PO185

HIV Comorbid Infection and Liver-Directed AAV-Based Gene Therapy in Adults with Severe and Moderately Severe Hemophilia B: Efficacy and Safety Results from Phase 2b and the Pivotal Phase 3 HOPE-B Trials 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec

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Introduction

- An important subset within the hemophilia community is people living with human immunodeficiency virus (HIV)
  - HIV infection was a complication of blood transfusions during the era of contamination of blood products and their derivatives with blood-borne viruses in the 1980s[1-3]
  - Therapy for HIV has reduced the viral burden and allowed many patients to live longer, healthier lives[4]
- Concerns about increased hepatotoxicity of liver-directed adeno-associated viral (AAV) vectors[5-7] in patients receiving potentially hepatotoxic HIV medications, such as efavirenz,[8] have excluded this population from participating in many of the gene therapy hemophilia trials
- However, adult patients with hemophilia B (PwHB) with controlled HIV comorbid infection were not excluded from enrollment in phase 2b (NCT03489291)[9] and phase 3 HOPE-B (NCT03569891)[10] trials
- Both trials evaluate the efficacy and safety of etranacogene dezaparvovec (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
  - Etranacogene dezaparvovec is the first approved liver-directed AAV-based gene therapy product for the treatment of participants with severe or moderately severe hemophilia B in the US, Europe, UK, and Canada

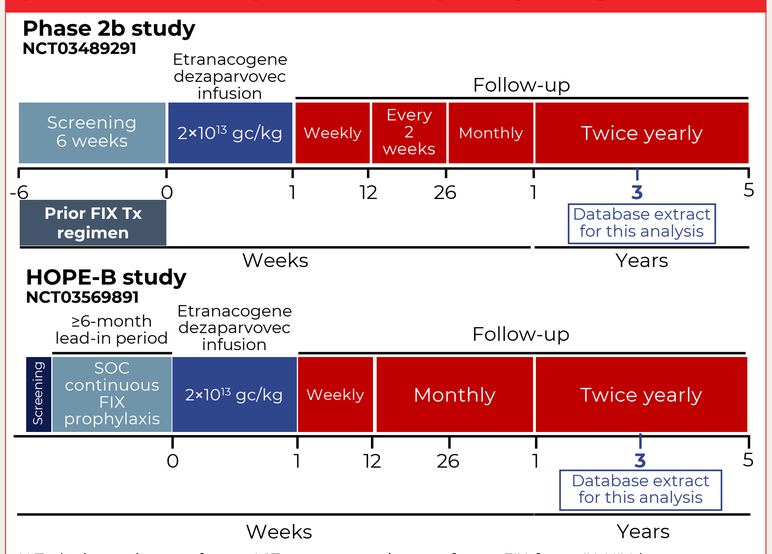
Objective

- **To evaluate the efficacy and safety of etranacogene dezaparvovec in the subset of adult PwHB with comorbid infection with HIV from both the phase 2b and the phase 3 HOPE-B trials**

Methods

- A single IV administration of 2×10^{13} gc/kg etranacogene dezaparvovec was administered to adult participants with severe or moderately severe hemophilia B in phase 2b and phase 3 HOPE-B trials (**Figure 1**)
- Eligibility criteria for both trials are seen in **Table 1**
  - Participants with HIV infection uncontrolled by antiviral therapy, as demonstrated by CD4+ counts ≤200/µL, were excluded from the studies
- Efficacy and safety outcomes of each participant with controlled HIV infection treated with etranacogene dezaparvovec were assessed
- Liver enzyme levels and activated partial thromboplastin time (aPTT)-based FIX activity levels were analyzed by a central laboratory
- Descriptive statistical analyses were used to report all results with a data cut at 3 years post administration of etranacogene dezaparvovec

Figure 1. Overview of phase 2b (NCT03489291) and phase 3 HOPE-B (NCT03569891) study designs



ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIX, factor IX; HIV, human immunodeficiency virus; ULN, upper limit of normal

Results

STUDY PARTICIPANTS

- Among 57 participants who received etranacogene dezaparvovec in phase 2b and phase 3 HOPE-B trials, 5 had comorbid HIV infection (**Table 2**)
- Median [range] age was 49 years [38-54]
  - Four participants had a history of treated hepatitis C virus infection with a negative viral load
- Three out of 5 participants with comorbid HIV infection had pre-existing AAV5 neutralizing antibodies with median [range] titer of 20 [0-99] (**Table 2**)

Table 1. Main eligibility criteria

Inclusion criteria Phase 2b	Exclusion criteria Phase 2b/Phase 3 HOPE-B
Male adult with congenital hemophilia B (known moderately severe or severe FIX deficiency*)	History of FIX inhibitor or positive FIX inhibitor test; previous gene therapy treatment; receipt of an experimental agent
>20 previous exposure days of treatment with FIX protein	Elevated (>2 × ULN) ALT, AST, total bilirubin, alkaline phosphatase and creatinine
	HIV+ not controlled with anti-viral therapy as shown by CD4+ counts ≤200/µL
Inclusion criteria Phase 3 HOPE-B	Known severe infection (including hepatitis B or C) or any other significant concurrent, uncontrolled medical condition
Male adult with congenital hemophilia B with known severe or moderately severe FIX deficiency†	Known coagulation disorder other than hemophilia B
>150 previous exposure days of treatment with FIX protein	Platelet count below 50 × 10^9/L, at screening and final lead-in visit
On stable prophylaxis for at least 2 months prior to screening	Hypersensitivity to FIX products, any component of the therapy or corticosteroids

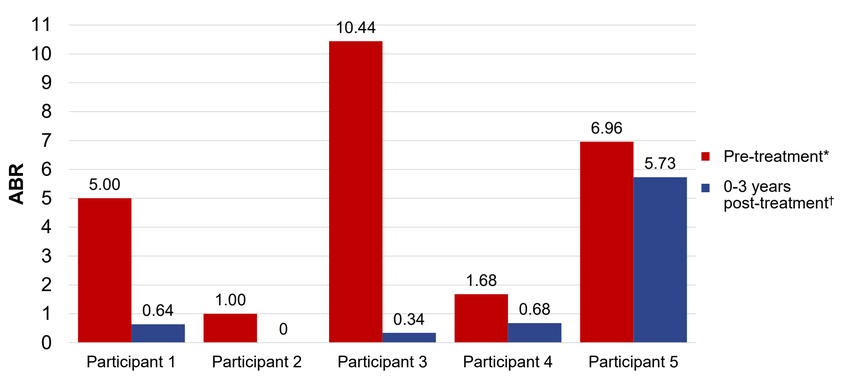
*Moderately severe deficiency (1-2% of normal circulating FIX) and a severe bleeding phenotype (on continuous routine FIX prophylaxis and/or on demand FIX replacement therapy with a history of frequent bleeding or chronic hemophilic arthropathy in one or more joints). Severe deficiency (<1% of normal circulating FIX) for which the participant is on continuous routine FIX prophylaxis or using on-demand FIX replacement therapy.
†≤2% of normal circulating FIX for which the participant was on continuous routine FIX prophylaxis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIX, factor IX; HIV, human immunodeficiency virus; ULN, upper limit of normal.

Table 2. Participant with comorbid HIV infection demographics at the day of infusion and medication use

Participant	Trial	Age, years	Prior history of HBV	Prior history of HCV	AAV5 NAb titer	Prior FIX use	Anti-HIV medication
Participant 1	Phase 2b	47	No	Yes	20	EHL prophylaxis	Cabotecavir, rilpivirin, dolutegravir, emtricitabine, tenofovir
Participant 2	Phase 2b	50	No	Yes	33	EHL prophylaxis	Efavirenz, emtricitabine, tenofovir rilpirvirine
Participant 3	HOPE-B	54	No	No	0	SHL prophylaxis	Lamivudin, abacavir, dolutegravir
Participant 4	HOPE-B	49	No	Yes	0	SHL prophylaxis	Dolutegravir, emtricitabine, tenofovir
Participant 5	HOPE-B	38	No	Yes	99	EHL prophylaxis	Emtricitabine, bictagravir, tenofovir
Participants 1-5, median [range]		49 [38-54]			20 [0-99]		

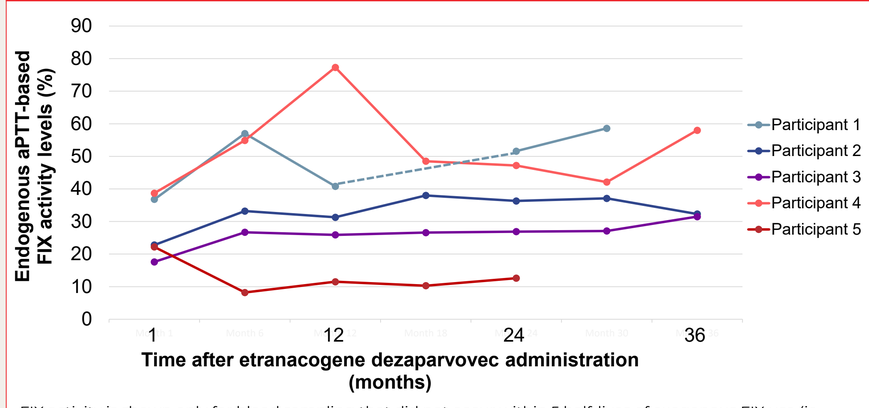
AAV5, adeno-associated virus type 5; EHL, extended half-life; FIX, factor IX; HBV, hepatitis B virus; HCV, hepatitis C virus; NAb, neutralizing antibody; SHL, standard half-life.

Figure 2. ABR (all bleeding types) with etranacogene dezaparvovec in participants with comorbid HIV infection



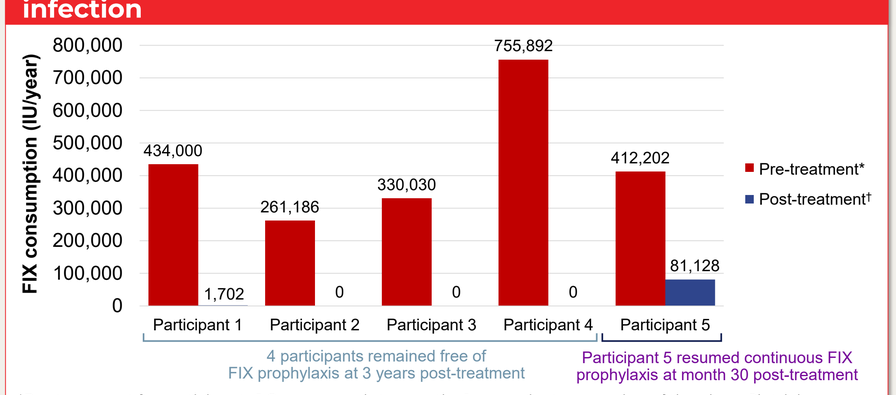
*Pre-treatment for participants 1-2 corresponds to over the 1-year prior to screening of the phase 2b trial, pre-treatment period for participants 3-5 corresponds to the >6-month lead-in period of HOPE-B trial.
†Post-treatment period refers to post-continuous prophylaxis.
ABR, annualized bleeding rate.

Figure 3. Endogenous aPTT-based FIX activity* levels after administration of etranacogene dezaparvovec in the 5 participants with comorbid HIV infection



FIX activity is shown only for blood sampling that did not occur within 5 half-lives of exogenous FIX use (ie, "uncontaminated" data). Dotted line represents missing data.
aPTT, activated partial thromboplastin time; FIX, factor IX.

Figure 4. FIX consumption (excluding invasive procedures) with etranacogene dezaparvovec in participants with comorbid HIV infection



*Pre-treatment for participants 1-2 corresponds to over the 1-year prior to screening of the phase 2b trial, pre-treatment period for participants 3-5 corresponds to the >6-month lead-in period of HOPE-B trial.
†Post-treatment period refers to post-continuous prophylaxis.
FIX, factor IX.

ABR

- Annualized bleeding rate (ABR) decreased post-treatment compared with previous FIX prophylaxis regimen (with extended half-life FIX products) for all participants who were HIV+ (**Figure 2**)
- Median [range] ABR pre-treatment was 5 [1.0-10.4], and post-treatment was 0.64 [0-5.73]
- Bleeds post-treatment were
  - Participant 1: 1 spontaneous and 1 traumatic bleed in year 2
  - Participant 2: no bleeds
  - Participant 3: 1 traumatic bleed in year 1
  - Participant 4: 2 traumatic bleeds in year 2
  - Participant 5: 3 spontaneous, 1 spontaneous, and 8 (5 spontaneous + 3 traumatic) bleeds in years 1, 2, 3, respectively

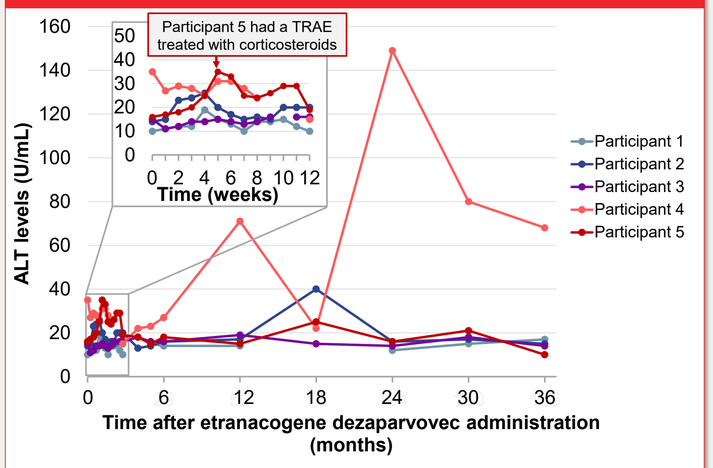
FIX ACTIVITY

- FIX activity levels in these participants were apparent from week 3 and were maintained for 3 years in the mild/normal range for 4/5 (80%) participants (**Figure 3**)
- Median [range] endogenous FIX at 3 years post-treatment was 32% [31.5%-58.0%]
- Participants 1 and 5 had uninterpretable endogenous FIX measurements at 3 years post treatment
  - Participant 5 eventually had his FIX levels declined to 2%-5% range, his bleeding phenotype returned, and he resumed prophylaxis per protocol at month 30 post-treatment
  - Participant 1 took on-demand replacement therapy the day before the 3-year visit

FIX REPLACEMENT PRODUCT USE

- Annualized FIX use (IU/year) was reduced between 80% and 100% (**Figure 4**):
- 4 participants remained free of FIX prophylaxis though 3 years post-treatment
  - Among which 3 participants received no FIX infusions
  - Participant 1 received 1,705 IU/year in year 1, and 3,400 IU/year in year 2
- Participant 5 resumed continuous FIX prophylaxis at month 30 post-treatment
  - FIX use was 34,937 in year 1, 4,102 in year 2, and 204,622 IU/year in year 3

Figure 5. ALT levels after administration of etranacogene dezaparvovec in the 5 participants with comorbid HIV infection



ALT, alanine transaminase; TRAE, treatment-related adverse events.

SAFETY

- No treatment-related serious adverse events (AEs) occurred
- Only 7 treatment-related AEs were reported in 3 participants
  - Treatment-related ALT elevation of moderate severity occurred in participant 5 (n/N=1/5, 20%, similar to participants without HIV comorbid infection) at 35 days post-treatment and resolved within 15 days with the use of corticosteroids (**Figure 5**)
  - ALT elevation of participant 4 at month 24 was judged related to alcohol use. No change in HIV medication was noted

Conclusions

- **Etranacogene dezaparvovec was observed to be safe and effective in a subset of study participants living with HIV, while receiving concomitant HIV medication**
- **These results support the use of etranacogene dezaparvovec for eligible participants with controlled comorbid HIV infection**
- **Owing to the small number of participants with HIV being enrolled in trials, long-term collection of data and special attention in the real-world setting is recommended**

Disclosures

Pipe: Regeneron/Intellia: Consultancy; Roche/Genentech: Consultancy; Sanofi: Consultancy; Takeda: Consultancy; Pfizer: Consultancy; Novo Nordisk: Consultancy; LFB: Consultancy; Freeline: Consultancy; HEMA Biologics: Consultancy; GenVentiv: Consultancy; Equilibra Bioscience: Consultancy; CSL Behring: Consultancy; BioMarin: Consultancy; Bayer: Consultancy; ASC Therapeutics: Consultancy; Apcintex: Consultancy; Spark Therapeutics: Consultancy; uniQure: Consultancy. **Gomez**: Chieisi USA, Inc., and Global Blood Therapeutics Inc: Consultancy. **Hermans**: Bayer, Takeda, Roche, CSL Behring, Novo Nordisk, Pfizer, Sobi, LFB, OctaPharma, Uniqure and Biomarin: Consultancy. **Giermasz**: Bayer: Honoraria, Membership on an entity's Board of Directors or advisory committees; BioMarin Pharmaceutical Inc.: Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel grants; uniQure: Honoraria, Membership on an entity's Board of Directors or advisory committees; Genentech: Honoraria, Membership on an entity's Board of Directors or advisory committees; Novo Nordisk: Honoraria, Membership on an entity's Board of Directors or advisory committees; Pfizer: Honoraria, Membership on an entity's Board of Directors or advisory committees; Sanofi Genzyme: Honoraria, Membership on an entity's Board of Directors or advisory committees; Bioverativ, Genentech/Roche, Biomarin, uniQure, American Thrombosis and Hemostasis Network: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Kampmann**: CSL Behring, Novo Nordisk, and BioMarin pharmaceuticals: Consultancy. **Lemons**: CSL Behring and NovoNordisk: Consultancy. **Galante**: CSL Behring: Current Employment. **LeQuellec**: CSL Behring: Current Employment. **Monahan**: CSL Behring: Current Employment.

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