IX-TEND: A Phase IV Observational, Long-term Follow-up Study on the Safety and Efficacy of Etranacogene Dezaparvovec in Patients with Hemophilia B

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Introduction

- Hemophilia B therapy goals include prevention and prompt treatment of spontaneous bleeding episodes[1,2]
  - However, factor IX (FIX) replacement, the current standard for long-term care of hemophilia B, is not curative[3-5]
- Etranacogene dezaparvovec is an adeno-associated virus type 5 vector containing a highly active FIX Padua transgene approved in the US and Europe[6,7]
- The Phase 3 HOPE-B trial (NCT03569891) evaluated the efficacy and safety of etranacogene dezaparvovec in patients with hemophilia B and demonstrated a significant reduction in bleeding and FIX consumption with a favorable safety profile[8]
- Long-term safety and efficacy data from real-world patient populations are essential for continuously assessing long-term outcomes in a broad, post-approval patient population and ensuring safety and efficacy standards are maintained[9,10]
- This Phase 4 IX-TEND study (NCT06008938) is an observational post-authorization cohort study that evaluates the long-term safety and efficacy of etranacogene dezaparvovec in the commercial healthcare setting
  - The IX-TEND study gathers data from multiple sources, such as local patient registries and investigator (PI) reports from various sites, and consolidates it into a unified analytical repository
  - The centralized database allows for a holistic analysis of gene therapy outcomes in different geographic regions and healthcare systems allowing us to assess the variability in treatment outcomes, safety profiles, and patient experiences across diverse real-world populations

Objective

- **To investigate the short- and long-term safety and effectiveness of commercial etranacogene dezaparvovec treatment in patients with hemophilia B**

Methods

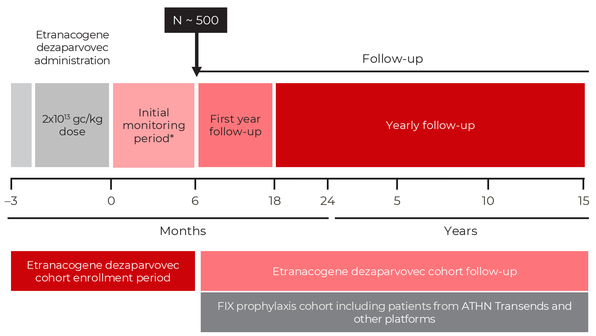
STUDY DESIGN

- This is an observational, post-authorization, multicenter, multi-country, long-term follow-up study to investigate the short- and long-term effectiveness and safety of treatment with etranacogene dezaparvovec in adults with hemophilia B
- This study will collect data from 2 patient cohorts for analysis with each cohort targeting enrollment of ~250 patients each (**Figure 1**)
- Patients with hemophilia B will be included and given either:
  - Commercially available etranacogene dezaparvovec as a single intravenous infusion (Etranacogene dezaparvovec cohort)
  - FIX prophylaxis while enrolled in the US American Thrombosis and Hemostasis Network (ATHN) Transcends (A Natural History Observational Cohort Study of the Safety, Effectiveness, and Practice of Treatment in People with Non-Neoplastic Hematologic Disorders) or in local registries in other countries (FIX prophylaxis cohort)
- Inclusion and exclusion criteria for each cohort are listed in **Table 1**
- Effectiveness and safety data during and after treatment at predetermined time points and medical history will be collected
  - Effectiveness of treatment will be assessed by monitoring bleeding episodes, FIX activity level, FIX replacement therapy use for episodic events, FIX replacement therapy use for surgical procedures, and target joints (**Table 2**)
  - Safety will be assessed by collecting all fatal adverse events (AEs), related serious AEs and all adverse events of special interest (AESIs), pregnancy data, abdominal / liver ultrasound, liver elastography, liver biopsies, clinical laboratory results, and FIX inhibitors (**Table 3**)
- For both cohorts, patients will be enrolled over a period of 5 years from enrollment of the first patient treated post-approval (June 15, 2023) and followed for 15 years
- Formal hypothesis testing is not planned; hence, control for type I error is not required

STUDY ENDPOINTS

- The primary and secondary endpoints for effectiveness and safety are summarized in **Table 4**
- The first analysis of the results is planned after ~50 patients have completed a 1-year follow-up
- The final report is expected in 2044

Figure 1: Study design



*Per USPI and SmPC recommendations, all follow-up testing should adhere to local recommendations.
ATHN, American Thrombosis and Hemostasis Network; FIX, factor IX.

DATA SOURCES

- **Figure 2** illustrates the project systems' high-level connections and data flow directions
- The Common Study Database serves as the central repository, integrating CSL electronic data capture, registry data (eg, ATHN Transcends), and external sources according to Clinical Data Interchange Standards Consortium standards
  - This database eliminates duplicate patients and data and generates the study export for SAS data set production
- At non-US sites, data collection via electronic Case Report Forms (eCRFs) will be based on patient medical charts to ensure alignment between eCRF and chart data
  - Clinical information will be abstracted from medical records and diagnostic reports at baseline and according to specified data collection time points

Table 1: Eligibility criteria

Etranacogene dezaparvovec cohort		FIX prophylaxis cohort	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
Patients with hemophilia B treated with commercial etranacogene dezaparvovec	Treatment with etranacogene dezaparvovec in a clinical trial setting	Adult patients with hemophilia B with written consent	None
Written informed consent within 3 months before or within 6 months after etranacogene dezaparvovec treatment, or within 6 months of when the study is initiated at the participating study site		Enrolled in ATHN Transcends Hemophilia Cohort (or similar registry)	
		Receiving FIX continuous prophylaxis therapy	

ATHN, American Thrombosis & Hemostasis Network; FIX, Factor IX.

Table 2: Effectiveness variables

Effectiveness variables	Etranacogene dezaparvovec cohort and FIX prophylaxis cohort
Bleeding episodes	Date, type (eg, traumatic, spontaneous), location (eg, joint, muscle, mucosal), and treated or not treated, severity: minor or major bleeding event
FIX activity level	Date of test, factor level (IU/dL), type of assay (one-stage and chromogenic assays)
FIX replacement therapy use data for episodic events	Use of FIX replacement therapy for episodic events (date, reason for treatment, bleeding event, prophylaxis before a procedure)
FIX replacement therapy use data for surgical procedures	Dose, regimen, frequency, type of product name / brand, dose interval including peri- and post-operative surgical procedures
Target joints*	Number of target joints, location, resolution

*A target joint is defined as three or more spontaneous bleeding events into a single joint within a consecutive 6-month period. Target resolution is defined as a recorded target joint with two or fewer spontaneous bleeding events within a consecutive 12-month period.
FIX, Factor IX.

Table 3: Safety variables

Safety variables	Etranacogene dezaparvovec cohort	FIX prophylaxis cohort
Fatal AEs	All fatal AEs (regardless of causality) which occur during or after etranacogene dezaparvovec treatment	All fatal AEs regardless of causality which occur during the follow-up period
Serious AEs	All related serious AEs which occur during or after etranacogene dezaparvovec treatment	All related serious AEs which occur during the follow-up period
AESIs	All AESIs which occur during or after etranacogene dezaparvovec treatment AESIs include: • Hepatotoxicity • Infusion reaction (including hypersensitivity) • New malignancy • Bleeding as a result of lack of efficacy* due to immune-mediated neutralization of the AAV5 vector capsid† • Thromboembolic events • Germline transmission • Transmission to third parties (horizontal transmission) • Development of FIX inhibitors	All AESIs (regardless of causality) which occur during the follow-up period AESIs include: • Hepatic fibrosis or cirrhosis • Infusion reaction (including hypersensitivity) • New malignancy • Thromboembolic events • Development of FIX inhibitors

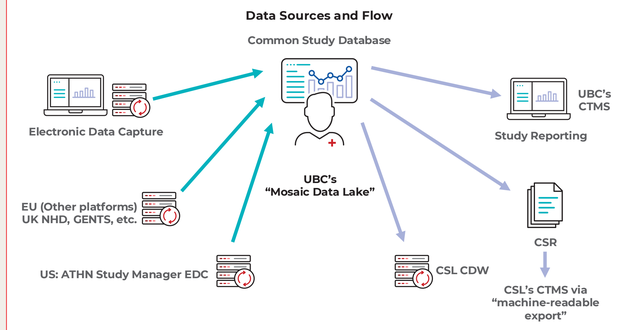
*Lack of efficacy is defined as no evidence that the gene therapy vector transduces cells, leading to the expression of circulating FIX. †Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV5 vector capsid will be assessed by evaluating the following protocol defined variables: 1)SAEs / AESIs: to evaluate if any other AEs may contribute to the observed bleeding pattern, 2) Abdominal / liver ultrasound scan findings: to evaluate if liver abnormalities may contribute to the observed bleeding pattern, 3) Clinical safety laboratory results: ALT / AST and CPK, 4) FIX inhibitors: to determine if FIX inhibitors have developed that may contribute to the observed bleeding pattern.
AAV5, adeno-associated virus type 5; AE, adverse events; AESI, adverse event of special interest; FIX, factor IX.

Table 4: Study endpoints

Primary endpoint	Secondary endpoints
Annualized bleeding rate in the etranacogene dezaparvovec cohort	FIX activity in the etranacogene dezaparvovec cohort
	Annualized bleeding rate
	Number of patients with zero bleeds in the etranacogene dezaparvovec cohort
	Annualized consumption of FIX replacement therapy
	Number of patients remaining free of previous continuous routine prophylaxis in the etranacogene dezaparvovec cohort
	Target joints*
	SAEs and AESIs

*A target joint is defined as three or more spontaneous bleeding events into a single joint within a consecutive 6-month period.
AESI, adverse event of special interest; FIX, factor IX; SAE, serious adverse event.

Figure 2: Data flow directions and high-level connections



ATHN, American Thrombosis and Hemostasis Network; CDW, clinical data warehouse; CTMS, clinical trial management system; CSL, CSL Behring; CSR, clinical study report; EDC, electronic data capture; EU, European Union; GENTS, Gene Therapy Software for Hemophilia; NHD, National Hemophilia Database; SAS, statistical analysis system; UBC, United BioSource Corporation; UK, United Kingdom.

Conclusions

- **Integrating data from local patient registries and PI reporting into this Phase 4 study is essential for enriching the understanding of gene therapy outcomes in hemophilia B patients treated with etranacogene dezaparvovec in a commercial setting**
  - **This study will provide long-term data on the effectiveness and safety of etranacogene dezaparvovec and build on its efficacy and safety profile in a larger population**
- **This approach fosters comprehensive data collection, enables variability analysis, and promotes standardized reporting**
- **Centralized data compilation promotes standardized reporting practices and data analysis methodologies, ensuring consistency and reliability in assessing safety and effectiveness endpoints across multiple sites**
- **This facilitates evidence-based regulatory compliance by accessing a unified dataset from different sources supporting regulatory compliance by providing robust evidence for post-authorization evaluations**

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