Durability of Bleeding Protection and Factor IX Activity Levels Are Demonstrated in Individuals With and Without Adeno-Associated Virus Serotype 5 Neutralizing Antibodies (Titers <1:700) With Comparable Safety in the Phase 3 HOPE-B Clinical Trial of Etranacogene Dezaparvovec Gene Therapy for Hemophilia B

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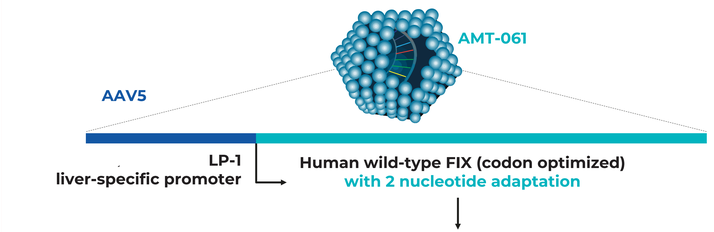
Introduction

- 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]
- A unique aspect of the HOPE-B trial was the enrollment of participants regardless of their baseline AAV5 neutralizing antibody (NAb) status

Figure 1. Etranacogene dezaparvovec



AAV5, adeno-associated virus 5; FIX, factor IX.

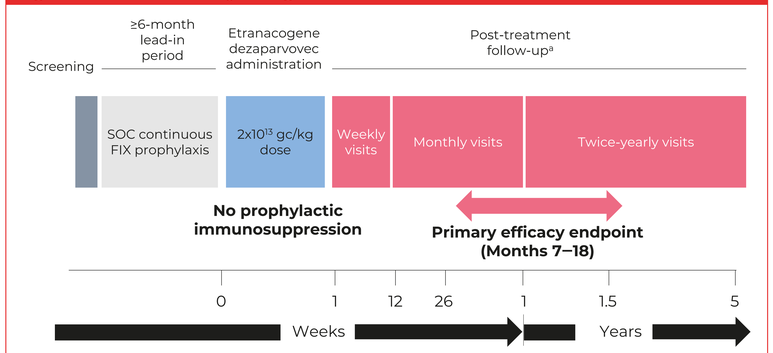
Aim

- To assess the efficacy and safety of etranacogene dezaparvovec in HOPE-B participants with (NAb+) and without (NAb-) pre-existing AAV5 NAbs over 18 and 24 months of follow-up

Methods

- HOPE-B: Phase 3, 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-month lead-in period (when FIX prophylaxis was received) and the first 12 months after receiving etranacogene dezaparvovec, then every 6 months during long-term follow-up (Years 2–5)
- Adverse events were continuously assessed

Figure 2. HOPE-B study design



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

Results

Study participants

- Of the 54 participants who received etranacogene dezaparvovec, 33 participants were AAV5 NAb- and 21 were AAV5 NAb+ at baseline (**Table 1**)
- Median (Q1–Q3) titer among AAV5 NAb+ participants was 56.9 (23.3–198.9); 20/21 (95%) AAV5 NAb+ participants had titers of <1:700 at baseline
- One participant with a markedly higher baseline AAV5 NAbs titer (1:3212) did not express FIX Padua or discontinue FIX prophylaxis

Table 1. Baseline demographics

	Total, N=54	Baseline AAV5 NAb+, n=21	Baseline AAV5 NAb–, n=33
Age, mean (SD, minimum–maximum), years	41.5 (15.8, 19–75)	44.5 (17.5, 19–75)	39.5 (14.5, 21–73)
Severity of HB at diagnosis, n (%)			
Severe (FIX <1%)	44 (81.5)	16 (76.2)	28 (84.8)
Moderately severe(FIX ≥1% and ≤2%)	10 (18.5)	5 (23.8)	5 (15.2)
Positive HIV status, n (%)	3 (5.6)	1 (4.8)	2 (6.1)
Prior hepatitis B, n (%)	9 (16.7)	5 (23.8)	4 (12.1)
Prior hepatitis C, n (%)	31 (57.4)	14 (66.7)	17 (51.5)
Pre-screening FIX treatment, n (%)			
Extended half-life	31 (57.4)	14 (66.7)	17 (51.5)
Standard half-life	23 (42.6)	7 (33.3)	16 (48.5)
Detectable AAV5 NAbs at baseline, n (%)[a]	21 (38.9)	-	-
Maximum titer	-	3212.3	-
Median titer (Q1–Q3)		56.9 (23.3–198.9)	

[a] Limit of detection for the NAb assay is 7.
AAV5, adeno-associated virus 5; FIX, factor IX; HB, hemophilia B; HIV, human immunodeficiency virus; NAb, neutralizing antibody; SD, standard deviation.

ABR

- At Months 7–18 and 7–24 post-dose, participants AAV5 NAb+ <1:700 and AAV5 NAb- at baseline demonstrated a low ABR (**Table 2; Figure 3**)
- Mean ABRs achieved at Months 7–18 and 7–24 were significantly improved compared with mean ABRs during the ≥6-month lead-in period of continuous FIX prophylaxis

Months 7–18
- AAV5 NAb+ <1:700: 1.30 (vs 4.29 in lead-in; p=0.0005)
- AAV5 NAb-: 0.93 (vs 3.80 in lead-in; p<0.0001)

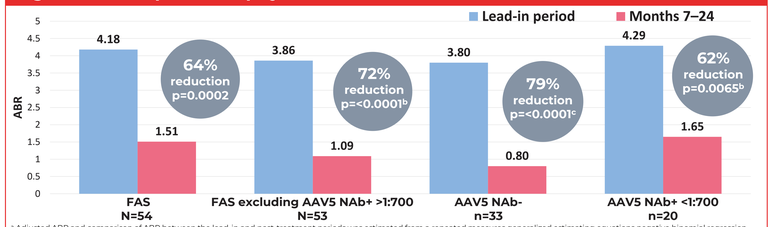
Months 7–24
- AAV5 NAb+ <1:700: 1.65 (vs 4.29 in lead-in; p=0.0065)
- AAV5 NAb-: 0.80 (vs 3.80 in lead-in; p<0.0001)

Table 2. Primary endpoint (ABR all bleeds) by baseline AAV5 NAb status

Population	≥6-month lead-in	Months 7–18 post-treatment			Months 7–24 post-treatment		
	Adjusted ABR (95% CI)[a]	Adjusted ABR (95% CI)[a]	Rate ratio (post-treatment/ lead-in) (95% CI)[a,b]	p-value[c]	Adjusted ABR (95% CI)[a]	Rate ratio (post-treatment/ lead-in) (95% CI)[a,b]	p-value[c]
FAS N=54	4.18 (3.21–5.44)	1.51 (0.81–2.82)	0.36 (0.20–0.64)	0.0002	1.51 (0.83–2.76)	0.36 (0.21–0.63)	0.0002
FAS excluding AAV5 NAb+ >1:700 at baseline N=53	3.86 (2.89–5.17)	1.07 (0.63–1.81)	0.27 (0.17–0.43)	<0.0001[d]	1.09 (0.67–1.79)	0.28 (0.17–0.46)	<0.0001[d]
AAV5 NAb- at baseline n=33	3.80 (2.56–5.65)	0.93 (0.44–1.98)	0.25 (0.14–0.43)	<0.0001[e]	0.80 (0.39–1.67)	0.21 (0.12–0.37)	<0.0001[e]
AAV5 NAb+ <1:700 at baseline n=20	4.29 (3.06–6.01)	1.30 (0.63–2.70)	0.30 (0.15–0.61)	0.0005[d]	1.65 (0.84–3.26)	0.39 (0.18–0.82)	0.0065[d]

[a] Adjusted ABR and comparison of ABR between the lead-in and post-treatment periods was estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate. [b] The upper limit of the CI of the rate ratio was compared to the non-inferiority margin of 1.8. If the upper limit was <1.8, then non-inferiority was declared. [c] One-sided p-value ≤0.025 for post-treatment/ lead-in <1 was regarded as statistically significant. [d] Post hoc analysis not controlled for Type I error. [e] Subgroup analysis not controlled for Type I error.
AAV5, adeno-associated virus serotype 5; ABR, annualized bleeding rate; CI, confidence interval; FAS, full analysis set; NAb, neutralizing antibody.

Figure 3. ABR[a] (all bleeds) by baseline AAV5 NAb status



[a] Adjusted ABR and comparison of ABR between the lead-in and post-treatment periods was estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate. [b] Post-hoc analysis not controlled for Type I error. [c] Subgroup analysis not controlled for Type I error.
AAV5, adeno-associated virus type 5; ABR, annualized bleeding rate; FAS, full analysis set; NAb, neutralizing antibody.

FIX activity

- Median (minimum–maximum) FIX activity levels were sustained throughout 24 months post-treatment (**Table 3**)

18 months
- AAV5 NAb+ <1:700: 32.0% (10.3–57.9)
- AAV5 NAb-: 35.0% (4.5–122.9)

24 months
- AAV5 NAb+ <1:700: 33.5% (9.1–88.3)
- AAV5 NAb-: 35.4% (4.7–99.2)

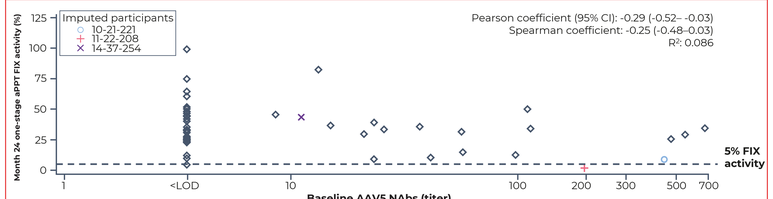
- At 18 and 24 months post-dose, no clinically meaningful or statistically significant correlation between an individual's baseline AAV5 NAb titer and FIX activity levels was identified, up to an AAV5 NAb titer of <1:700 (24-month Pearson coefficient: -0.29; Spearman coefficient: -0.25; R2: 0.086) (**Figure 4**)

Table 3. Summary of FIX activity[a] (%) by baseline AAV5 NAb status (FAS)

Pre-existing AAV5 NAb status		Baseline	6 months	12 months	18 months	24 months
AAV5 NAb-	**n**	**33**	**33**	**32**	**33**	**33**
	Median (min–max)	1.0 (1.0–2.0)	37.30 (8.4–97.1)	38.65 (5.9–113.0)	35.0 (4.5–122.9)	35.40 (4.7–99.2)
	Mean (SD)	1.15 (0.36)	40.61 (18.64)	44.82 (23.21)	39.87 (24.08)	38.55 (19.19)
AAV5 NAb+	**n**	**21**	**18**	**18**	**17**	**17**
	Median (min–max)	1.0 (1.0–2.0)	35.60 (8.2–90.4)	39.95 (8.5–73.6)	32.0 (10.3–57.9)	33.50 (9.1–88.3)
	Mean (SD)	1.24 (0.44)	35.91 (19.02)	35.54 (17.84)	31.14 (13.75)	32.98 (18.51)

[a] One-stage FIX activity assays. Only samples uncontaminated with exogenous FIX were included in analysis. LS mean from repeated measures linear mixed model with visit as a categorical covariate.
AAV5, adeno-associated virus serotype 5; FAS, full analysis set; FIX, factor IX; LS, least squares; max, maximum; min, minimum; NAb, neutralizing antibody; SD, standard deviation.

Figure 4. Baseline AAV5 NAb titers (<1:700) vs FIX activity level[a] over 24 months



[a] One participant with baseline titer of >3200 was not included in this analysis. Participants with undetectable NAbs were plotted at 7 on the horizontal axis, which was the limit of detection of this assay. Uncontaminated data were used, i.e. blood sampling did not occur within 5 half-lives of exogenous FIX use. Participants with no uncontaminated data had their values assigned to the baseline value. If there were missing uncontaminated values for Month 24, then the single uncontaminated value closest in time to Month 24 was used. Any such imputed values are shown.
Baseline was the value obtained immediately prior to dosing or the value obtained at Visit L-Final in cases where the value immediately prior to dosing was missing.
AAV5, adeno-associated virus 5; aPTT, activated partial thromboplastin time; CI, confidence interval; FIX, factor IX; NAb, neutralizing antibody.

Safety

- The safety profile of etranacogene dezaparvovec was similar between NAb subgroups
- Over 24 months, corticosteroid-treated transaminase elevations occurred in 6/33 (18.2%) participants AAV5 NAb- at baseline and 3/21 (14.3%) participants AAV5 NAb+ at baseline
- Infusion-related reactions occurred in 2/33 (6.1%) participants AAV5 NAb- at baseline and 5/21 (23.8%) participants AAV5 NAb+ at baseline; there was no statistically significant association between infusion-related reactions and baseline AAV5 NAb status (p=0.0956)

Conclusions

- Pre-existing AAV5 NAb status was assessed but not used as an exclusion criteria in the HOPE-B trial
- Throughout 24 months of follow-up, participants AAV5 NAb- and NAb+ (<700 titer) at baseline receiving etranacogene dezaparvovec demonstrated:
  - significant reductions in ABR
  - freedom from continuous FIX prophylaxis
  - comparable and acceptable safety profile
- FIX activity levels were stable, with no association between baseline AAV5 NAb status (up to titer <1:700) and the long-term durability of FIX expression throughout 24 months' follow-up
- A single dose of etranacogene dezaparvovec can increase FIX activity levels, reduce bleeds and provide freedom from FIX prophylaxis, even in the presence of pre-existing AAV5 NAbs (<1:700)

Acknowledgments

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