PO037

Four-year results of etranacogene dezaparvovec in haemophilia B patients with pre-existing AAV5 neutralising antibodies: Phase 3 HOPE-B trial

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Introduction

- Gene therapy using an adeno-associated virus serotype 5 (AAV5) vector has the potential to revolutionise the treatment of haemophilia B (HB)
- However, neutralising antibodies (NAbs) may hinder delivery of the therapeutic gene by the AAV5 vector to the target cell, resulting in suboptimal or absent endogenous factor IX (FIX) levels[1]
- The Phase 3 HOPE-B trial (NCT03569891), studying the effect of a single dose of etranacogene dezaparvovec (CSL222, HEMGENIX®) in individuals with HB included participants with pre-existing AAV5 neutralising antibodies (NAb+); unique for haemophilia adeno-associated virus (AAV) gene therapy trials[2–4]
- Herein, previously unreported 4-year outcomes in NAb+ participants are presented

Objective

- **To evaluate long-term efficacy and safety of etranacogene dezaparvovec in the HOPE-B trial over 4 years in NAb+ participants**

Table 1: Baseline demographics in NAb+ participants

Characteristic	NAb+ participants (n=21)
Age, mean (SD, min–max), years	44.5 (17.5, 19–75)
Positive HIV status, n (%)	1 (4.8)
Prior hepatitis B, n (%)	5 (23.8)
Prior hepatitis C, n (%)	14 (66.7)
Severity of HB at diagnosis, n (%)	
Severe (FIX <1%)	16 (76.2)
Moderately severe (FIX ≥1% and ≤2%)	5 (23.8)
Pre-screening FIX treatment, n (%)	
Extended half-life	14 (66.7)
Standard half-life	7 (33.3)
Participants with zero reported bleeds during lead-in period, n (%)	3 (14.3)
Median (IQR) NAb titre	56.9 (23.3–198.9)

FIX, factor IX; HB, haemophilia B; HIV, human immunodeficiency virus; IQR, interquartile range; NAb+, with pre-existing neutralising antibodies; SD, standard deviation.

Results

EFFICACY

- Twenty subjects had a titre ≤678, 1 had a titre of 3,212, no patient had titre between 678 and 3,212; see **Figure 2** for NAb+ patient disposition
- All but two participants (excluded participants: high NAb titre 3,212, n=1; received ~10% dose, n=1) expressed FIX Padua
- Unadjusted annualised bleeding rate (ABR) for all bleeds decreased from 4.64 in lead-in to 1.18 in Months 7–48 post-treatment (75% reduction); ABR for spontaneous bleeds reduced from 2.17 to 0.46 in Months 7–48, with all participants free of spontaneous bleeds in Year 4 (**Figure 3**)
- Mean endogenous FIX activity levels were 35.9% (n=18) at Month 6 and stable at 33.7% (n=14) in Year 4 (**Figure 4**)
- FIX consumption decreased by 90%, from 245,476 IU/year during lead-in to 23,975 IU/year during Months 7–48 post-treatment (p<0.0001)
  - One patient returned to prophylaxis in Year 3 (previously reported), no subject returned to prophylaxis in Year 4

SAFETY

- Of the 339 reported events, 69% were mild, 25% were moderate and 6% were severe (**Figure 5**)
- No inhibitor development or thrombotic events were reported
- The most frequent adverse event (AE) was alanine transaminase elevation; 3 (14.3%) subjects received a transient course of reactive corticosteroid treatment. There are no signs of long-term hepatotoxicity
- Serious AEs (SAEs) unrelated to treatment were previously reported (hepatocellular carcinoma [HCC], n=1; death, n=1)
- During Year 4, 2 SAEs (glossopharyngeal schwannoma, n=1; myelodysplastic syndrome, n=1) were reported and confirmed unrelated to treatment by molecular analysis

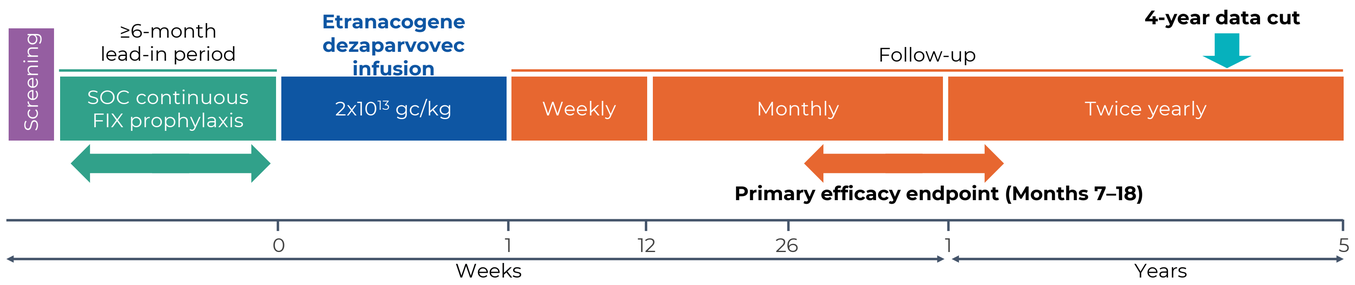
During 4 years of follow-up:

- **Mean ABR reduced by 75%**
- **FIX use reduced by 90%**
- **Stable FIX activity at 33.7% in Year 4**
- **No late treatment-related toxicities**

Methods

- 54 adult male participants with severe or moderately severe HB (FIX ≤2%) received a single infusion of etranacogene dezaparvovec after a ≥6-month lead-in period on their regular continuous FIX prophylaxis. Of these, 21 were NAb+ (**Figure 1**; **Table 1**)
- Efficacy and safety endpoints in NAb+ participants are reported over 4 years post-treatment (**Figure 2**)

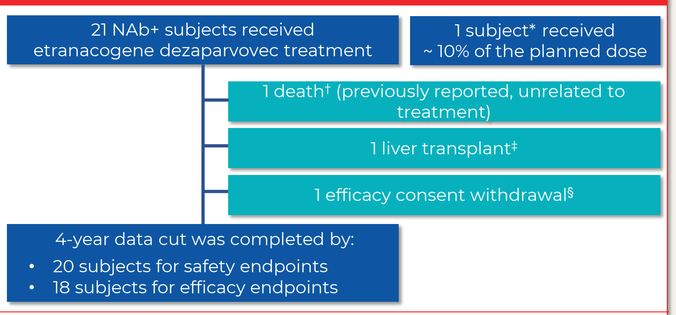
Figure 1: HOPE-B study design



- Phase 3, open-label, single-dose, single-arm, international trial (NCT03569891) in adult males with severe or moderately severe haemophilia B (FIX activity ≤2% of normal)
- Key exclusion criteria: FIX inhibitors, active hepatitis B/C infection, uncontrolled HIV infection, evidence of advanced liver fibrosis

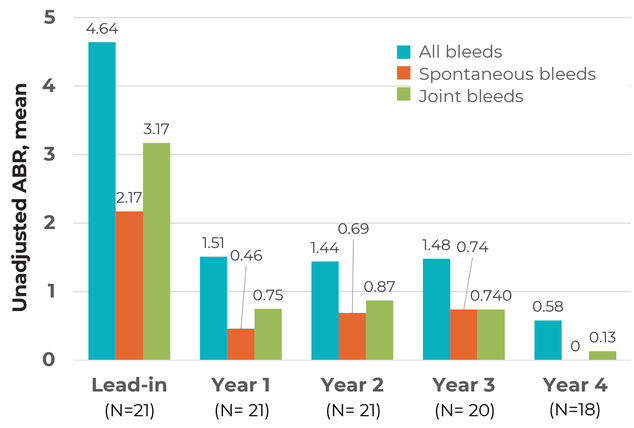
FIX, factor IX; gc, genome copies; HIV, human immunodeficiency virus; SOC, standard of care.

Figure 2: NAb+ participant disposition



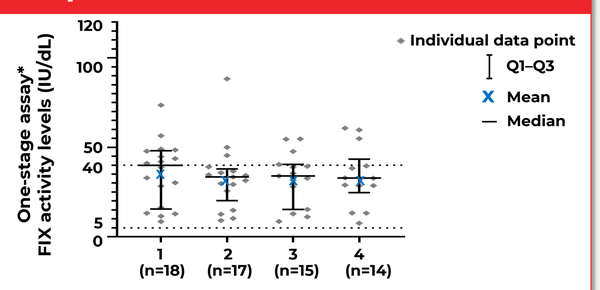
*One subject discontinued the infusion of etranacogene dezaparvovec due to a TEAE of Hypersensitivity after receiving ~10% of the full dose; they were excluded from the Responder Analysis Set. †One subject discontinued due to a non-treatment-related TEAE of Cardiogenic shock that resulted in death at 464 days postdose. ‡This subject was excluded from the efficacy analyses but included in the safety analyses. §One subject with the highest baseline AAV5 titre of 1:3,212 withdrew consent after 24 months postdose (this subject continues to be followed for safety through review of medical records).
AAV5, adeno-associated virus serotype 5; NAb+, with pre-existing neutralising antibodies; TEAE, treatment-emergent adverse event.

Figure 3: ABRs in NAb+ participants during ≥6-month lead-in vs Year 1–4 post-treatment



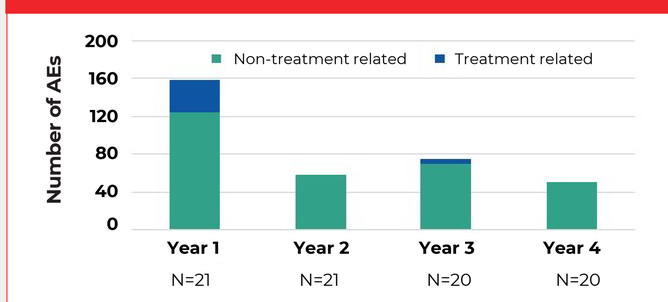
ABR, annualised bleeding rate; NAb+, with pre-existing neutralising antibodies.

Figure 4: Endogenous FIX activity levels in NAb+ participants at Year 1–4 post-treatment



*One-stage activated partial thromboplastin time (aPTT) FIX activity assay. Only uncontaminated samples included in the analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use. FIX, factor IX; Q1–Q3, interquartile range; NAb+, with pre-existing neutralising antibodies.

Figure 5: AEs in NAb+ participants by relation to treatment



AE, adverse event; NAb+, with pre-existing neutralising antibodies.

Conclusions

- **Etranacogene dezaparvovec is the only gene therapy providing adults with pre-existing NAbs long-term (≥4-year) stable FIX activity levels in the mild/normal range and bleed protection, with a favourable safety profile**

Disclosures

RK: is a consultant for Sobi, Sanofi, Roche/Chugai, Pfizer, Octapharma, Bayer, BioMarin, Takeda, Novo Nordisk, Grifols, Biotest and CSL Behring. **PVdV:** is a consultant for Bayer. **DQ:** is a consultant for Bayer, BioMarin, CSL Behring, Genentech/Roche, Novo Nordisk, Pfizer, Sanofi and Takeda, Speaker Bureau for: Bayer, BioMarin, CSL Behring, Genentech/Roche, Novo Nordisk, Pfizer, Sanofi and Takeda. **RSK:** is a consultant for BioMarin, CSL Behring, LFB and Pfizer. **FW, SLQ and PM:** are employees of CSL Behring. **CH:** is a consultant for Bayer, Takeda, Roche, CSL Behring, Novo Nordisk, Pfizer, Sobi, LFB, Octapharma, uniQure and BioMarin.

References

1. Batty P, *et al*. *Hemasphere*. 2021;5(3):e540
2. Pipe SW, *et al*. *N Engl J Med*. 2023;388:706–718
3. Coppens M, *et al*. *The Lancet Haematology*. 2024;11(4):e265–e275
4. HEMGENIX. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/hemgenix-epar-product-information_en.pdf. Accessed December 2024

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