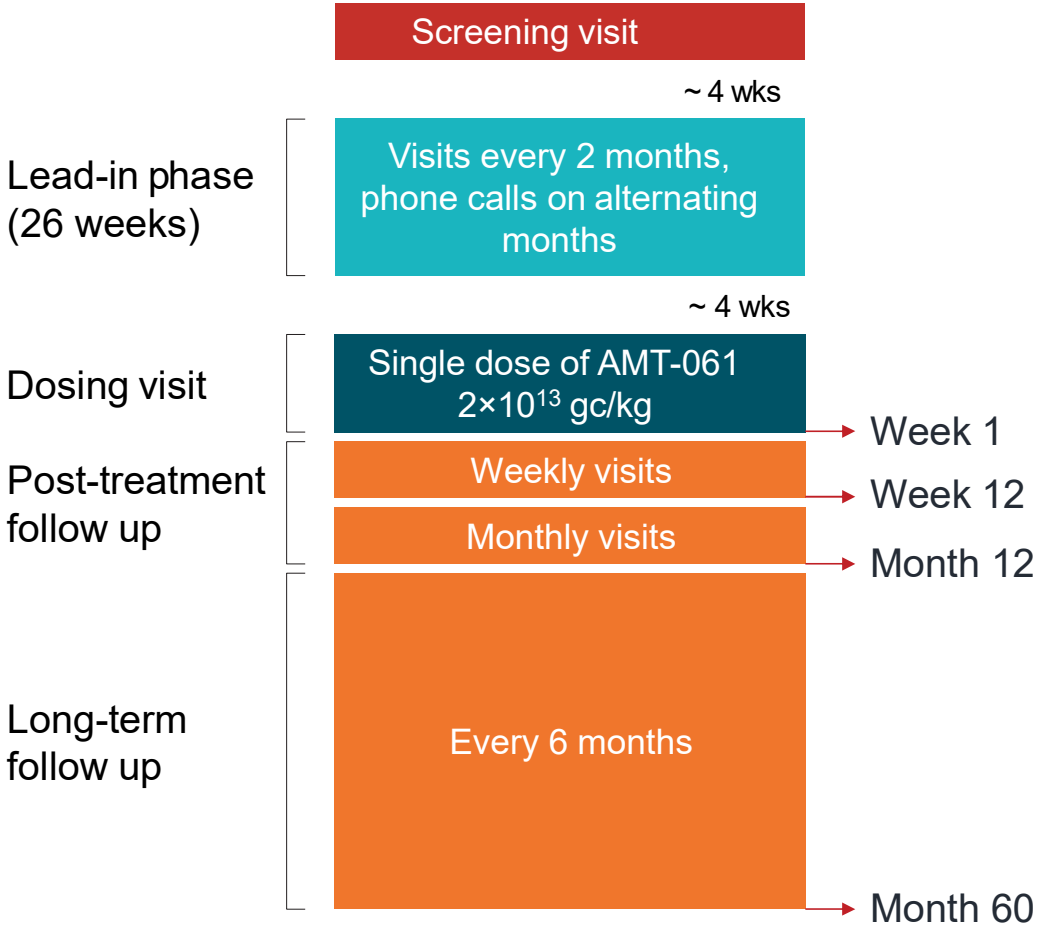
- Male adults ≥18 years
- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months

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



HIV, human immunodeficiency virus; NAbs, neutralizing antibodies; wks, weeks.

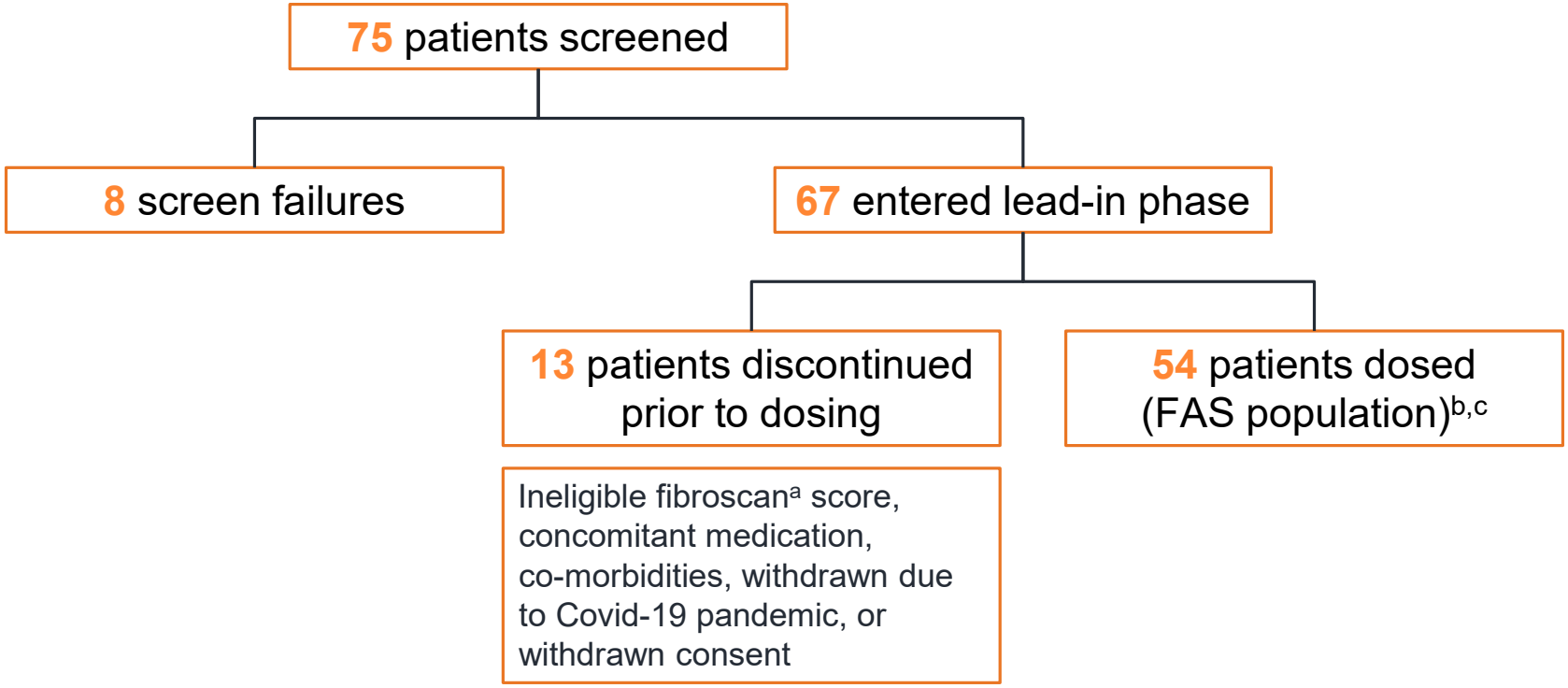
HOPE-B study endpoints

- **Primary endpoints**
  - FIX activity (central one stage aPTT) at 26 weeks after dosing
  - 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 follow up
  - Safety

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

Patient disposition

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



[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

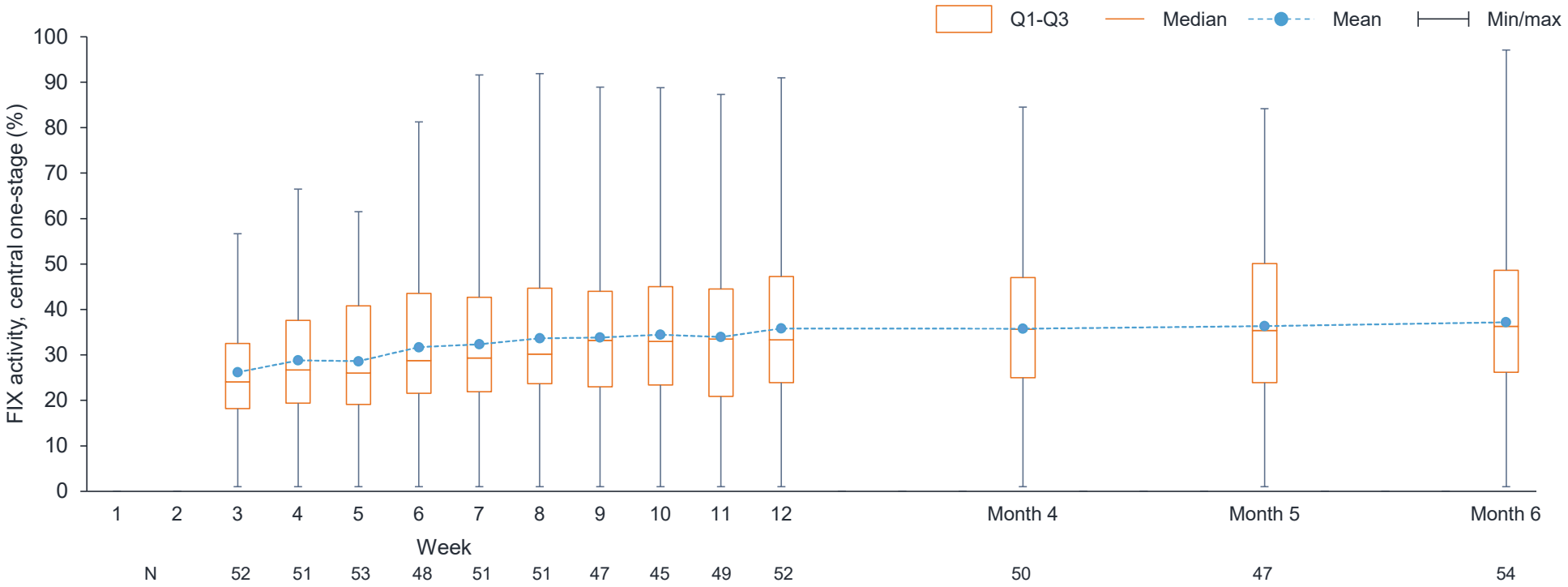
Baseline demographics

	Full analysis set (N = 54)
Age, mean (SD, min-max), years	41.5 (15.8, 19-75)
Severity of hemophilia B at time of diagnosis, n (%) Severe (FIX <1%) Moderately severe (FIX ≥1% and ≤2%)	 44 (81.5) 10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior hepatitis B infection, n (%)	3 (5.6)
Prior hepatitis C infection, n (%)	27 (50.0)
Pre-screening FIX treatment (n, %) Extended half-life Standard half-life	 31 (57.4) 23 (42.6)
Detectable NAbs at baseline, n (%, max titer)	23 (42.6, 3212.3)
0 bleeds in lead-in, n (%)	16 (29.6)
Cumulative bleeds in lead-in, n	123

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

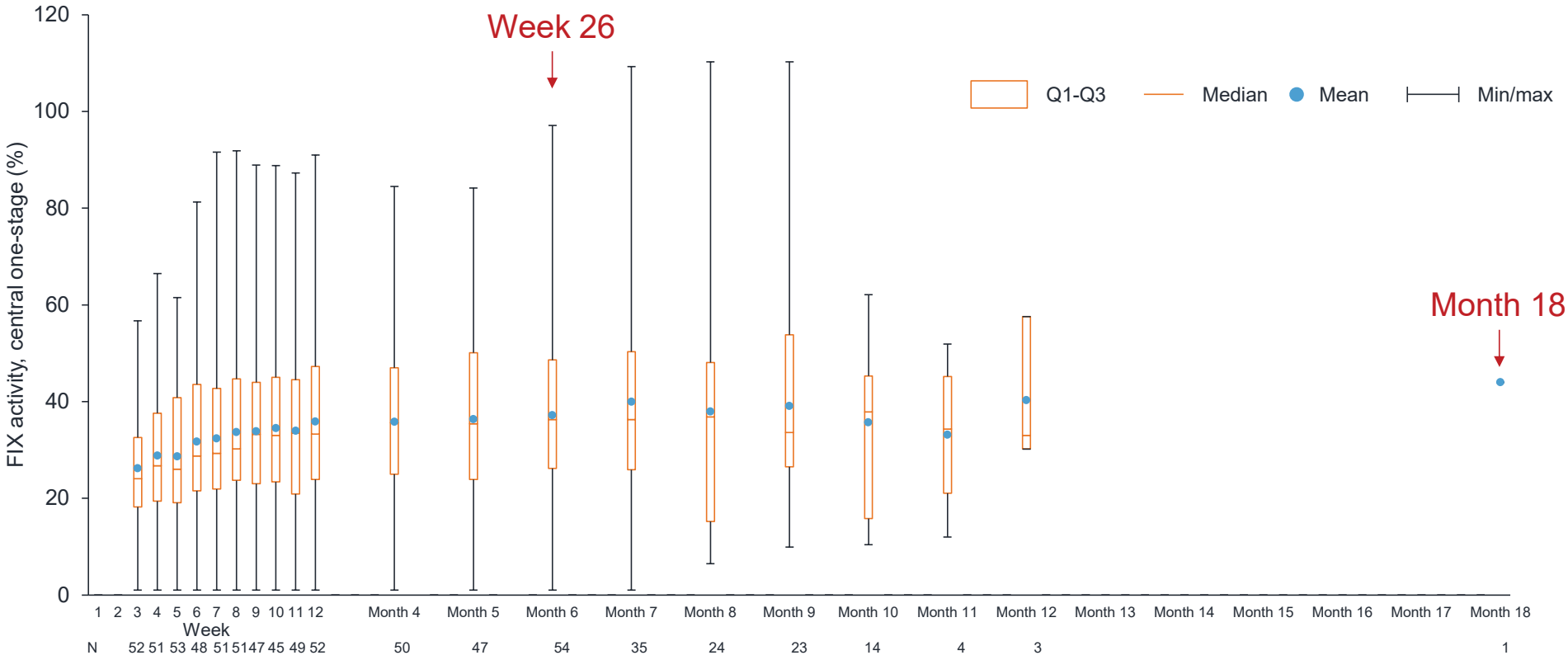
Overview of FIX activity[a]: Up to 26 weeks (month 6)

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



[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.

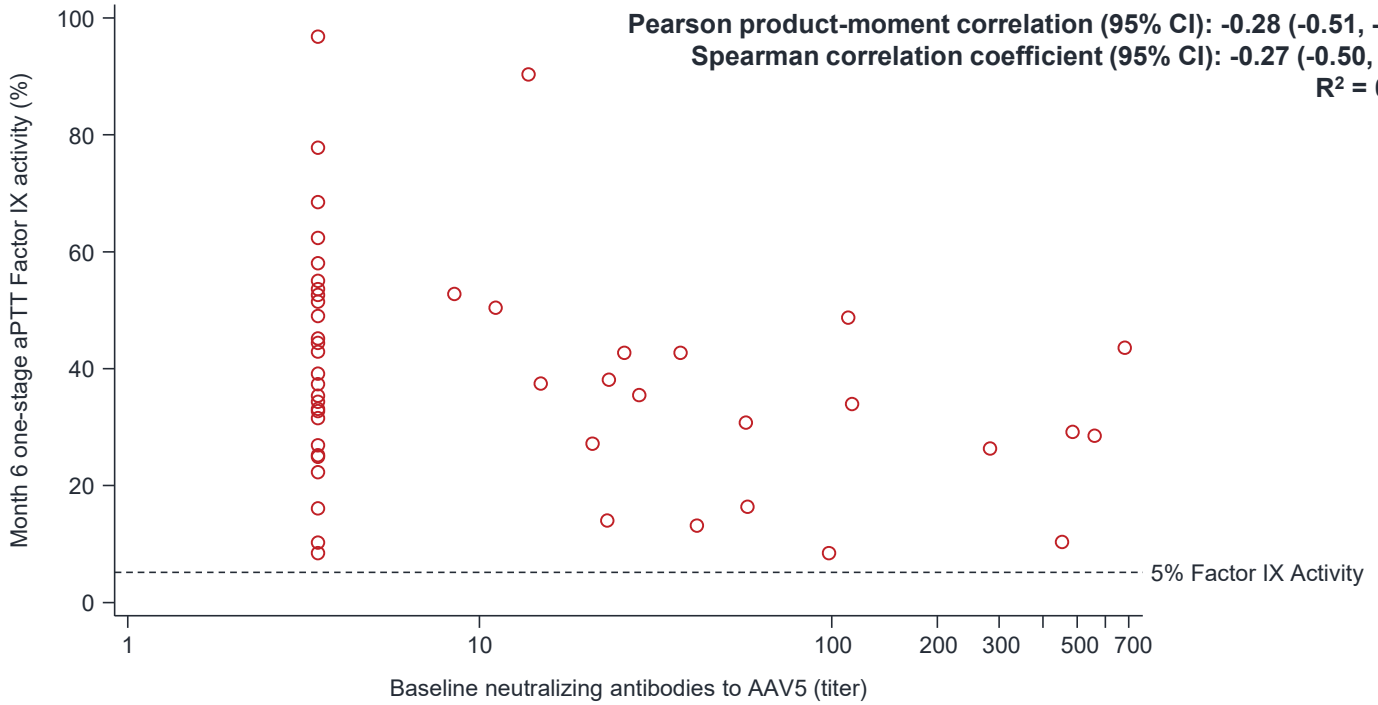
Overview of FIX activity[a]: Beyond 26 weeks



[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.

Pre-existing NAb titers vs week 26 FIX activity[a]

- **No correlation of pre-existing NAbs with FIX activity** was identified up to a titer of 678.2
  - $R^2 = 0.078$
- One patient with a titer of 3212.3 did not respond (data not shown)



[a]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; NAb, neutralizing antibody.

Bleeds in the first 26 weeks

	Lead-in N = 54	Week 0-26 N = 54
Total cumulative bleeds (treated), n	123 (107)	21 (10)
Spontaneous (treated), n	42 (37)	7 (3)
Traumatic (treated), n	66 (55)	11 (5)
Other* (treated), n	15 (15)	3 (2)
Patients with 0 bleeds, n (%)	16 (30%)	39 (72%)

Relative to lead-in, in the 26 weeks post-etranacogene dezaparvovec:

- **Total bleeds decreased by 83%**
- **Treated bleeds decreased by 91%**

*Other comprises bleeds associated with unrelated medical/dental procedures and of unknown etiology.
The post-treatment period was the number of days of observation within the time interval, excluding information prior to Day 21. Only bleeds that were assessed by the investigator to be new and true were considered.
2 patients remaining on prophylaxis had no bleeds in the lead in and 2 untreated bleeds (1 traumatic/1 spontaneous) post-treatment, and 5 treated bleeds (3 spontaneous/2 unknown) in lead in and none post-treatment, respectively

FIX replacement use in the first 26 weeks

	Lead-in N = 54	Week 0-26 N = 54
Patient on prophylaxis[a], n (%)	54 (100%)	2 (4%)
FIX usage (IU/yr/pt), mean (SD)[b]	290,769 (170,148)	12,537[a] (36,218)

- In the Per-Protocol population[c], **98% of patients were able to discontinue prophylaxis** and remain prophylaxis-free

[a]Two patients remain on prophylaxis (1 patient received a partial infusion, 1 patient FIX expression remained <2%).
[b]The post-treatment period was the number of days of observation within the time interval, inclusive of Day 21 onwards. FIX use in abstract annualized from Day 22 (inclusive). Factor IX replacement therapy use for invasive procedures is not included in analysis
[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
IU, international unit; SD, standard deviation; yr, year.

Treatment-related AEs with an incidence ≥5% (safety population; post-treatment period)

- 53 patients had 324 AEs post-treatment, of which 37 patients had a total of 88 TRAE
  - The majority (79.6%) of treatment-related AEs were mild
- 9 patients received steroid treatment for transaminase elevations
  - All discontinued steroid use prior to Week 26
  - FIX activity was preserved in the mild range (8%-39%)
- 7 patients experienced infusion related reactions*
  - Infusion discontinued in 1 patient (received ~10% of dose)
  - Infusion completed successfully in remaining 6
    - Interrupted in 3, received antihistamines and steroids and restarted
    - No interruption in 3

AE, preferred term	N = 54 n (%)
At least one related incident AE[a]	37 (68.5)
Influenza like illness	7 (13.0)
Headache	7 (13.0)
ALT increased	7 (13.0)
AST increased	5 (9.3)
Fatigue	4 (7.4)
Blood creatine phosphokinase increased	4 (7.4)
Nausea	4 (7.4)
Infusion-related reactions	4 (7.4)
Dizziness	3 (5.6)
Arthralgia	3 (5.6)

- **No inhibitors to FIX were reported**
- **No relationship between safety and NAbs was observed**

*Here the set of “infusion related reactions” is broader than just the preferred term “infusion-related reactions”.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRR, infusion-related reaction.
[a]An Incident AE is an adverse event that began or worsened within the period. Related = possibly related or related.

Conclusions

- **First report** of a phase 3 study in patients with Hemophilia B and the **largest gene therapy trial cohort** reported to date
- Mean FIX activity **significantly increased to near-normal levels** at 26 weeks post-etranacogene dezaparvovec, meeting the first co-primary endpoint
  - No requirement for prophylactic immunosuppression
  - 52/53 patients receiving a full dose responded
  - Included patients with pre-existing anti-AAV5 titers up to 678
- Patients were able to **discontinue prophylaxis**
- **Bleeding was abolished in the majority** of patients throughout the 26 weeks
- Most common safety findings were transaminase elevations requiring steroid treatment and infusion-related reactions, supporting **a safety profile consistent with early phase studies**
- Final analysis is **planned at 1 year** to support marketing authorization applications

NAbs, neutralizing antibodies.