PO040

Four-year results of etranacogene dezaparvovec in haemophilia B patients without pre-existing AAV5 neutralising antibodies: Phase 3 HOPE-B trial

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Introduction

- In contrast to most adeno-associated virus (AAV)-based gene therapy clinical trials, the Phase 3 HOPE-B trial (NCT03569891) demonstrated the superiority of etranacogene dezaparvovec (CSL222, HEMGENIX®) over continuous factor IX (FIX) prophylaxis both in patients with and without pre-existing neutralising antibodies (NAbs)[1-3]
- Long-term data on HOPE-B participants without NAbs (NAb-) are necessary for accurate indirect comparison to other haemophilia B (HB) gene therapy trials

Objective

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

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, 33 were NAb- (**Figure 1**; **Table 1**)
- Efficacy and safety endpoints in this NAb- group are reported over 4 years post-treatment

Table 1: Baseline demographics

Characteristic	NAb- participants (n=33)
Age, mean (SD, min–max), years	39.5 (14.5, 21–73)
Positive HIV status, n (%)	2 (6.1)
Prior hepatitis B, n (%)	4 (12.1)
Prior hepatitis C, n (%)	17 (51.5)
Severity of HB at diagnosis, n (%)	
Severe (FIX <1%)	28 (84.8)
Moderately severe (FIX ≥1% and ≤2%)	5 (15.2)
Pre-screening FIX treatment, n (%)	
Extended half-life	17 (51.5)
Standard half-life	16 (48.5)
Participants with zero reported bleeds during lead-in period, n (%)	11 (33.3)

FIX, factor IX; HB, haemophilia B; HIV, human immunodeficiency virus; NAb-, without pre-existing neutralising antibodies; SD, standard deviation.

Results

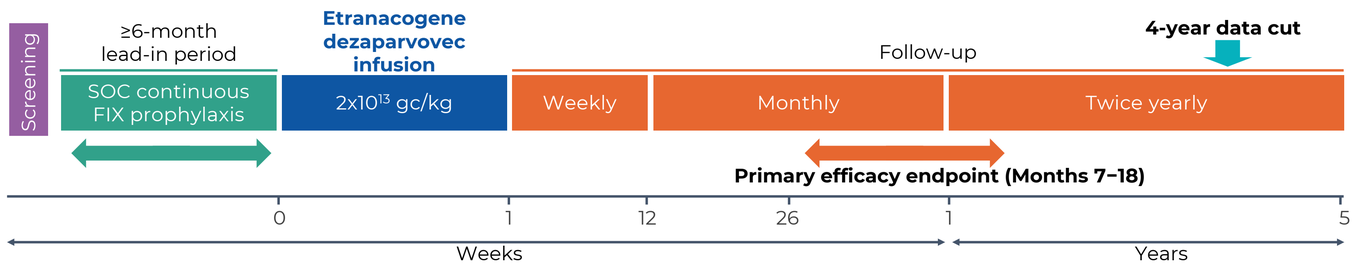
EFFICACY

- All 33 NAb- participants completed 4-year follow-up
- Annualised bleeding rate (ABR), spontaneous (AsBR) and joint (AjBR) were reduced compared to lead-in period year on year after etranacogene dezaparvovec infusion (**Figure 2**)
- Over four years of follow-up, mean adjusted ABR for all bleeds reduced by 85%, AsBR reduced by 89%, and AjBR reduced by 94% during Months 7–48 post-treatment (p<0.0001) (**Figure 3**)
- FIX-treated bleeds made up 81.6% of total bleeds during lead-in and 37.2% post-treatment
- All 33 NAb- participants expressed FIX Padua
- Mean (standard deviation, n) endogenous FIX activity level was 40.6% (18.6, n=33) at Month 6, remained stable over 4 years post-treatment, and was 39.0% (16.8, n=33) at Year 4 (**Figure 4**)
  - Median (range, n) FIX activity level at Year 4 was 35.7 (4.7–80.1, n=33)
- No participants returned to continuous FIX prophylaxis
- FIX consumption decreased by 99%, from 264,888 IU/year during lead-in to 1,878 IU/year during Months 7–48 post-treatment (p<0.0001)

During 4 years of follow-up:

- **Mean ABR reduced by 85%**
- **0 patients returned to prophylaxis**
- **Stable FIX activity at 39%**
- **Favourable safety profile**

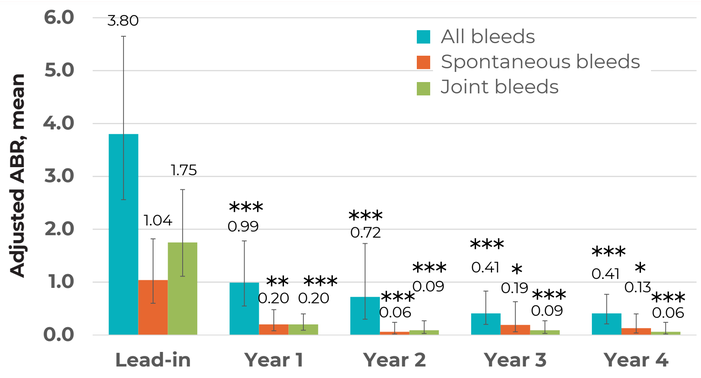
Figure 1: HOPE-B study design



- 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

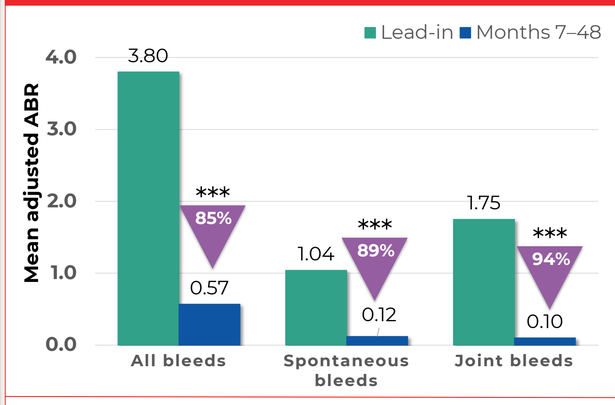
FIX, factor IX; gc, genome copies; HIV, human immunodeficiency virus; SOC, standard of care.

Figure 2: ABRs in NAb- participants during ≥6-month lead-in vs Years 1–4 post-treatment (n=33)



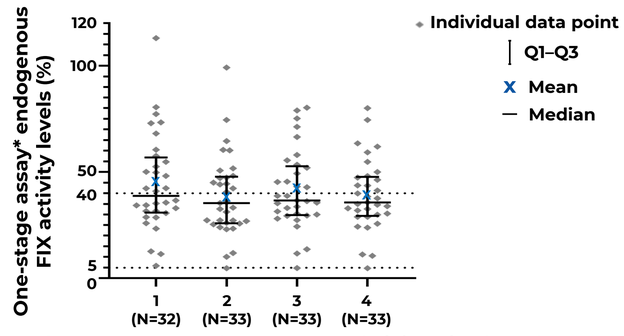
*p<0.01, **p<0.0001, ***p<0.0001 vs lead-in period. Error bars show 95% confidence interval. ABR, annualised bleeding rate; NAb-, without pre-existing neutralising antibodies.

Figure 3: Comparison of ABR between lead-in and Months 7–48 overall in NAb- participants



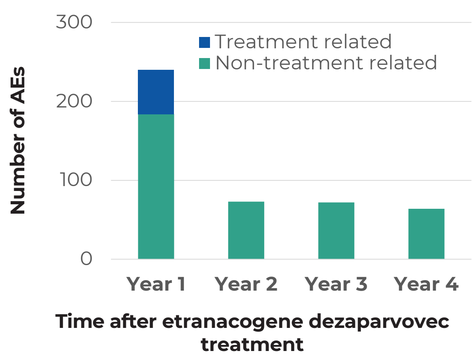
***p<0.0001 vs lead-in period. ABR, annualised bleeding rate; NAb-, without pre-existing neutralising antibodies.

Figure 4: Endogenous FIX activity levels in NAb- participants in Years 1–4 post-treatment



*One-stage activated partial thromboplastin time (aPTT) FIX activity assay. Only uncontaminated samples were included in analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use. FIX, factor IX; NAb-, without pre-existing neutralising antibodies; Q1–Q3, interquartile range.

Figure 5: AEs in NAb- participants by relation to treatment (n=33)



AE, adverse event; NAb-, without pre-existing neutralising antibodies.

Results

SAFETY

- **No events of genotoxicity associated with AAV5 integration were observed**
- Of the 455 reported adverse events (AEs) (**Figure 5**), 78% were mild, 19% moderate and 3% severe. There were **no treatment-related serious AEs, inhibitor development or thrombotic events**
- The most frequent AE was an elevation in alanine transaminase, with 6/33 (18.2%) of participants receiving a reactive transient course of corticosteroid treatment
- No persistent late hepatotoxicity was observed, even in participants who experienced early liver inflammation and those with a history of chronic viral hepatitis

Conclusions

- **All AAV5 NAb- HOPE-B trial participants expressed FIX Padua; mean FIX activity was in the near-normal range and was stable over 4 years**
- **Durable bleed protection was achieved with no patients returning to continuous FIX prophylaxis**
- **Treatment-related AEs were nearly absent after the first 6 months following gene therapy; specifically, no events of AAV5-associated genotoxicity and no persistent late hepatotoxicity were observed**

Disclosures

PR: Grant/Research support from: BioMarin, CSL Behring, Pfizer, Sobi, Takeda and LFB, Consultant for: BioMarin, CSL Behring, Pfizer, Sobi, Takeda and LFB. **NOC:** Grant/Research support from: Sobi, Consultant for: AstraZeneca, CSL Behring and Sobi, Speaker Bureau of: Bayer, CSL Behring, Takeda, Sobi and Sanofi. **PV:** Consultant for: CSL Behring, Roche, CAP-DCF, Bayer HealthCare, LeoPharma, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Sanofi-Aventis and ThromboGenics. **PK:** Consultant for: BioMarin, CSL Behring and Novo Nordisk AS, Speaker Bureau of: CSL Behring. **RL:** Consultant for: CSL Behring and Novo Nordisk. **FW, PM and SLQ:** Employees of CSL Behring. **FL:** Grant/Research support from: CSL Behring, Takeda, uniQure, Sobi, Consultant for: CSL Behring, Takeda, uniQure, BioMarin, Roche.

Acknowledgements

Medical writing support was provided by Mario Pahl, Bioscript Group, Macclesfield, UK, in accordance with Good Publication Practice guidelines, and funded by CSL Behring.

Presented at the 18th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) meeting, Milan, Italy; February 4–7, 2025.

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Funding

This study was funded by CSL Behring.

CSL Behring