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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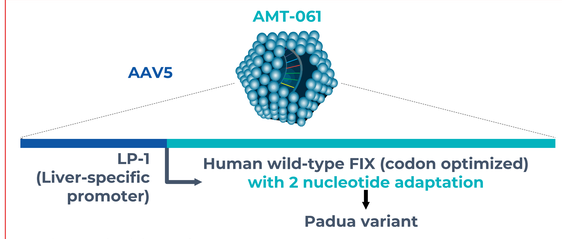
Introduction

- 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



AAV, adeno-associated virus; FIX, factor IX.

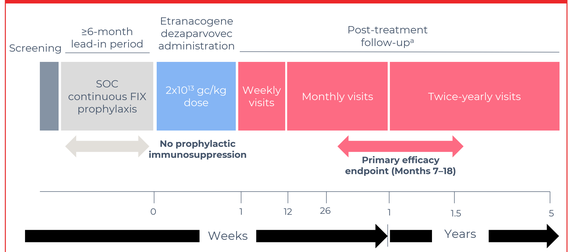
Aim

- 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 ≤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 ($2x10^{13}$ 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



[a] At least quarterly contact (±2 weeks) between site staff and subjects to monitor occurrence of adverse events. Last subject visit planned Q1 2025.
ABR, annualized breeding rate; FIX, factor IX; gc/kg, genome copies/kilogram; SOC, standard of care.

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

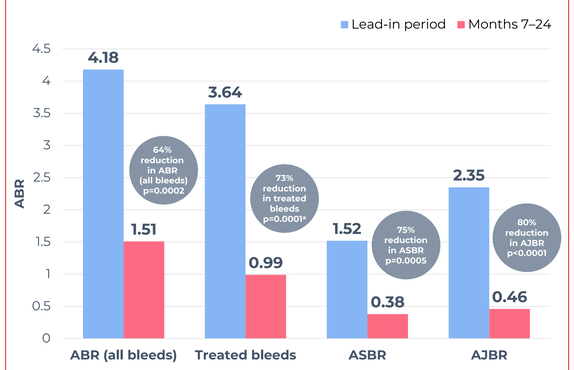
	Full analysis set, N=54
Age, mean (SD, min–max), years	41.5 (15.8, 19–75)
Severity of HB at diagnosis, n (%) Severe (FIX <1%) Moderately severe (FIX ≥1% and ≤2%)	 44 (81.5) 10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior hepatitis B infection, n (%)	9 (16.7)
Prior hepatitis C infection, n (%)	31 (57.4)
Pre-screening FIX treatment, n (%) Extended half-life Standard half-life	 31 (57.4) 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

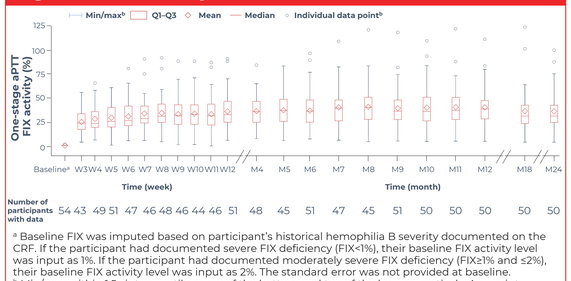


[a] P-value for treated bleeds is not Type I error controlled.
ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; ASBR, annualized spontaneous bleeding rate.

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

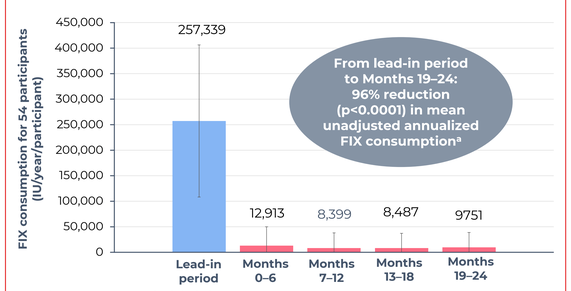


[a] Baseline FIX was imputed based on participant's historical hemophilia B severity documented on the CRF. If the participant had documented severe FIX deficiency (FIX<1%), their baseline FIX activity level was input as 1%. If the participant had documented moderately severe FIX deficiency (FIX≥1% and ≤2%), their baseline FIX activity level was input as 2%. The standard error was not provided at baseline.
[b] Min/max within 1.5x interquartile range of the bottom and top of the box, respectively. Any points outside of the whiskers are plotted individually.
aPTT, activated partial thromboplastin time; CRF, case report form; FIX, factor IX; M, Month; W, Week.

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



[a] Error bars represent standard deviation.
FIX, factor IX; IU, international unit.

Safety

- The safety profile is consistent with previously presented data[1]
  - 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 analysis[3]

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

Acknowledgments

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