Etranacogene dezaparvovec-drlb hemophilia B gene therapy Phase 2b trial final results: Stable and durable FIX level expression over 5 years

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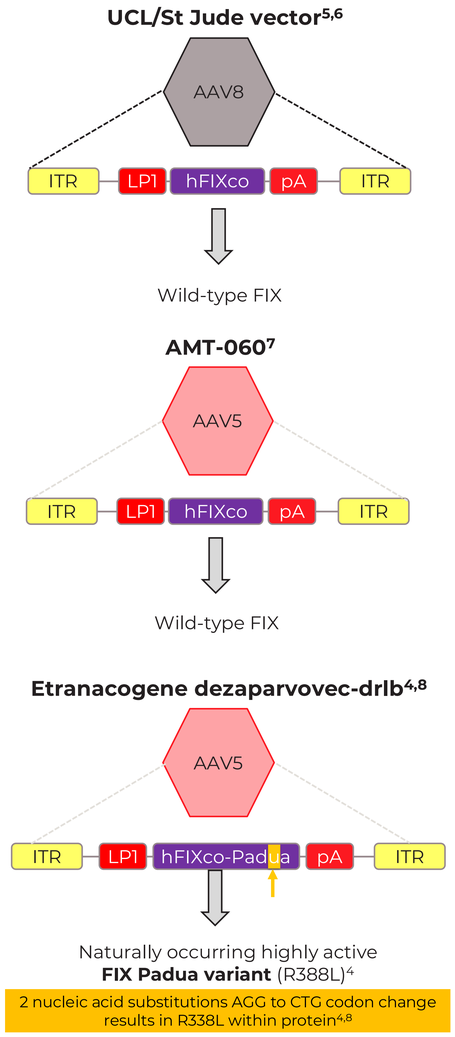
Background

- Etranacogene dezaparvovec-drlb, the successor of CSL220 (formerly AMT-060) (**Figure 1**), is an approved gene therapy for hemophilia B (HB)[1-3]
- Sustained and stable FIX activity post-etranacogene dezaparvovec-drlb administration has been reported up to 4 years, allowing patients to discontinue prophylaxis[3]

Objective

- **To report 5-year outcomes of etranacogene dezaparvovec-drlb from a Phase 2b open-label, single-dose, single-arm, multi-center trial (NCT03489291; Figure 2) in adults with severe or moderately severe HB (FIX activity ≤2% of normal; N=3)[3,4]**

Figure 1. Evolution of AAV vectors for hemophilia 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.

Methods

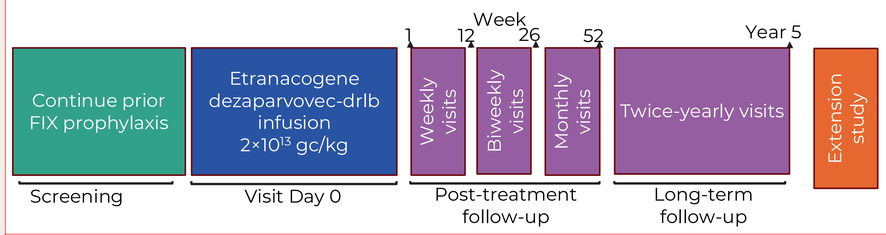
- **The primary endpoint was FIX activity levels ≥5% at Week 6 post-dosing[3,4]**
  - Secondary endpoints included laboratory parameters, bleeding rates and adverse events (AEs)[3,4]
- To be included, patients were required to be on routine prophylaxis (**Table 1**)[3,4]
  - Patients with pre-existing neutralizing antibodies (NAbs) to AAV5 were not excluded

Table 1. Baseline demographics[4]

	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, annualized bleeding rate; EHL, extended half-life; HB, hemophilia B; NAbs, neutralizing antibodies.

Figure 2. Study design



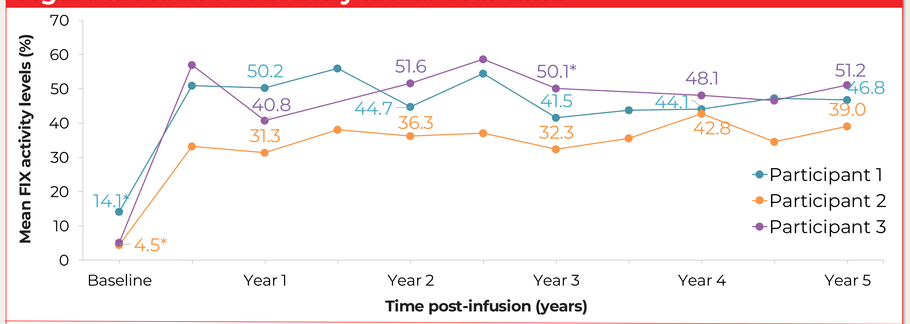
FIX, factor IX; gc, genome copies.

Results

SUSTAINED FIX ACTIVITY OVER 5 YEARS OF FOLLOW-UP

- Post-etranacogene dezaparvovec-drlb administration, mean (standard deviation [SD]; range) FIX activity (N=3) increased to 30.57% (6.97; 23.9–37.8) at Week 6, using the one-stage aPTT assay
- Mean (SD; range) FIX activity remained stable and in the non-hemophilia range from Year 1 (40.77% [9.45; 31.3–50.2]) to Year 5 (45.7% [6.18; 39.0–51.2]) (**Figure 3**)

Figure 3. Mean FIX activity levels over time



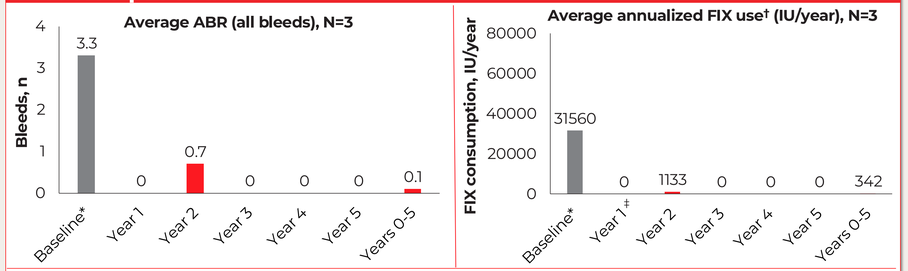
FIX activity measured by using a one-stage aPTT assay. Samples at baseline may have included activity from exogenous FIX replacement.
*Contaminated result from a blood sample obtained within 5 half-lives of previous FIX therapy.
aPTT, activated partial thromboplastin time; FIX, factor IX.

Results

HEMOSTATIC PROTECTION

- No bleeding episodes were reported from Year 3 to 5 (**Figure 4**)
  - No FIX was infused outside of invasive procedures
- ABR for the cumulative follow-up period was 0.22 at Year 3, 0.17 at Year 4 and 0.14 at Year 5
- Bleed protection was sustained in patients with pre-existing NAbs to AAV5 (mean titer = 25 at dosing)

Figure 4. Number of bleeds and FIX consumption excluding invasive procedures



*Data collected retrospectively 1 year before screening from medical records. †Excluding use for invasive procedures. ‡Post-continuous prophylaxis period. FIX, factor IX; IU, international units; SEM, standard error of the mean.

Results

FAVORABLE SAFETY PROFILE ACROSS 5-YEAR FOLLOW-UP

- 1 patient experienced 2 mild AEs (possibly treatment related) shortly after dosing
- No patients developed FIX inhibitors
- No thrombosis events occurred
- No clinically significant liver enzyme elevations related to treatment
- No patient required corticosteroids

Conclusion

- **Sustained and stable FIX activity post-etranacogene dezaparvovec-drlb administration was observed over 5 years in all patients, enabling discontinuation of routine prophylaxis, irrespective of anti-AAV5 NAbs at baseline**
- **All participants (N=3) enrolled in the extension study (NCT05962398) for long-term efficacy and safety assessment**

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Disclosures

AvD is a consultant for BioMarin, Sanofi Genzyme, Novo Nordisk, Pfizer, uniQure, and Hematherix; **AG** is a consultant for Bioverativ, Genentech/Roche, BioMarin, and uniQure and serves as a speaker bureau of Bioverativ and Genentech/Roche; **EG** serves as a consultant for Genentech, Global Blood Therapeutics, CSL Behring, and Bayer; **PEM** and **SLQ** are employees of CSL Behring; **SWP** received a grant/research support from Bayer, BioMarin, Freeline, Novo Nordisk, and Roche/Genentech and is a consultant for ApcinteX, ASC Therapeutics, Bayer, Be Bio, BioMarin, CSL Behring, HEMA Biologics, Novo Nordisk, Pfizer, Regeneron/Intellia, Roche/Genentech, Sanofi, Spark Therapeutics, Takeda. Member of scientific advisory board for Equilibra Bioscience and Gene Ventiv.

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