

Adults With Severe or Moderately Severe Hemophilia B Receiving Etranacogene Dezaparvovec in the HOPE-B Phase 3 Clinical Trial Continue to Experience a Stable Increase in Mean Factor IX Activity Levels and Durable Hemostatic Protection After 24 Months' Follow-up

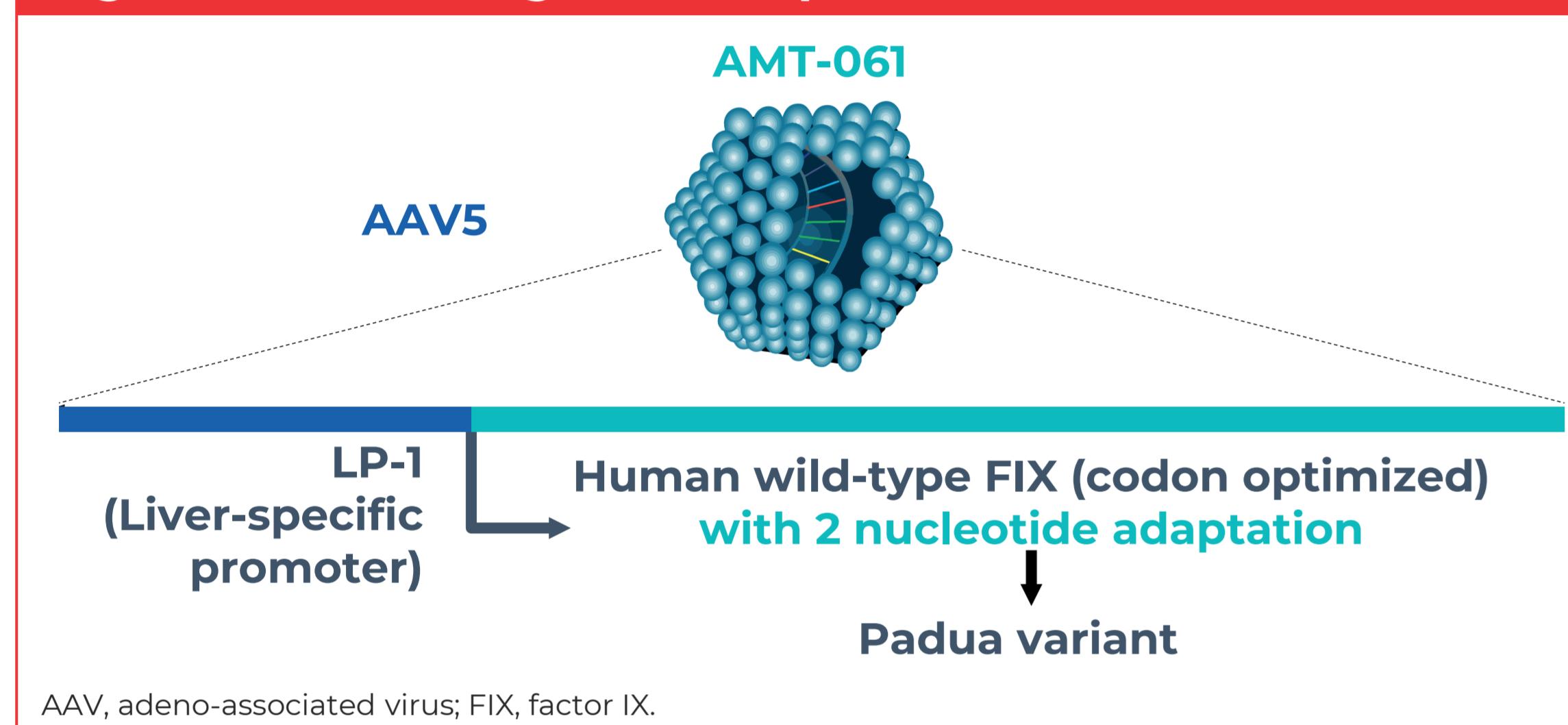
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Introduction

- Etranacogene dezaparvovec (formerly AMT-061), an investigational gene therapy for hemophilia B, is an adeno-associated virus serotype 5 (AAV5) vector, containing a codon-optimized, highly active factor IX (FIX) Padua R338L transgene under the control of a liver-specific promoter (**Figure 1**)
- The Phase 3 HOPE-B clinical trial (NCT03569891) of etranacogene dezaparvovec met its primary efficacy endpoint, providing hemostatic protection superior to standard of care FIX prophylaxis over 52 weeks of follow-up after stable FIX Padua expression (defined as Months 7–18)^{1,2}
- However, the potential for liver-directed AAV to sustain long-term clotting factor expression remains unknown, with most human experience derived from early phase clinical trials

Figure 1. Etranacogene dezaparvovec



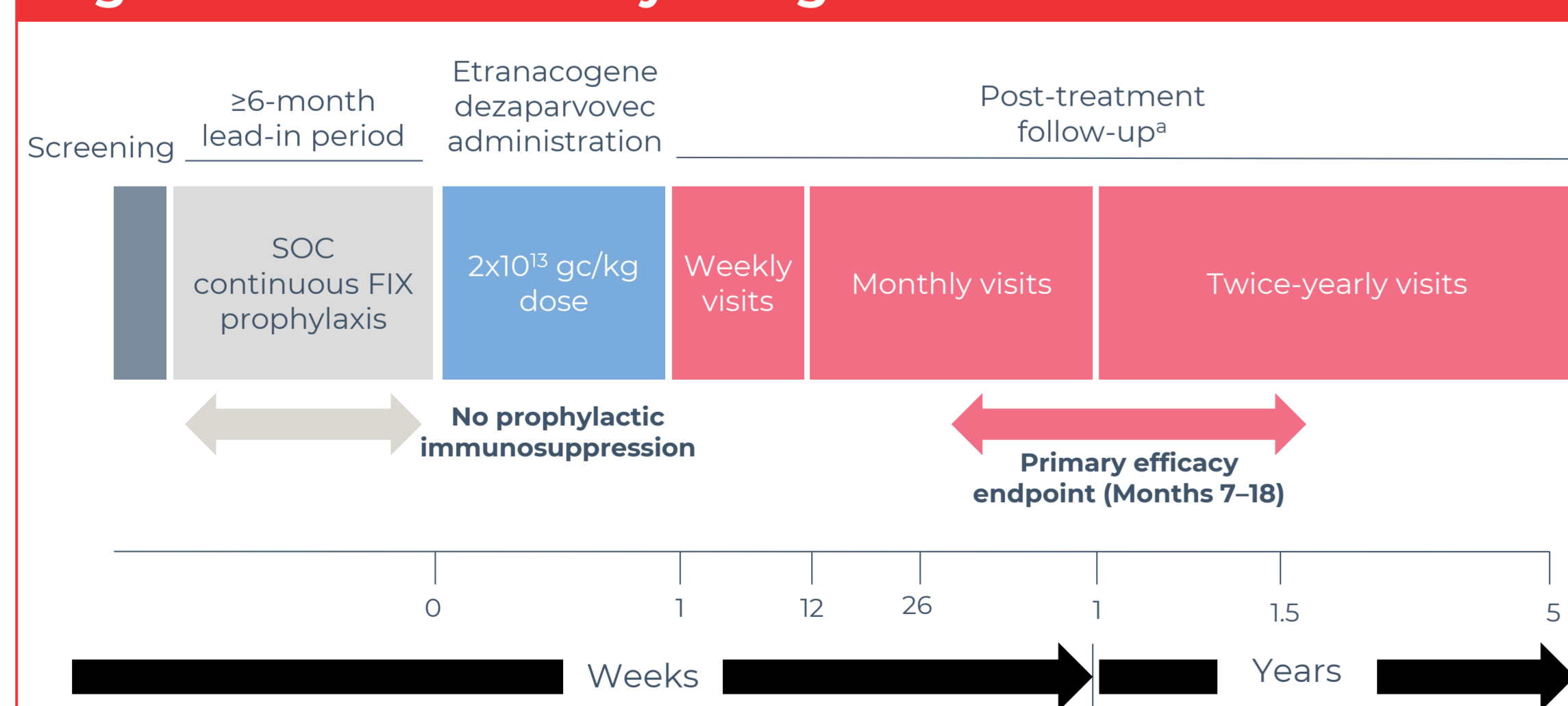
Aim

- To present updated efficacy and safety data from the pivotal Phase 3 HOPE-B clinical trial over 24 months' follow-up

Methods

- Open-label, single-dose, single-arm, international trial (NCT03569891)² in adult males with severe or moderately severe hemophilia B (FIX activity $\leq 2\%$ of normal) on routine FIX prophylaxis (for ≥ 2 months), with/without pre-existing AAV5 NABs (**Figure 2**)
- Participants were infused with a single dose of etranacogene dezaparvovec (2×10^{13} gc/kg), following a ≥ 6 -month lead-in period receiving FIX prophylaxis
- FIX activity, annualized bleed rate (ABR), and FIX infusions were assessed frequently during the ≥ 6 months lead-in period (when FIX prophylaxis was received) and first 12 months after receiving etranacogene dezaparvovec, then every 6 months during the long-term follow-up (Years 2–5)
- Adverse events (AEs) were continuously assessed

Figure 2. HOPE-B study design



Results

Study participants

- Of the 54 participants who received etranacogene dezaparvovec (**Table 1**):
 - 53 participants received the full dose
 - One only received a partial dose (due to an infusion-related reaction)
 - 52 completed 24 months of follow-up

Table 1. Baseline demographics

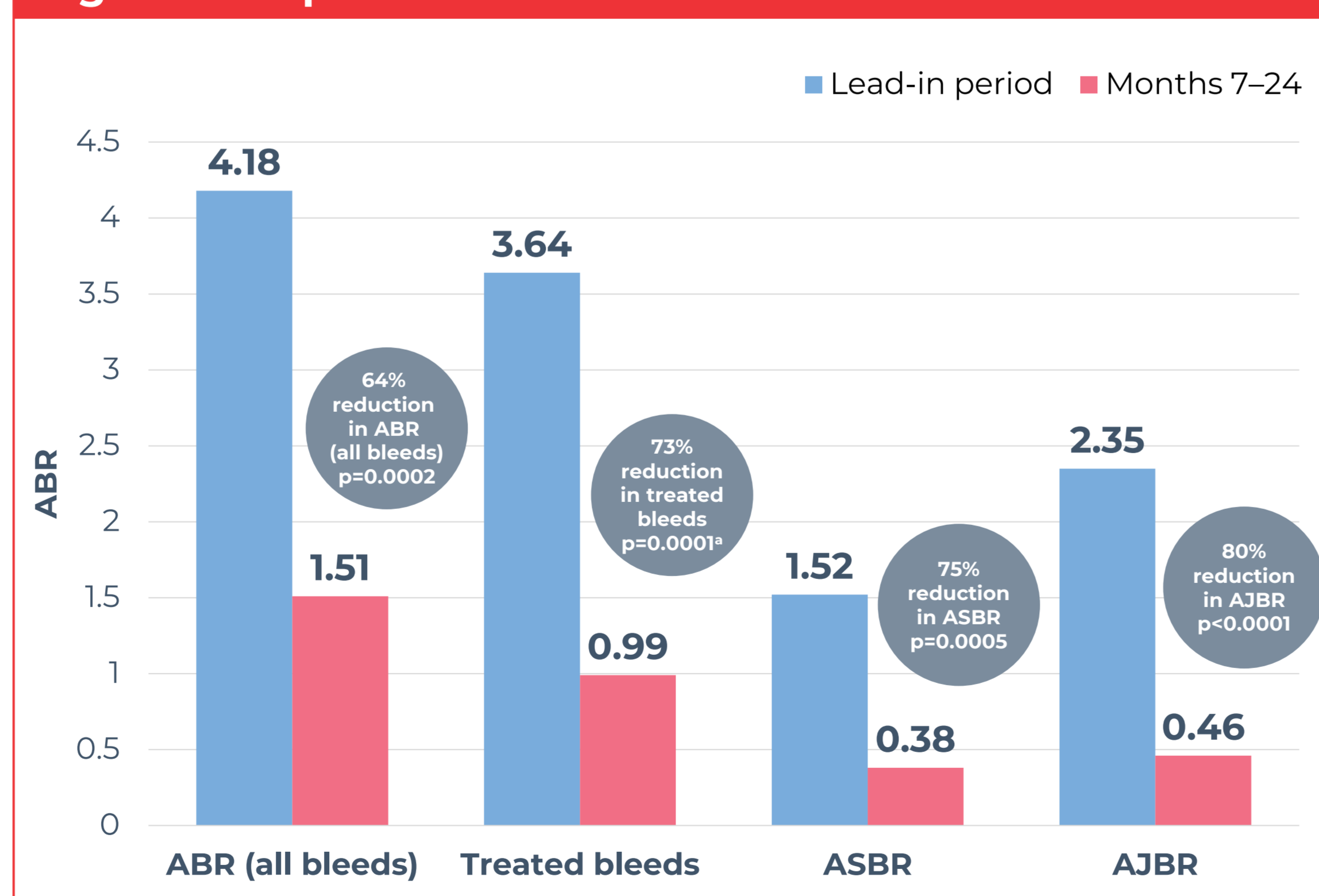
| | Full analysis set, N=54 |
|---|-------------------------|
| Age, mean (SD, min-max), years | 41.5 (15.8, 19–75) |
| Severity of HB at diagnosis, n (%) | |
| Severe (FIX $< 1\%$) | 44 (81.5) |
| Moderately severe (FIX $\geq 1\%$ and $\leq 2\%$) | 10 (18.5) |
| Positive HIV status, n (%) | 3 (5.6) |
| Prior hepatitis B infection, n (%) | 9 (16.7) |
| Prior hepatitis C infection, n (%) | 31 (57.4) |
| Pre-screening FIX treatment, n (%) | |
| Extended half-life | 31 (57.4) |
| Standard half-life | 23 (42.6) |
| Detectable AAV5 NABs at baseline, n (%) | 21 (38.8) |
| Participants with zero reported bleeds at lead-in period, n (%) | 14 (25.9) |

AAV5, adeno-associated virus 5; FIX, factor IX; HB, haemophilia B; HIV, human immunodeficiency virus; NABs, neutralizing antibodies; SD, standard deviation.

ABR

- Compared with the ≥ 6 -month lead-in period, mean ABR for all bleeds during Months 7–24 post-treatment was significantly reduced by 64% (**Figure 3**)
 - Mean ABR lead-in period vs Months 7–24: 4.19 vs 1.51; $p=0.0002$
 - The bleed reduction that satisfied the primary endpoint of the trial during Months 7–18 was sustained for Months 7–24
 - Mean ABR for all other bleed types was reduced at Months 7–24 compared with the ≥ 6 -month lead-in period

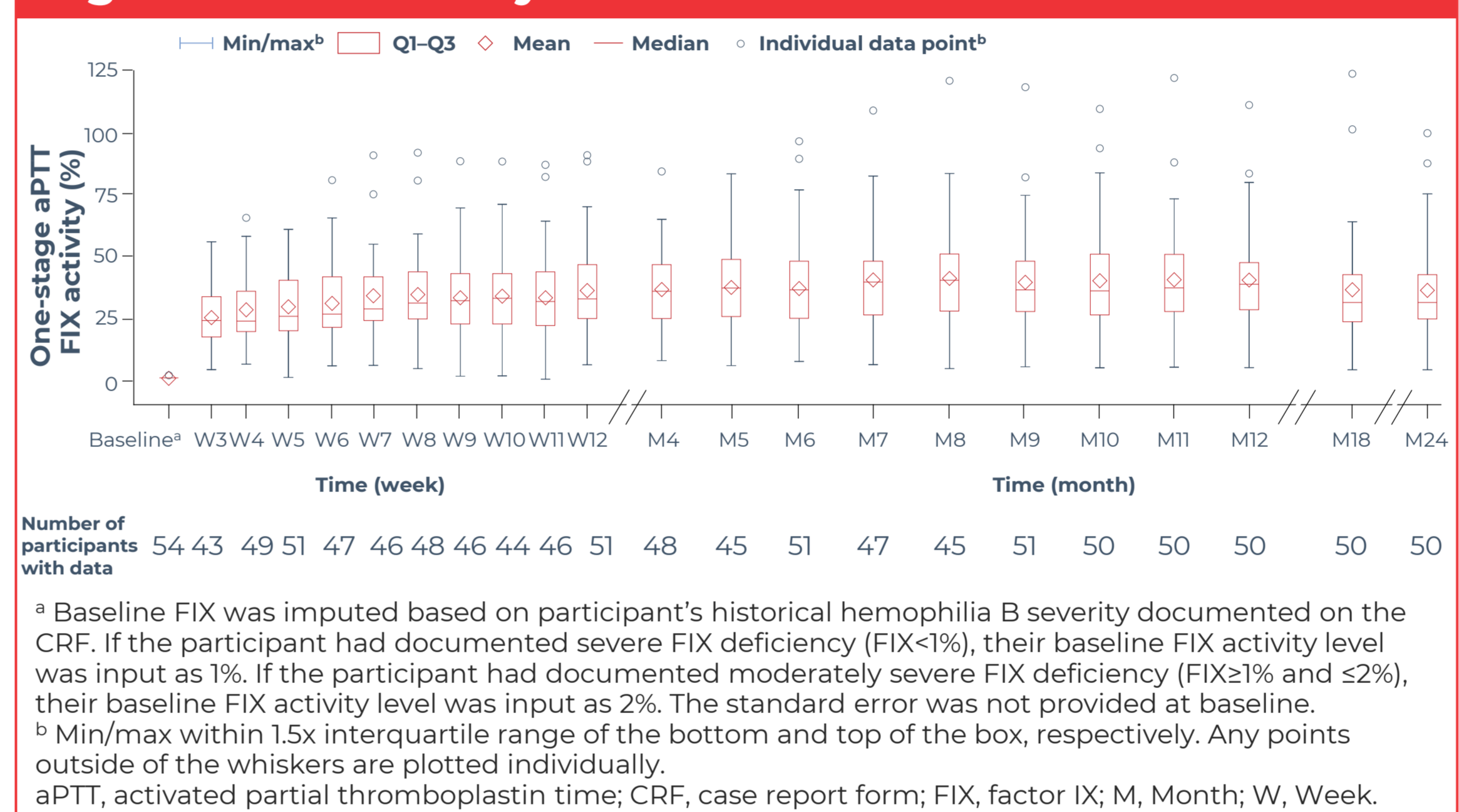
Figure 3. Improvement in ABR



FIX activity

- Mean (standard deviation [SD]; min-max) FIX activity levels were sustained for up to 24 months post treatment (**Figure 4**)
 - Month 6: 39.0% (± 18.7 ; 8.2–97.1) (n=51)
 - Month 18: 36.9% (± 21.4 ; 4.5–122.9) (n=50)
 - Month 24: 36.7% (± 19.0 ; 4.7–99.2) (n=50)
- These values represented a significant increase from baseline (mean: 1.19; SD: 0.39) with a least squares mean FIX activity increase of:
 - Month 6: 36.18% (standard error [SE]: 2.432%; 95% confidence interval [CI]: 31.41–40.95; $p < 0.0001$)
 - Month 18: 34.31% (SE: 2.444%; 95% CI: 29.52, 39.11; $p < 0.0001$)
 - Month 24: 34.13% (SE: 2.325%; 95% CI: 29.57, 38.69; $p < 0.0001$; p-value not adjusted for multiplicity)

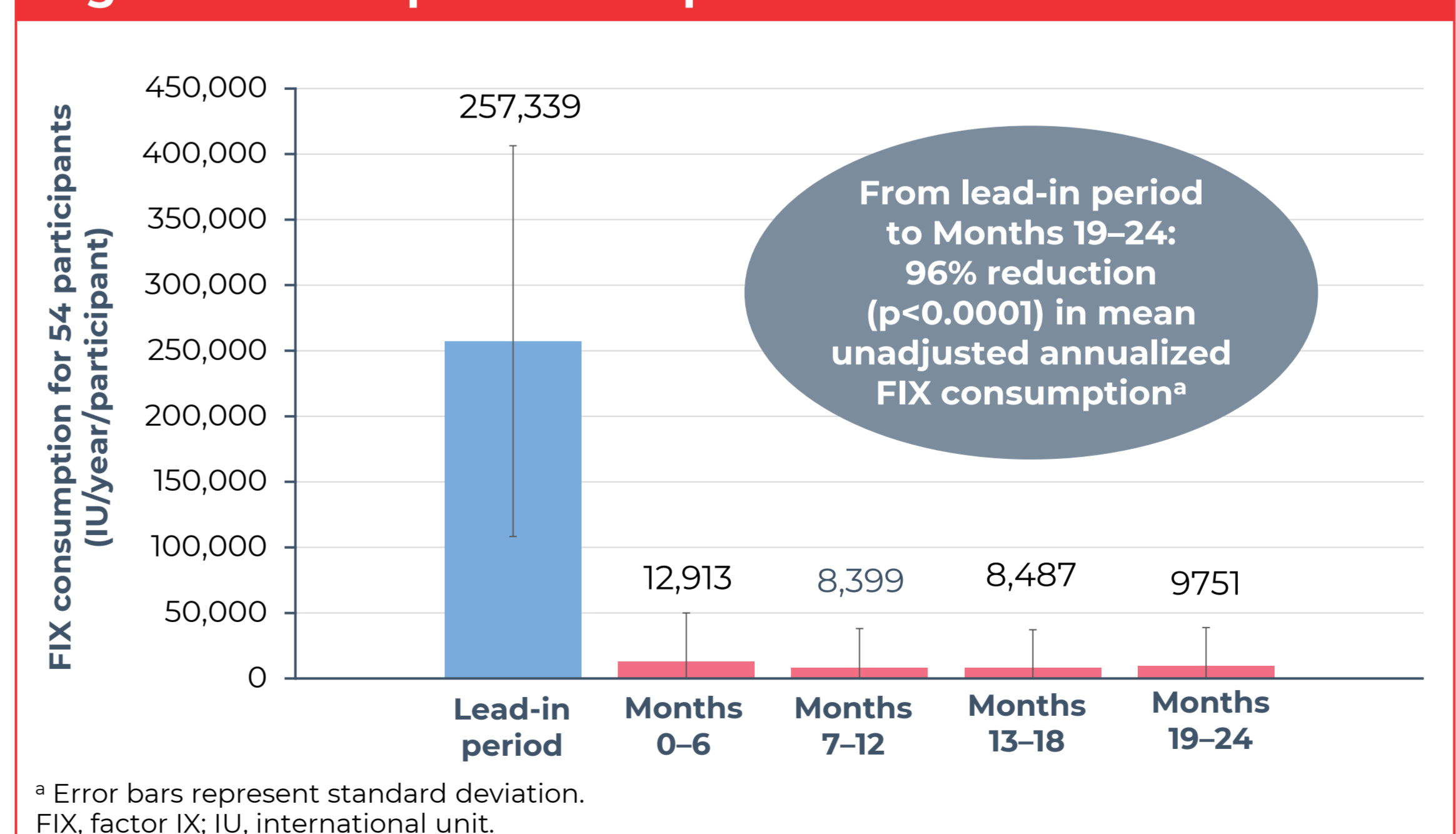
Figure 4. FIX activity levels over 24 months



FIX replacement product use

- Use of FIX replacement product was significantly decreased from baseline
- There was a 96% reduction in mean unadjusted annualized FIX consumption from the lead-in period to Months 19–24 (**Figure 5**)
- Of the 54 participants, 52 (96.3%) discontinued and remained free of continuous FIX prophylaxis from Day 21 to Month 24, including 20 participants with baseline AAV5 NAB titers up to 1:700
 - One participant with a markedly higher AAV5 NABs titer (1:3212) and one participant who received only a partial vector dose (due to an infusion-related reaction) did not express FIX Padua or discontinue FIX prophylaxis

Figure 5. FIX replacement product use



Safety

- The safety profile is consistent with previously presented data¹
 - Most treatment-emergent AEs (TEAEs) were mild (76.1%; moderate: 20.6%; severe: 3.2%)
 - 93 TEAEs in 38/54 participants were treatment related (TRAEs) (**Table 2**)
 - Only one TRAE occurred during Months 18–24
- Alanine aminotransferase increase (with or without increased aspartate transaminase), reported as an AE, occurred in 11 participants
 - Nine (16.7%) received supportive care with reactive corticosteroids for a mean duration of 79.8 days (SD: 26.6; range: 51–130 days)
 - All participants discontinued steroid use prior to Week 26
 - FIX expression was maintained
- No serious AEs related to treatment
- One death was reported, unrelated to study treatment
 - A 75-year-old participant died from cardiogenic shock (at ~ 15 months following infusion), preceded by a urinary tract infection
- One case of hepatocellular carcinoma (previously reported) – unrelated to study treatment following a detailed molecular analysis³

Table 2. Most common TRAEs (incidence >5%)

| | Post-treatment Period (N = 54) | |
|---------------------------|--------------------------------|-----------|
| | Participants, n (%) | Events, n |
| ALT increased | 9 (16.7) | 10 |
| Headache | 8 (14.8) | 9 |
| Influenza-like illness | 7 (13.0) | 8 |
| AST increased | 5 (9.3) | 6 |
| Blood CPK increased | 4 (7.4) | 6 |
| Dizziness | 4 (7.4) | 4 |
| Fatigue | 4 (7.4) | 4 |
| Nausea | 4 (7.4) | 4 |
| Arthralgia | 3 (5.6) | 3 |
| Infusion-related reaction | 3 (5.6) | 3 |

CPK, creatine phosphokinase; ALT, alanine transaminase; AST, aspartate transaminase; TRAE, treatment-related adverse event.

Conclusions

- The HOPE-B study demonstrates that etranacogene dezaparvovec can provide durability of disease correction with acceptable safety up to 24 months' in people with hemophilia B
- After 24 months following a single dose of etranacogene dezaparvovec
 - Stable FIX Padua expression was observed in participants with AAV NAB undetected or $< 1:700$ titer
 - Reductions in ABR remained durable and superior to FIX prophylaxis
 - All participants who discontinued prophylaxis remained off prophylaxis
- Safety profile was consistent with previous reports with limited early reactive corticosteroid exposure in a minority of participants

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