PO038

Stable and durable factor IX levels over 4 years after etranacogene dezaparvovec gene therapy administration in a Phase 2b trial in patients with haemophilia B

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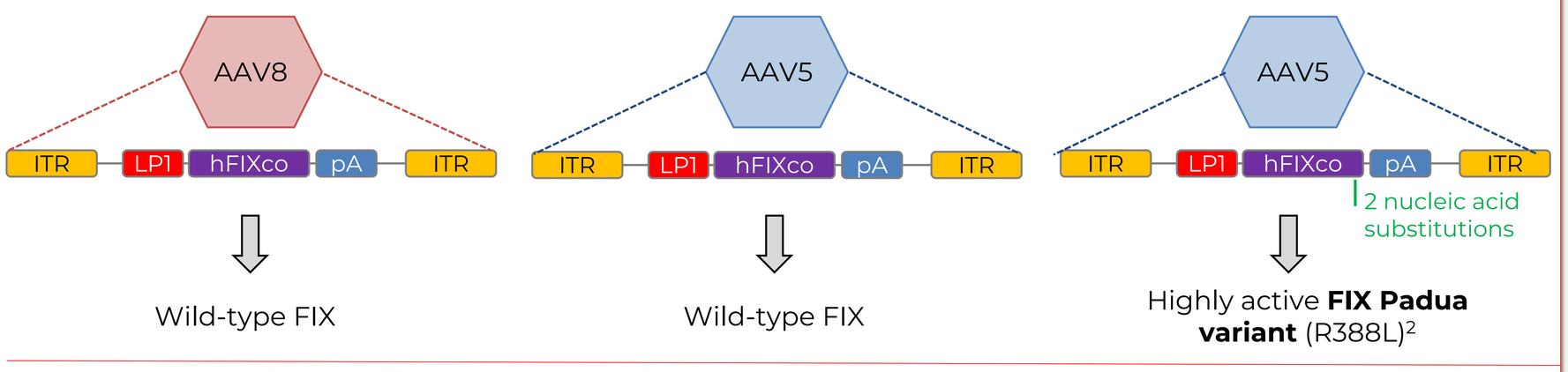
Introduction

- Etranacogene dezaparvovec, the successor of AMT-060 (**Figure 1**), is an approved gene therapy for haemophilia B (HB)[1]
- Sustained and stable FIX activity post-etranacogene dezaparvovec administration has been reported up to 3 years, allowing patients to discontinue prophylaxis[2]

Figure 1. Evolution of AAV vectors for haemophilia B gene therapy



AAV, adeno-associated virus; FIX, factor IX; ITR, inverted terminal repeat; LP1, liver promoter 1; pA, poly A; rAAV, recombinant adeno-associated virus.

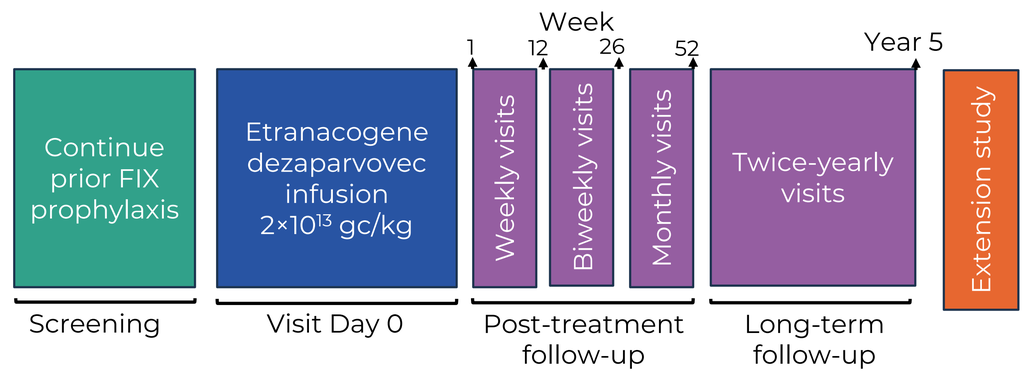
Objective

- **To report 4-year outcomes of etranacogene dezaparvovec from a Phase 2b open-label, single-dose, single-arm, multi-centre trial (NCT03489291; Figure 2) in adults with severe or moderately severe HB (FIX ≤2%; N=3)[2]**

Methods

- The primary endpoint was FIX activity levels ≥5% at Week 6 post-dosing[2]
  - Secondary endpoints included laboratory parameters, bleeding rates and adverse events (AEs)[2]
- To be included, patients were required to be on routine prophylaxis (**Table 1**)[2]
  - Patients with pre-existing neutralising antibodies (NAbs) to AAV5 were not excluded

Figure 2. Study design



FIX, factor IX; gc, genome copies.

Table 1. Baseline demographics[2]

	Participant		
Characteristic	**1**	**2**	**3**
Age at enrollment (years)	43	50	47
Weight (kg)	89	81	82
Baseline FIX activity levels (%)	1	<1	<1
Prescreening FIX treatment	Prophylaxis (EHL)	Prophylaxis (EHL)	Prophylaxis (EHL)
ABR 1 year before screening*	3	1	5
Anti-AAV5 NAb status at screening* (titer)†,‡	Positive (48)	Positive (44)	Positive (25)
Anti-AAV5 NAb status at day of dosing* (titer)†,‡	Positive (22)	Positive (33)	Positive (20)

Participants 2 & 3 were previously excluded from another AAV-based gene therapy trial for HB based on anti-AAV NAb titer.
*Total bleeds (treated + untreated). †AAV5 NAb data considered positive if titer was ≥2. ‡Luciferase cell-based assay.
ABR, annualised bleeding rate; EHL, extended half-life; HB, haemophilia B; NAbs, neutralising antibodies.

Results

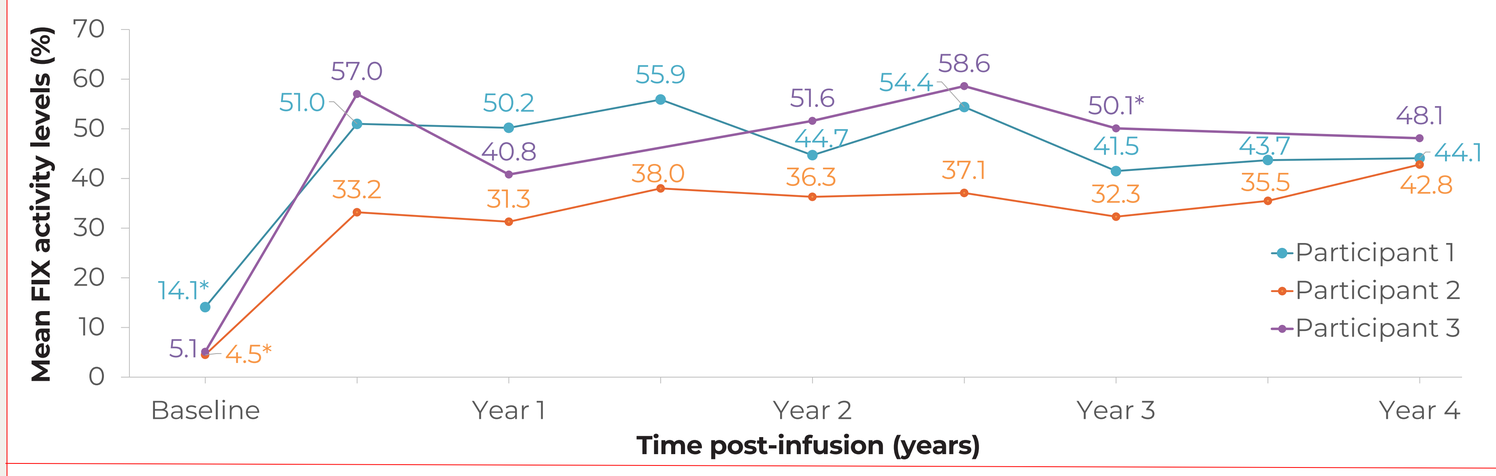
SUSTAINED FIX ACTIVITY

- Post-etranacogene dezaparvovec administration, mean (standard deviation [SD]) FIX activity (N=3) increased to 30.57% (6.97) at Week 6, using the one-stage aPTT assay
- Mean (SD; range) FIX activity (N=3) remained stable and in the non-haemophilia range from Year 1 (40.77% [9.45; 31.3–50.2]) to Year 4 (45.00% [2.76; 42.8–48.1]) (**Figure 3**)

HAEMOSTATIC PROTECTION

- No bleeding episodes were reported from Year 3 to 4 (**Table 2**)
  - No FIX was infused outside of invasive procedures
- ABR for the cumulative follow-up period was 0.22 at Year 3 and 0.17 at Year 4

Figure 3. Mean FIX activity levels over time



FIX activity measured by using a one-stage aPTT assay. Samples at baseline may have included activity from exogenous FIX replacement. *Contaminated result from a blood sample obtained within 5 half-lives of previous FIX therapy. aPTT, activated partial thromboplastin time; FIX, factor IX.

Table 2. Number of bleeds and FIX consumption excluding invasive procedures

	Number of bleeds (all bleeds)			FIX consumption (IU/year)		
	Participant			Participant		
Year	**1**	**2**	**3**	**1**	**2**	**3**
Baseline[2]	3*	1*	6*	24,000*	7,681*	63,000*
1	0	0	0	0	0	1,705
2	0	0	2	0	0	3,400
3	0	0	0	0	0	0
4	0	0	0	0	0	0

*Data collected retrospectively 1 year before screening from medical records.
ABR, annualised bleeding rate; FIX, factor IX.

Results

NO APPARENT IMPACT OF PRE-EXISTING NABS ON DURABILITY OF BLEED PROTECTION

- Bleed protection was sustained in patients with pre-existing NAbs to AAV5 (mean titer = 25 at dosing)

SAFETY

- As reported previously:[2]
  - 1 patient experienced 2 mild AEs (possibly treatment related) shortly after dosing
- No patients developed FIX inhibitors
- No thrombosis events occurred

During 4 years of follow-up:

No patients returned to prophylaxis

No clinically significant liver enzyme elevations related to treatment

No patient required corticosteroids

Conclusions

- **Sustained and stable FIX activity post-etranacogene dezaparvovec administration was observed over 4 years in all patients, enabling discontinuation of routine prophylaxis, irrespective of anti-AAV5 NAbs at baseline**

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Disclosures

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