PO028

Adult Patients With Hemophilia B and With a History of Chronic HCV/HBV Infection Receiving Liver Directed Gene Therapy Demonstrated Long-Term Bleeding Protection And Sustained FIX Activity: Efficacy and Safety Results 3 Years After Administration of a Single Dose of Etranacogene Dezaparvovec

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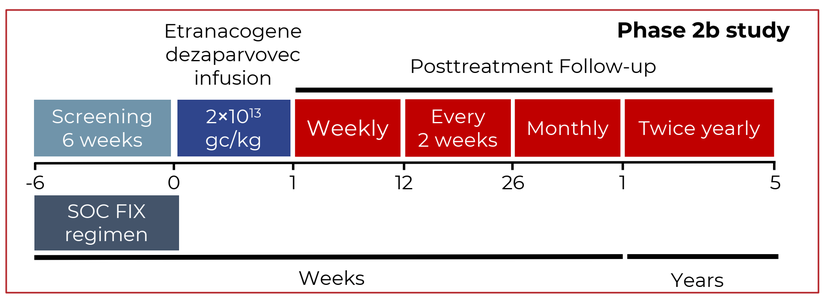
Introduction

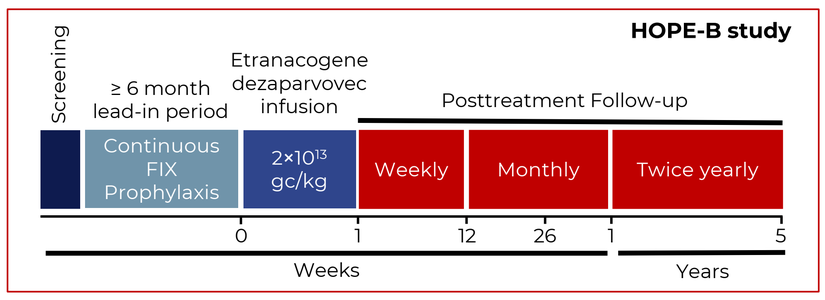
- Liver-targeted recombinant adeno-associated virus (rAAV) gene therapy for hemophilia B has become a real-world therapeutic option for an adult population burdened with prevalent co-morbid chronic hepatitis C virus (HCV) and hepatitis B virus (HBV)[1] .
- The phase 2b (NCT03489291) and pivotal phase 3 HOPE-B (NCT03569891) trials evaluated the efficacy and safety of etranacogene dezaparvovec (CSL222, formerly AMT-061), an AAV5 vector, containing a codon-optimized, highly active factor IX (FIX) Padua R338L transgene under the control of the liver-specific promoter LP-1[2,3] .
- A history of chronic HCV and / or HBV was not an exclusion criteria in the phase 2b or HOPE-B trials

Objective

- **To evaluate the efficacy and safety of etranacogene dezaparvovec in the subset of phase 2b and HOPE-B participants with a history of chronic HCV and / or HBV.**

Figure 1: Phase 2b and HOPE-B Study Design





SOC, standard of care; FIX, Factor IX; gc/kg, genome copies/kilogram

Methods

- Adult male participants with severe or moderately severe hemophilia B (FIX activity ≤ 2%) were infused with a single dose of etranacogene dezaparvovec (2x10[13] gc/kg) as shown in **Figure 1.**
  - HOPE-B participants had a ≥ 6-month lead-in period, preceding infusion, in which they received standard of care FIX prophylaxis and recorded data about their bleeds.
- Relevant exclusion criteria included:
  - Alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, or alkaline phosphatase levels > 2x the upper limit of normal (ULN)
  - Active HCV (HCV RNA detectable)
  - Active HBV (HBV DNA detectable or HBV surface antigen [HBsAg] reactive)
  - Uncontrolled HIV infection (CD4+ T cell count ≤ 200 cells/μL)
  - HOPE-B only: advanced liver fibrosis (FibroScan™ score of ≥ 9 kPa)
- Regular liver ultrasounds, liver chemistries, and alpha fetoprotein levels were collected along with activated partial thromboplastin time (aPTT)-based FIX activity and bleeding data.
- Guidance was provided for oral corticosteroid treatment in response to early posttreatment ALT elevations to > ULN or ≥ 2x the participant's baseline.
- Data shown includes all participants with at least one uncontaminated FIX activity measurement (> 5 half-lives from an exogenous FIX use) in the posttreatment period.
  - Two HOPE-B participants were excluded from the analyses shown on this poster. These participants did not have efficacy and remained on exogenous FIX prophylaxis (one received only a 10% partial dose; one had a baseline AAV5 neutralizing antibody [NAb] titer of 1:3212).

Results

STUDY PARTICIPANTS

- 57 participants received etranacogene dezaparvovec in the phase 2b (n=3) and HOPE-B (n=54) trials. 55 of the 57 had at least one posttreatment uncontaminated FIX activity measurement (**Table 1**).
- 34 of the 55 participants (62%) had a history of chronic HCV and / or HBV infection (HCBV+).
  - All 3 phase 2b participants had a history of chronic HCV; 2 of the 3 had co-morbid HIV infection.
- HCBV+ participants were older than HCBV- participants.

Table 1: Baseline Characteristics

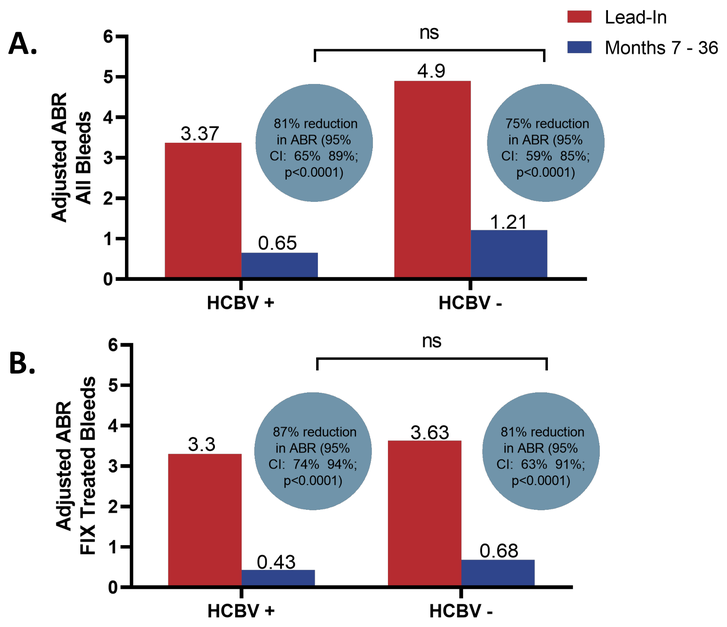
Participants with ≥ 1 posttreatment uncontaminated FIX activity measurement	HCBV + n=34	HCBV- n=21
Clinical Trial		
Phase 2b	3	-
HOPE-B	31	21
Hepatitis infection history		
HCV only (HCV RNA udt)	21	-
HBV only (HBeAb rt, HBsAg nrt, HBV DNA udt)	2	-
HCV / HBV (HCV RNA udt, HBsAg nrt, HBV DNA udt)	7	-
HCV / HIV (HCV RNA udt, HIV DNA nrt, CD4+ count > 200 μL)	4	-
Age, y, median (range)	49 (31 – 75)	26 (19 – 54)
Detectable AAV5 NAbs, n (range of NAb titer)	17 (8.5 – 678.2)	5 (23.3 – 449.9)
Baseline ALT > ULN*, n (%)	2 (5.9)	3 (14.3)
Baseline ALT value, U/L, median (range)	15.5 (7 – 109)	22 (8 – 65)

*Baseline ALT is the pre-dose value collected on the day of etranacogene dezaparvovec dosing and ULN = 41 U/L.
HCBV, history of chronic hepatitis C or B virus; HCV, hepatitis C; udt, undetectable; HBV, hepatitis B; HBeAb, hepatitis B e-antibody; rt, reactive; HBsAg, hepatitis B surface antigen; nrt, nonreactive; y, years; AAV5, adeno-associated virus 5; NAbs, neutralizing antibodies; ALT, alanine aminotransferase; ULN, upper limit of normal; U/L, units/liter

ABR

- In HOPE-B, the annualized bleeding rate (ABR) for all bleeds and for FIX-treated bleeds (**Figure 2A / 2B**) was significantly reduced in posttreatment months 7- 36 compared to the lead-in period in both HCBV+ and HCBV- participants.
- There was no significant difference in the treatment effect for all bleeds or for FIX-treated bleeds between HCBV+ and HCBV- participants.

Figure 2: ABRs in All Bleeds and FIX-Treated Bleeds*

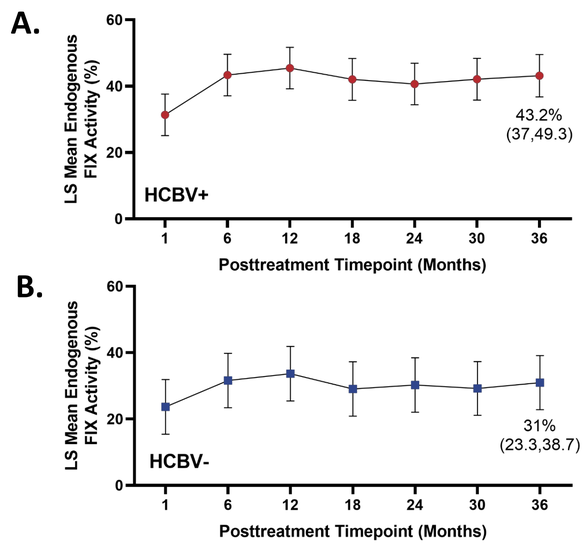


*Phase 2b had no lead-in period; data represents ABRs in HOPE-B HCBV+ (n=31) and HCBV- (n=21) participants. Results are from a negative binomial generalized estimating equation using uncontaminated at-risk time as an off-set term adjusted for analysis phase, HCBV, and the interaction of analysis phase and HCBV.
ns, not significant; ABR, annualized bleeding rate; HCBV, history of chronic hepatitis C or B virus; CI, confidence interval; FIX, Factor IX

FIX ACTIVITY

- Stable and clinically relevant endogenous FIX activity was observed up to 36 months posttreatment in both the HCBV+ and HCBV- groups in all but one participant (**Figure 3A / 3B**).
- One HCBV+ participant, who experienced an early >2x baseline ALT elevation (**Figure 4B**, green symbols) treated with corticosteroids, returned to prophylaxis at Month 30 due to loss of etranacogene dezaparvovec expression (FIX activity decreased to < 5% with increased clinical bleeding).

Figure 3: Endogenous FIX Activity*

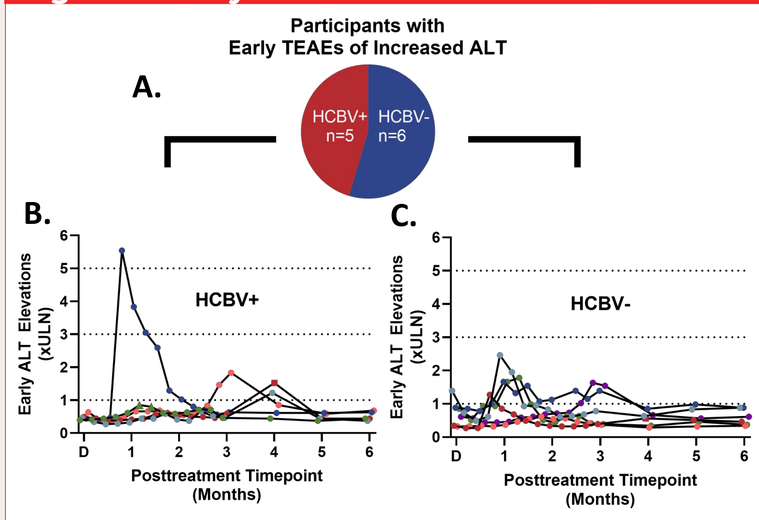


*Endogenous FIX activity was assessed with a one-stage aPTT-based assay. Data represents LS mean and 95% CI from subjects who had an uncontaminated value at the given collection visit (n= 29 – 34 HCBV+ and n= 19 – 21 HCBV- participants at each time point). Results use a mixed model for repeated measures treating subjects as random effects with an auto-regressive co-variance structure, adjusted for hepatitis group, visit, and the interaction of hepatitis group and visit.
FIX, Factor IX; CI, confidence interval; LS, least square; HCBV, History of chronic hepatitis C or B virus

LIVER SAFETY

- Twelve early (≤ 4 months posttreatment) treatment emergent adverse events (TEAEs) of "Increased ALT" were observed in 11 participants as shown in **Figure 4A**. 9 of the 11 participants (4 HCBV+; 5 HCBV-) received corticosteroids as treatment for these elevations.
- One HCBV+ participant had a peak ALT elevation > 5x ULN that normalized with corticosteroid treatment (**4B**). All other early ALT elevations in either HCBV+ or HCBV- participants were < 3x ULN (**4B / 4C**).
- As previously reported, a per-protocol abdominal ultrasound at 1-year posttreatment identified a hepatocellular carcinoma in one HCBV+ participant[3]. Molecular analysis demonstrated that this cancer was not related to etranacogene dezaparvovec treatment.

Figure 4: Early TEAEs of Increased ALT



Each line represents an individual participant with a TEAE of "Increased ALT" within 4 months following infusion with etranacogene dezaparvovec in HCBV+ (**B**) or HCBV- (**C**) participants. In one HCBV+ subject (green symbols), ALT elevation was > 2x baseline only. These elevated values are indicated with triangles. In another HCBV+ subject (red symbols), ALT elevations were observed in local laboratory data only. For these timepoints, local laboratory values are represented (square symbol). All other data are central laboratory values.
TEAE, treatment emergent adverse event; ALT, alanine aminotransferase; HCBV, History of chronic hepatitis C or B virus; ULN, upper limit of normal

Conclusions

- **All participants in phase 2b and the majority of participants in HOPE-B had a history of chronic HCV and / or HBV infection without active viral disease or evident pre-existing severe liver fibrosis'**
- **Etranacogene dezaparvovec was observed to be safe and effective in this subpopulation and had similar safety and efficacy characteristics as participants without a history of chronic HCV and / or HBV infection.**
- **These results support use of etranacogene dezaparvovec for eligible participants with co-morbid controlled chronic HCV or HBV.**

Disclosures

Disclosures: O'Connell: Sobi: Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; F. Hoffmann-La Roche Ltd: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; UniQure: Membership on an entity's Board of Directors or advisory committees; Freeline: Membership on an entity's Board of Directors or advisory committees; Novo Nordisk: Speakers Bureau. **Verhamme:** CSL Behring, Roche, CAP-DCF, Bayer HealthCare; LeoPharma; Boehringer Ingelheim; Daiichi Sankyo; Pfizer; Sanofi-Aventis; ThromboGenics: Consultancy. **Meijer**: Alexion and CSL Behring: Speakers Bureau; Bayer: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; UniQure: Consultancy; Octapharma: Membership on an entity's Board of Directors or advisory committees. **van der Valk**: Bayer: Consultancy. **Kazmi**: BioMarin Pharmaceuticals, CSL Behring: Consultancy. **Galante**: CSL Behring: Current Employment. **LeQuellec**: CSL Behring: Current Employment. **Church**: CSL Behring: Current Employment. **Lucas**: CSL Behring: Current Employment. **Castaman**: CSL Behring, Pfizer, Sobi, Speaker Bureau of: Bayer, Biomarin, Roche, Sobi, Grifols, LFB, Novo Nordisk, Werfen, Kedrion, uniQure: Research Funding. **Monahan**: CSL Behring: Current Employment.

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