STUDY PROTOCOL

Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Study Number:	CSL222_5002
Medicinal Product	Etranacogene dezaparvovec (Hemgenix®)
Marketing Authorization Holder:	CSL Behring GmbH (CSL) Emil-von-Behring-Strasse 76 35041 Marburg Germany
Protocol Version:	original v3.0
Protocol Date:	23 May 2024
Compliance:	This study will be conducted in accordance with standards of pharmacovigilance practices. Good Clinical Practice ICH guideline should serve as guidance document. Local (eg, country specific) and regional (eg, European Union directives) regulations may apply and must be followed.

Observational Study Information

Title	Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA
Protocol version identifier	original v3.0
Date of last version of protocol	23 May 2024
Marketing Authorization Holder	CSL Behring GmbH (CSL) Emil-von-Behring-Strasse 76 35041 Marburg Germany [redacted]
Medicinal Product	Etranacogene dezaparvovec (Hemgenix®): gene therapy medicinal product, single-dose infusion of 2 x 10^{13} gene copies/ kg body weight Prophylactic FIX replacement: plasma-derived and recombinant coagulation FIX products, prophylactic dosing and route of administration according to corresponding Summary of Product Characteristics (SmPC)

Research question and objectives	This non-interventional study aims to evaluate the overall effectiveness and tolerability of gene therapy etranacogene dezaparvovec (Hemgenix®) compared to a prophylaxis with recombinant or plasma-derived FIX products in patients with severe or moderately severe haemophilia B. The study represents a non-randomized Routine Practice Data Collection using data documented by haemophilia sites that are routinely captured for reporting to the German Haemophilia Registry (DHR).
	
	Effectiveness and tolerability will be assessed based on patient-relevant endpoints resulting from G-BA resolution mandating this study:
	
	Primary endpoint:
	
	Annualized bleeding rate (ABR): All treated bleeding
	
	Secondary endpoints:
	
	• Survival**:** Overall survival
	• Morbidity**:**
	  • Bleeding: ABR for
	  ▪ Severe bleeding
	  ▪ Life-threatening bleeding
	  ▪ Joint bleeding
	  • Pain: Brief Pain Inventory – Short Form (BPI-SF)
	  • Joint status: Hemophilia Joint Health Score (HJHS)
	• Health-related quality of life:
	Haemophilia-specific Health-related Quality of Life Questionnaire for Adults (Haemo-QoL-A)
	• Tolerability:

	• Adverse events (AE) • Serious AE (AE leading to death or hospitalization) • Adverse events of special interest (AESI) and serious AESI ▪ Thromboembolic events ▪ Development of FIX inhibitors ▪ Symptomatic liver damage ▪ Malignant neoplasms **Exploratory endpoints**: • <u>FIX utilization</u> • Annualized infusion rate of prophylactic FIX concentrates (number of infusions) • Annualized infusion rate of on-demand FIX concentrates (number of infusions) • <u>Return to prophylactic FIX therapy</u> (etranacogene dezaparvovec only) <u>Duration of study:</u> Enrollment is expected to begin in Q3 to Q4 2024[1] (first patient first visit) after study approval and official commencement resolution from G-BA. Enrollment will end on 1 January 2026 to allow for a minimum of three years follow-up time until 31 December 2028 (end of registry reporting period available for new benefit assessment). Data will be collected at study sites until 31 December 2028 (last patient last visit).

[1] Depending on the time it takes to implement the changes in the DHR registry.

Inclusion and Exclusion Criteria	Patients must meet all of the following criteria to be included in the study: • Adults with severe or moderately severe haemophilia B (congenital FIX deficiency; ≤ 5 % endogenous FIX activity) • Pre-treatment with either recombinant- or plasma-derived FIX concentrates • Signed informed consent Patients that meet any of the following criteria will be excluded: • Currently participating in an interventional clinical trial • Known history of FIX inhibitors • Known advanced hepatic fibrosis or cirrhosis • Other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy • Known intolerance/hypersensitivity to any FIX concentrates and/or etranacogene dezaparvovec (active substance or to any of the excipients)

Study design	Non-interventional, non-randomized data collection using secondary data from the DHR. Potential inhomogeneity between treatment arms with regard to the following baseline confounders will be addressed by propensity score methods (average treatment effect fine stratification weights or inverse probability of treatment weights): • Residual FIX activity • Age • Dosage (intensity of prophylaxis) 12 months prior to study enrollment • Joint status • ABR 12 months prior to study enrollment Time-to-event endpoints are estimated in the context of a Cox regression. For binary endpoints and count data / rate endpoints, a generalized linear model is used. Scores will be analyzed as binary endpoints using pre-specified responder thresholds.
Country of study	Germany
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Table of Contents

1 List of Abbreviations

Abbreviation	Definition
AAV5	Adeno-Associated Virus serotype 5
AbD	Routine Practice Data Collection and Evaluation (Anwendungsbegleitende Datenerhebung)
ABR	Annualized Bleeding Rate
ACT	Appropriate Comparative Therapy
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft
ATE	Average Treatment Effect (in the whole population)
BO-Ä	Professional Code for Physicians in Germany (Berufsordnung Ärzte)
BPI-SF	Brief Pain Inventory – Short Form
(c)DNA	(complementary) Deoxyribonucleic Acid
CFC	Clotting Factor Concentrate
CI	Confidence Interval
CNS	Central Nervous System
COV	Close-Out Visit
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CSL	CSL Behring GmbH
DHG	German Haemophilia Society (Deutsche Hämophiliegesellschaft e.V.)
DHR	German Haemophilia Registry (Deutsches Hämophilieregister)
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
ED	Exposure Day
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMR	Electronic Medical Records
ePRO	Electronic Patient Reported Outcome
EU	European Union
FIX	Coagulation Factor IX

Abbreviation	Definition
FPI	First Patient In
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GCP	Good Clinical Practice
GCSP	Global Clinical Safety & Pharmacovigilance
GEE	Generalized Estimating Equations
GKV-SV	National Association of Statutory Health Insurance Funds
GLM	Generalized Linear Model
GTH	Society for Thrombosis and Haemostasis Research
Haemo-QoL-A	Haemophilia-specific Quality of Life Questionnaire for Adults
HIV	Human Immunodeficiency Virus
HJHS	Hemophilia Joint Health Score
HOPE-B	Health Outcomes with Padua gene - Evaluation in Haemophilia B (HOPE-B, NCT03569891) Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe haemophilia B
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISTH	International Society on Thrombosis and Haemostasis
IGH	Haemophiliac Interest Group (Interessengemeinschaft Hämophiler e.V.)
IPTW	Inverse Probability of Treatment Weights
IRB/ IEC	Institutional Review Boards/ Independent Ethics Committees
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ITI	Immune Tolerance Induction
IU	International Unit
IV	Intravenous
IRB	Institutional Review Board
LP1	Liver-specific Promotor 1
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
PASS 2023	Non-Inferiority Test for the Ratio of two Negative Binomial Rates

Abbreviation	Definition
PedNET	Pediatric Network on haemophilia management
PEI	Paul Ehrlich Institute
pH	Potential of Hydrogen (pH=-lg [H^+])
PICO	Patient-Intervention-Comparator-Outcome
PRO	Patient-reported Outcome
PT	Preferred Term
PTP	Previously Treated Patients
QM	Quality Management
RMV	Routine Monitoring Visits
SAE	Serious Adverse Event
SAESI	Serious Adverse Event of Special Interest
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SIV	Site Initiation Visit
SMD	Standardized Mean Differences
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SGB V	Book Five of the Social Code
SLR	Systematic Literature Review
TF	Transfusion Act
TTE	Time-to-Event
WFH	World Federation of Hemophilia
WHO	World Health Organization

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3 Abstract / Summary

Title

Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic factor IX (FIX) replacement in adults with severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Protocol original v3.0 23 May 2024

Main author: [redacted]

Rationale and background

With its resolution from 12 May 2023, the G-BA requested CSL Behring to conduct a Routine Practice Data Collection and Evaluations (anwendungsbegleitende Datenerhebung, AbD) comparing gene therapy etranacogene dezaparvovec (Hemgenix®) to FIX prophylaxis treatment (recombinant or plasma-derived FIX products) in adult patients with severe and moderately severe haemophilia B without a history of FIX inhibitors.

The present study aims to fulfill this requirement.

Research question and objectives

The objective of this non-interventional study is to evaluate the overall effectiveness and tolerability in patients with severe or moderately severe haemophilia B treated with the gene therapy etranacogene dezaparvovec (Hemgenix®) compared to a prophylaxis with FIX products (both plasma-derived and recombinant). The study represents a non-randomized AbD using data documented by German haemophilia sites that is routinely captured for reporting to the German Haemophilia Registry (Deutsches Hämophilieregister, DHR). Effectiveness and tolerability will be assessed based on patient-relevant endpoints resulting from the G-BA's resolution mandating this study and a non-randomized, adjusted comparison will be conducted. Results will be subject to a new benefit assessment for etranacogene dezaparvovec by G-BA due to commence on 2 November 2029.

Study design

This is a non-interventional, non-randomized AbD using data documented by haemophilia sites that is routinely captured for reporting to DHR (secondary use of data collected within the infrastructure of the DHR). Patients will be enrolled and allocated to the intervention arm (etranacogene dezaparvovec) or comparator arm (FIX replacement) based on treatment at time

of enrollment and observed until end of data collection on 31 December 2028. Patients treated with FIX at time of enrollment but switched to etranacogene dezaparvovec within the first two years after enrollment will be allocated to the intervention arm of the study and reference date (baseline) will be set to the date of treatment with etranacogene dezaparvovec.

Statistical methods:

The comparison of both interventions is carried out with appropriate statistical methods. Pre-specified confounders as well as patient characteristics are evaluated descriptively and standardized mean differences (SMDs) are reported for all pre-specified confounders. Inhomogeneity between treatment arms with regard to pre-specified baseline confounders (please refer to section on "variables") will be addressed by propensity score methods (average treatment effect fine stratification weights or inverse probability of treatment weights). The weighting approach will be selected by comparing confounder balance in terms of SMDs after weighting.

Duration of study:

Enrollment is expected to begin in Q3 to Q4 2024[2] (first patient first visit) after approval and official commencement resolution from G-BA. Enrollment will end on 1 January 2026 to allow for a minimum of three years follow-up time until 31 December 2028 (end of yearly registry reporting period available for new benefit assessment in 2029). Data will be collected at study sites until 31 December 2028 (last patient last visit).

Population

The study is aimed at adult patients with severe or moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors.

Inclusion Criteria

Patients must meet all of the following criteria to be included in the study:

- Adults with severe or moderately severe haemophilia B (congenital FIX deficiency; ≤ 5 % endogenous FIX activity)
- Pre-treatment with either recombinant- or plasma-derived FIX concentrates

[2] Depending on the time it takes to implement the changes in the DHR registry.

- Signed informed consent

Exclusion criteria

Patients that meet any of the following exclusion criteria cannot take part in this study:

- Currently participating in an interventional clinical trial
- Known history of FIX inhibitors
- Known advanced hepatic fibrosis or cirrhosis
- Other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy
- Known intolerance/hypersensitivity to any FIX concentrates and/or etranacogene dezaparvovec (active substance or to any of the excipients)

Variables

Exposure/Treatments under study

- Etranacogene dezaparvovec (Hemgenix®): according to EC-approved dosing as a single dose of 2 x 10^{13} gene copies per kg body weight corresponding to 2 mL/kg body weight, administered as an intravenous (IV) infusion after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection [1]
- FIX products, either plasma-derived or recombinant FIX replacement concentrates (including normal-half-life and extended-half-life FIX products): prophylactic EC approved dosing as stated in the corresponding summary of product characteristics (SmPC), administered as repeated IV infusion. In addition, approved FIX products will be applied on-demand as needed in routine care, following dosing and administration according to SmPC.

Outcomes of interest/Endpoints

The following endpoints are subject to investigation in this study:

Primary endpoint:

- Annualized bleeding rate (ABR): All treated bleeding

Secondary endpoints:

- Survival**:** Overall Survival

- Morbidity:
    - Bleeding: ABR for
        - Severe bleeding
        - Life-threatening bleeding
        - Joint bleeding
    - Pain: Brief Pain Inventory – Short Form (BPI-SF):
        - BPI-SF (scale no. 5) Worsening
        - BPI-SF (scale no. 5) Improvement
    - Joint status: Hemophilia Joint Health Score (HJHS):
        - HJHS Worsening
- Health-related quality of life:

  Haemophilia-specific Health-related Quality of Life Questionnaire for Adults (Haemo-QoL-A): Worsening and Improvement in
    - Total Score
    - Physical Functioning
    - Role Functioning
    - Worry
    - Consequences of Bleeding
    - Emotional Impact
    - Treatment Concerns
- Tolerability:
    - Adverse events (AE)
    - Serious AE (AE leading to death or hospitalization)
    - Adverse events of special interest (AESI) and serious AESI
        - Thromboembolic events
        - Development of FIX inhibitors

        - Symptomatic liver damage
        - Malignant neoplasms

- Exploratory endpoints:
    - FIX utilization
        - Annualized infusion rate of prophylactic FIX concentrates (number of infusions)
        - Annualized infusion rate of on-demand FIX concentrates (number of infusions)
    - Return to prophylactic FIX therapy (etranacogene dezaparvovec only)

Covariates to be addressed in analysis

The following confounders will be included in the analysis based on pre-specification via systematic literature review and validation with clinical haemophilia experts:

- Residual factor activity
- Age
- Dosage (intensity of prophylaxis) 12 months prior to study enrollment
- Joint status
- ABR 12 months prior to study enrollment

Estimated /Targeted Number of Patients

All patients fulfilling inclusion while not fulfilling exclusion criteria will be included in the study. As the study is conducted in a standard of care setting, the actual numbers of subjects per study population cannot be controlled. Also, as haemophilia B is a rare disease, there is a finite number of patients that can be enrolled.

Sample size calculations were performed based on results of the HOPE-B pivotal study [2] using two approaches:

1. Using a shifted null hypothesis ($RR_0 = 0.5$) and alpha = 0.05 (two-sided). Further assumptions: power = 0.8, 1:5 patient ratio (intervention:comparator), rate ratio = 0.16 (ABR: all treated bleeding)

2. Using a a standard null hypothesis ($RR_0 = 1$), but alpha = 0.01 (two-sided). Further assumptions: power = 0.8, 1:5 patient ratio (intervention:comparator), rate ratio = 0.16 (ABR: all treated bleeding)

The following sample sizes result:

1. Shifted null hypothesis: 103 patients (17 intervention, 86 comparator) for primary endpoint (ABR: all treated bleeding)
2. Standard null hypothesis ($RR_0 = 1$) with alpha = 0.01: 53 patients (9 intervention, 44 comparator) for primary endpoint (ABR: all treated bleeding)

Assumptions for sample size calculation will be re-evaluated at first and second interim analysis 18 and 36 months after study commencement using actual observed event rates and effect sizes.

Please refer to the statistical analysis plan (SAP; section 4.4) for details on sample size calculations.

Taking into account the non-randomised comparison and the shifted null hypothesis boundaries, there is a high potential for bias, which will be discussed accordingly in the study report.Data analysis

Patient characteristics and SMDs for patients included in the analyses will be reported both weighted and unweighted. Patient characteristics and SMDs will be reported unweighted for patients trimmed from adjusted analyses.

Time-to-event (TTE) endpoints are estimated in the context of a Cox regression. For binary endpoints and count endpoints, a generalized linear model is used. Scores will be analyzed as binary endpoints using pre-specified responder thresholds.

Survival curves and median survival time as well as hazard ratios are used for the representation of the TTE endpoints. Binary endpoints are analyzed using Risk Ratio as effect measure. Count endpoints will be evaluated using Rate Ratio as effect measure.

For all effect measures 95% confidence interval limits are presented. AE are summarized in terms of absolute and relative frequencies as well as time to first event by treatment episode.

Please refer to the SAP for details.

Milestones

In addition to the final analysis, various interim analyses are planned. These have been scheduled based on the G-BA decision but originally also taking into account data availability at the respective points in time. See SAP section 4.5 for details.

Milestone	Actual/Planned Date
G-BA resolution mandating the study	12 May 2023
Submission of study protocol and SAP to G-BA	12 October 2023
Written results of assessment of study protocol and SAP by G-BA and IQWiG	1 February 2024
Re-submission of study protocol and SAP	28 March 2024
Decision of DHR steering committee regarding implementation of requested required data fields	22 April 2024
Re-submission of study protocol and SAP due to DHR decision not to implement all requested changes	23 May 2024
Approval by G-BA under the condition of additional changes to study protocol and SAP	August2024
Study start / Start of data collection	Q3 to Q4 2024 [1]
First status report 6 months after study commencement • Status report • Baseline data	Submission: March 2025 Data cut: November 2024 (DHR data available in 2024 only covers time before study commencement)
Interim analysis 18 months after study commencement • Status report • Baseline data • Interim outcome analysis • Sample size re-estimation (if possible) • Feasibility assessment	Submission: March 2026 Data cut: November 2025 (DHR data available until 31 December 2024)
Interim analysis 36 months after study commencement • Status report • Baseline data	Submission: September 2027 Data cut: May 2027 (DHR data available until 31 December 2026)

Milestone	Actual/Planned Date
• Interim outcome analysis • Sample size re-estimation • Feasibility assessment	
Interim analysis 54 months after study commencement • Status report • Baseline data • Interim outcome analysis • Feasibility assessment	Submission: March 2029 Data cut: November 2028 (DHR data available until 31 December 2027)
Final analysis for benefit assessment[2]	Submission: 2 November, 2029 Data cut: July 2029 (DHR data available until 31 December 2028)
End of data collection	31 December 2028

[1] Depending on the time it takes to implement the intended changes in the DHR registry. This is beyond the control of CSL Behring.

[2] Based on the current timelines, the time from study start to end of data collection would only allow for about 15 months of including patients in the etranacogene dezaparvovec arm to ensure sufficient observation time after the treatment switch. Postponing the final submission from November 2029 to November 2030 could allow for 2029 data from DHR to be included in the final analysis. This would increase the time to include patients in the etranacogene dezaparvovec arm from about 15 to about 27 months and thus likely increase the robustness of available evidence significantly. In case a G-BA resolution is passed to adjust timelines and postpone the final submission of the dossier, the timepoint of latest possible switch from FIX to etranacogene dezaparvovec would be adjusted accordingly to enable 3 years of data collection for all patients. The changes would be subject to an amendment and communicated to G-BA.

4 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.0	09 October 2023	-	-	Initial protocol setup
2.0	28 March 2024	Observational study information table	Expected enrollment date was corrected from originally May 2024 to Q3 to Q4 2024.	Delay in response due to modified timelines by G-BA
		3. Abstract/ Summary	Milestones were adjusted regarding mandatory content of status reports and interim analyses according to G-BA's requirements as well as the changes in the timeline for resubmission of study documents. Expected enrollment date was corrected from originally May 2024 to Q3 to Q4 2024. A paragraph was added taking into account the non-randomised comparison and the shifted null hypothesis boundaries and hence a high potential for bias, which will be discussed accordingly in the study report. The exclusion criteria were adapted according to the recommendations of the clinical experts. The exclusion of active	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

			and/ or uncontrolled chronic infections was integrated into the exclusion criteria of other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy.	
		5. Milestones	Milestones were adjusted regarding mandatory content of status reports and interim analyses according to G-BA's requirements as well as the changes in the timeline for re-submission of study documents. Expected enrollment date was corrected from originally May 2024 to Q3 to Q4 2024.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		7.2.1 Effectiveness: Annualized Bleeding Rate (ABR)	The endpoint definition was increasingly specified based on the recommendation of the clinical experts in order to avoid misunderstandings.	The adaptation was performed in accordance to the recommendations of the clinical experts.
		7.3.2 Effectiveness: Bleeding	The endpoint definition was increasingly specified based on the recommendation of the clinical experts in order to avoid misunderstandings.	The adaptation was performed in accordance to the recommendations of the clinical experts.
		7.3.3 Effectiveness: Pain	Tolerance windows were added for the twice annual assessment. BPI-SF assessments for patients included in this study are to be carried out at baseline and twice per year (every 6 months +/- 2.5	Implementation of G-BA requests and recommendations from resolution dated 01

			months) during follow up. Responder analysis was adapted to qualify patients as responders who show an average rating of at least 15 % of the scale range above the baseline value at the end of observation period.	February 2024
		7.3.4 Effectiveness: Joint status	Tolerance windows were added for the twice yearly assessment. HJHS assessments for patients included in this study are to be carried out at baseline and twice per year (every 6 months +/- 2.5 months) during follow up. Responder analysis was adapted to qualify patients as responders who show an average rating of at least 15 % of the scale range above the baseline value at the end of observation period	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		7.3.5 Effectiveness: Health-related Quality of Life	Tolerance windows were added for the twice yearly assessments. HRQoL assessments for patients included in this study are to be carried out at baseline and twice per year (every 6 months +/- 2.5 months) during follow up. Responder analysis was adapted to qualify patients as responders who show an average rating of at least 15 % of the scale range above the baseline value at the end of	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

			observation period	
		7.3.6 Tolerability	The intended classification of adverse events by MedDRA SOC/PT performed by an external CRO was removed after weighing up the effort and informative value for the Routine Practice Data Collection as suggested by G-BA. In consequence, SOC/PT was removed from sections 7.3.6.1 and 7.3.6.2 as well.	Implementation of G-BA´s suggestion
		8.1.1. Research design and rationale, section number and region of sites, countries involved	The restriction to study sites treating at least 10 patients was removed. It is planned to conduct this trial in all study sites treating haemophilia B patients in routine practice in Germany.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.2 Selection of subject population	The paragraph has been modified due to new DHR updates. In consultation with the DHR, CSL Behring has compiled a list of modifications to the DHR dataset required to capture inclusion and exclusion criteria and other data necessary for the analysis of each of the requested endpoints. This proposal has been submitted to the DHR and is awaiting final approval and implementation.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

		8.2.2 Exclusion Criteria	The exclusion criteria were adapted according to the recommendations of the clinical experts. The exclusion of active and/ or uncontrolled chronic infections was integrated into the exclusion criteria of other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy.	The adaptation was performed in accordance to the recommendations of the clinical experts.
		8.4.1 Inclusion/ Exclusion criteria	Required variables for operationalization of inclusion and exclusion criteria were added in table format.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.4.2 Outcomes: Annualized Bleeding Rate (ABR)	The endpoint definition was increasingly specified based on the recommendation of the clinical experts in order to avoid misunderstandings.	The adaptation was performed in accordance to the recommendations of the clinical experts.
		8.4.2 Outcomes: Bleeding endpoint	The endpoint definition was increasingly specified based on the recommendation of the clinical experts in order to avoid misunderstandings.	The adaptation was performed in accordance to the recommendations of the clinical experts.
		8.4.2 Outcomes: Joint status	The depictability status of endpoint joint status in accordance with new DHR data fields was updated.	New data fields were implemented by DHR to 2024
		8.4.2	The operationalization of	New data fields

		Outcomes: Tolerability endpoints	tolerability endpoints in accordance with new DHR data fields was updated.	were implemented by DHR to 2024
		8.4.2 Outcomes: Tolerability endpoints	For tolerability endpoints, the coding of free text fields using MedDRA by an external CRO was removed. In consequence, SOC/PT was removed as well.	Implementation of G-BA´s suggestion
		8.4.2 Outcomes: Exploratory endpoints	The operationalization of exploratory endpoints in accordance with new DHR data fields was updated.	New data fields were implemented by DHR to 2024
		8.4.2 Outcomes: Exploratory endpoints	The operationalization of exploratory endpoints was amended by deleting answer optiones “other/ unknown”.	Other and unknown reasons for therapy do not necessarily represent on-demand FIX utilization.
		8.4.2 Outcomes	The statement that financial incentives are given in order to increase patient documentation was removed. The issue is addressed in section 14.1.3.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.4.3 Covariates	In response to G-BA, a separate discussion of confounders was conducted and a paragraph pointing out this new annex to A1 was included.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.4.3 Covariates: Dosage	The depictability status of confounders in accordance with	New data fields were

		(intensity of prophylaxis) 12 months prior to study enrollment	new DHR data fields was updated.	implemented by DHR to 2024
		8.4.3 Covariates: Joint status	The depictability status of confounders in accordance with new DHR data fields was updated.	New data fields were implemented by DHR to 2024
		8.4.3 Covariates: Joint status	"Global Gait score" was added to the subscores that need to be assessed besides the HJHS total score for depiction of the confounder "Joint status".	Added for the completeness of the data
		8.4.3 Covariates	The statement that financial incentives are given in order to increase patient documentation was removed. The issue is addressed in section 14.1.3.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.4.3 Covariates: Further parameters	The operationalization of "AAV5 status" for subgroup analysis in accordance with new DHR implementations was updated.	New data fields were implemented by DHR to 2024
		8.4.4 Patient characteristics	Patient baseline characteristics were added in table format.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.5 Data Source DHR	The paragraph stating a potential use of an alternative study database has been	Implementation of G-BA requests and

			removed after exchange with DHR and in response to G-BA. Due to several haemophilia AbDs being conducted in parallel and after extensive exchange with the DHR, an alternative study database is no longer needed. CSL Behring is currently in dialogue with the DHR in order to discuss and implement all necessary modifications of the DHR for the collection of the required data as part of the AbD before the actual start of the AbD. Modifications are currently subject to the decision of DHR's steering committee.	recommendations from resolution dated 01 February 2024
		8.7.1 Sample size estimation	The mistake in the citation regarding ABR from HOPE B study results has been corrected by removal of EPAR as data source. ABR data has always been directly taken from HOPE B trial results. Two paragraphs were added to re-emphasize the intended sample size which was however already mentioned in other sections of the SP as well as in the SAP. A paragraph was added taking into account the non-randomised comparison and the shifted null hypothesis boundaries and hence a high	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

			potential for bias, which will be discussed accordingly in the study report. Numbers in Table 21 and Table 22 for row "HOPE-B: major bleeding" were corrected due to calculation error.	
		8.7.2 Statistical methodology	Figure 2 was corrected: SMRW was replaced once by IPTW However, no further need for correction was seen, as statistical methodology was already chosen according to G-BAs request. Inhomogeneity between treatment arms with regard to pre-specified baseline confounders will be addressed by PSM (ATE fine stratification weights or inverse probability of treatment weights IPTW).	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.7.4 Secondary analysis	Adjustmets were made to match with changes in SAP.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		8.7.5.1	The operationalisation of the predefined subgroups on "AAV5 status" were modified to positive and negative (instead of a fixed titer) to correspond to latest plans on DHR data fields.	Alignment with DHR's latest plans

		8.7.6 Feasibility assessment	More specific rules regarding feasibility assessment have been added. In addition, the content of interims analyses was adjusted according to G-BA's requirements; while a feasibility assessment will be submitted with all three interim analyses, a sample size re-estimation will be included in the first and second interim analysis.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		14.1., 14.1.1 and 14.1.2	The paragraph on SDV was adjusted to match requirements. General monitoring procedures were added as well as a chapter on for-cause monitoring visits.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		14.1.3 Minimization of missing data	Tolerance windows were added for the assessments every 6 moths +/- 2.5 months. Additional measures were added to outline further plans besides financial incentives to minimize missing data.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
		15. Plans for disseminating and communicating study results	Milestones were adjusted regarding mandatory content of status reports and interim analyses according to G-BA's requirements. Expected enrollment date was corrected from originally May 2024 to Q3	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

			to Q4 2024, hence minor corrections were made to the data that will be available for the respective interim analyses.	
3.0	23 May 2024	2 Responsible Parties	Project Lead and Medical responsibilities were adjusted.	Modification due to changes in responsibilities.
		3 Abstract/ Summary	Milestones were adjusted due to modifications in study protocol based on new DHR updates which lead to re-submission of study protocol to G-BA on 23 May 2024 and therefore a delay of study start.	Modification due to decision of DHR's steering committee of 22 April 2024 which decided not to implement all requested changes
		5 Milestones	Milestones were adjusted due to modifications in study protocol based on new DHR updates which lead to re-submission of study protocol to G-BA on 23 May 2024 and therefore a delay of study start.	Modification due to decision of DHR's steering committee of 22 April 2024
		8.2 Selection of subject population	In consultation with the DHR, CSL Behring has compiled a list of modifications to the DHR dataset required to fully capture inclusion and exclusion criteria and other data necessary for the analysis of each of the requested endpoints. This proposal has been submitted but required implementation of some data fields was rejected by the DHR steering committee. Hence, the paragraph has been	Modification based on decision of DHR's steering committee of 22 April 2024

			modified based on new DHR updates.	
		8.4.1 Inclusion/ Exclusion criteria	Depictability of required data fields and the operationalization were adapted based on new DHR updates.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.4.2 Outcomes: Pain	Depictability of required data fields and the operationalization were adapted based on new DHR updates.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.4.2 Outcomes: Joint status	Depictability of required data field was adapted based on new DHR updates.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.4.2 Outcomes: HRQoL	Depictability of required data fields and the operationalization were adapted based on new DHR updates.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.4.2 Outcomes: Tolerability endpoints	Depictability of required data fields and the operationalization were adapted based on new DHR updates.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.4.2 Outcomes: Exploratory	Clarification through footnote was adapted based on new DHR updates.	Modification based on decision of DHR's

		endpoints		steering committee of 22 April 2024
		8.4.3 Covariates	Depictability of required data fields was adapted based on new DHR updates.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.4.4 Patient characteristics	In consultation with the DHR, CSL Behring has compiled a list of modifications to the DHR dataset required to fully capture inclusion and exclusion criteria and other data necessary for the analysis of each of the requested endpoints. This proposal has been submitted but required implementation of some data fields was rejected by the DHR steering committee due to technical difficulties. Hence, 2 patient characteristics were removed due to no depictability possibilities within the DHR.	Modification based on decision of DHR's steering committee of 22 April 2024
		8.5 Data Source: German Haemophilia Registry (DHR)	Information on the DHR steering committee's decision was added in a paragraph regarding the implementation of new DHR data fields.	Modification based on decision of DHR's steering committee of 22 April 2024
		15 Plans for Disseminating and Communi-cating Study	Milestones were adjusted due to modifications in study protocol based on new DHR updates which lead to re-submission of	Modification due to decision of DHR's steering committee of 22

		Results	study protocol to G-BA on 23 May 2024 and therefore a delay of study start.	April 2024
		17 Signature on Behalf of Marketing Authorization Holder	The list of responsibilities for the marketing authorisation holder has been adjusted.	Modification due to changes in responsibilities.

5 Milestones

In addition to the final analysis, various interim analyses are planned. These have been scheduled based on the G-BA decision but also taking into account data availability at the respective points in time. See SAP section 4.5 for details.

Milestone	**Actual/Planned Date**
G-BA resolution mandating the study	12 May 2023
Submission of study protocol and SAP to G-BA	12 October 2023
Written results of assessment of study protocol and SAP by G-BA and IQWiG	1 February 2024
Re-submission of study protocol and SAP	28 March 2024
Decision of DHR steering committee regarding implementation of requested required data fields	22 April 2024
Re-submission of study protocol and SAP due to DHR decision not to implement all requested changes	23 May 2024
Approval by G-BA under the condition of additional changes to study protocol and SAP	August 2024
Study start / Start of data collection	Q3 to Q4 2024 [1]
First status report 6 months after study commencement • Status report • Baseline data	Submission: March 2025 Data cut: November 2024 (DHR data available in 2024 only covers time before study commencement)
Interim analysis 18 months after study commencement • Status report • Baseline data • Interim outcome analysis • Sample size re-estimation (if possible) • Feasibility assessment	Submission: March 2026 Data cut: November 2025 (DHR data available until 31 December 2024)
Interim analysis 36 months after study commencement • Status report	Submission: September 2027 Data cut: May 2027 (DHR data available until 31 December 2026)

Milestone	Actual/Planned Date
• Baseline data • Interim outcome analysis • Sample size re-estimation • Feasibility assessment	
Interim analysis 54 months after study commencement • Status report • Baseline data • Interim outcome analysis • Feasibility assessment	Submission: March 2029 Data cut: November 2028 (DHR data available until 31 December 2027)
Final analysis for benefit assessment[2]	Submission: 2 November 2029 Data cut: July 2029 (DHR data available until 31 December 2028)
End of data collection	31 December 2028

[1] Depending on the time it takes to implement the intended changes in the DHR registry. This is beyond the control of CSL Behring.

[2] Based on the current timelines, the time from study start to end of data collection would only allow for about 15 months of including patients in the etranacogene dezaparvovec arm to ensure sufficient observation time after the treatment switch. Postponing the final submission from November 2029 to November 2030 could allow for 2029 data from DHR to be included in the final analysis. This would increase the time to include patients in the etranacogene dezaparvovec arm from about 15 to about 27 months and thus likely increase the robustness of available evidence significantly. In case a G-BA resolution is passed to adjust timelines and postpone the final submission of the dossier, the timepoint of latest possible switch from FIX to etranacogene dezaparvovec would be adjusted accordingly to enable 3 years of data collection for all patients. The changes would be subject to an amendment and communicated to G-BA.

6 Rationale and Background

6.1 Haemophilia B

Haemophilia B is a rare haemorrhagic disorder characterised by a partial or complete deficiency of coagulation factor IX (FIX) manifesting as spontaneous or prolonged bleeding episodes [3]. Haemophilia B is caused by an X-linked recessive mutation of the F9 gene, therefore primarily male patients are affected whereas symptomatic female carriers generally present with milder clinical manifestation [4]. The incidence for haemophilia B is much lower than haemophilia A, accounting for approximate 15 % of the total haemophilic population [5].

The disease severity is categorized as severe (< 1 % residual FIX activity), moderately severe (1–5 % residual FIX activity) or mild (> 5 to < 40 % residual FIX activity) according to residual plasma factor levels which resembles the biological effectiveness of blood coagulation [6]. Patients with severe haemophilia B account for approximately 30-40 % of haemophilia B cases [7]. Adult patients with severe haemophilia are at highest risk of spontaneous bleeding, mainly into joints (most commonly the ankle, knee, and elbow joints, and frequently the hip, shoulder, and wrist joints) and muscle tissue (in particular iliopsoas and gastrocnemius) presenting as haemarthroses or muscle haematomas [8]. Recurrent bleeding into joint spaces results in chronic arthropathy associated with stiffness and joint deformation, finally leading to severe physical impairment [9]. Therefore, prophylaxis with clotting factor concentrates (CFC) is referred to as regular replacement therapy; it stands in contrast to episodic replacement therapy (on-demand therapy), which is defined as the administration of CFCs only at times when bleeding occurs [8]. The most serious complication of replacement therapy is the development of neutralizing antibodies against the exogenously factor concentrates although factor inhibitor occurrence in haemophilia B is less common than in haemophilia A. According to international literature, factor inhibitor formation affects about 3-5 % of patients with haemophilia B [8, 10]. Until recently, the mainstay of treatment for severe or moderately severe haemophilia B patients without inhibitors was regular FIX prophylaxis.

The current treatment options for haemophilia B have several limitations. Treatment with prophylactic regular intravenous (IV) injections of FIX is not curative and very demanding due to the need for frequent IV infusions and concomitant risk for infection and thromboses related to the placement of indwelling catheters. Periodic or regular FIX infusion result in peaks and troughs in plasma factor levels allowing for breakthrough bleeding episodes. Due to these factors, poor adherence to treatment is a concern and a major contributing factor to failure of prophylaxis, associated with increased risk of bleeding and subsequent joint damage, thereby

adding to the all-cause morbidity and mortality rate. There is also a risk of developing neutralizing antibodies against the administered FIX. The burden of the disease is high, both for the individual subject and their families, and for society. Due to (long-term) impairments in mobility and functional status, subjects may not be able to fully participate in social activities, such as sports, school, or work. Living with haemophilia can have a substantial effect on mental wellbeing, particularly among young people and signs of major depressive disorder are not uncommon. The economic burden for the society is significant [2].

However, advances in medical treatment focusing on gene replacement now enable an alternative treatment concept within haemophilia B, changing the management and prognosis of affected patients. While other gene therapies are likely to follow within the next years, etranacogene dezaparvovec is the first and as of today the only approved gene therapy for haemophilia B in Europe.

6.2 Benefit assessment for etranacogene dezaparvovec

Etranacogene dezaparvovec (Hemgenix®) is a gene therapy medicinal product. Hemgenix® is administered as a single-dose IV infusion (see section 6.4.1). Etranacogene dezaparvovec received conditional marketing authorization as an orphan drug by the European Commission on 20 February 2023 for the following indication: “Treatment of severe and moderately severe haemophilia B (congenital FIX deficiency) in adult patients without a history of FIX inhibitors”.

According to § 35a of the Book Five of the Social Code (SGB V), the Federal Joint Committee (G-BA) evaluates the additional benefit of reimbursable medicinal products with new active ingredients, and pharmaceutical companies are obliged to submit a dossier on product benefit when a new product is launched on the German market or authorized for new indications. The purpose of early benefit assessment in Germany is to compare newly authorized drugs to an appropriate comparative therapy (ACT) in order to establish a ruling on their additional benefit, which serves as the basis for price negotiations between the manufacturer and the National Association of Statutory Health Insurance Funds (GKV-SV).

CSL Behring submitted a dossier for the early benefit assessment on 1 May 2023. The benefit assessment procedure is currently ongoing and G-BA´s resolution on the added benefit is expected for 19 October 2023.

6.3 Routine Practice Data Collection and Evaluations for etranacogene dezaparvovec

On 12 May 2023, G-BA requested the Routine Practice Data Collection and Evaluations (anwendungsbegleitende Datenerhebung, AbD) according to § 35a paragraph 3b SGB V for etranacogene dezaparvovec (Hemgenix®) [11]. The resolution was preceded by a G-BA resolution of 4 August 2022 [12], which initiated the procedure as well as a concept development by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) of 13 January 2023 [13]. In preparation of the present study protocol and statistical analysis plan, an advice meeting was held between CSL Behring and G-BA which took place on 9 August 2023.

Along with the resolution mandating the AbD, G-BA passed a resolution restricting reimbursement of etranacogene dezaparvovec to physicians participating in the AbD on 12 May 2023 [14].

Prior to the initiation of the specific procedures mandating the AbD for etranacogene dezaparvovec, IQWiG was commissioned to develop methodological guidance for this new form of evidence generation, which was published as a rapid report in January 2020 [15].

As required by the G-BA code of procedure, two out of three G-BA resolutions on etranacogene dezaparvovec included a public consultation procedure allowing for a participation of stakeholders, including clinical haemophilia experts. Table 1 summarizes the relevant G-BA procedures as well as their public consultations.

Table 1: Relevant G-BA procedures concerning the AbD for etranacogene dezaparvovec

G-BA procedure	Resolution date	Public consultation
Initiation of a procedure to request AbD for etranacogene dezaparvovec	4 August 2022	None
Requirement of AbD	12 May 2023	Written statements on IQWiG concept development: 13 February 2023 Exchange of expertise on IQWiG concept development: 6 March 2023
Restriction of the Authority to Supply Care	12 May 2023	Written statements: 23 March 2023 (no oral hearing conducted)
Abbreviations: AbD: Routine Practice Data Collection and Evaluations (anwendungsbegleitende Datenerhebung); G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)		

The G-BA resolution from 12 May 2023 [11] defined a number of aspects for the AbD for etranacogene dezaparvovec. The population to be included in the study as well as intervention, comparator, and outcomes are defined by a Patient-Intervention-Comparator-Outcome (PICO) scheme as depicted in Table 2.

Table 2: PICO scheme for AbD for etranacogene dezaparvovec [11]

Category	Requirements of G-BA resolution
Population	Adults with severe and moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors.
Intervention	• Etranacogene dezaparvovec The marketing authorization and the dosage information in the product information of etranacogene dezaparvovec must be taken into account. It is assumed that the patients within the approved label of etranacogene dezaparvovec are eligible for prophylaxis (not for a sole treatment on-demand). A treatment on-demand alone is not considered an adequate comparator therapy. A treatment on-demand must however be possible in all study arms.
Comparator	• Prophylactic FIX treatment The marketing authorization and the dosage information in the product information of FIX products must be taken into account. It is assumed that the patients within the approved label of etranacogene dezaparvovec are eligible for prophylaxis (not for a sole treatment on-demand). A treatment on-demand alone is not considered an adequate comparator therapy. A treatment on-demand must however be possible in all study arms.

Outcome	Mortality
	• Deaths
	
	Morbidity
	• Pain measured with a validated instrument
	• Joint function measured with a validated instrument
	• Bleeding
	  o Severe bleeding
	  o Life-threatening bleeding
	  o Joint bleeding
	  o Treated bleeding
	
	Health-related quality of life
	
	Side effects
	• Serious adverse events (operationalized as events leading to hospitalization or death; overall rate)
	• Specific adverse events (with indication of the respective severity)
	  o Thromboembolic events
	  o Development of FIX inhibitors
	  o Symptomatic liver damage
	  o Malignant neoplasms

Category	Requirements of G-BA resolution
Supplementary information on the question	Supplementary information on: • Number of factor concentrates consumed, separated by on-demand and prophylactic treatment • Time of return to prophylactic treatment
Abbreviation: AbD: Routine Practice Data Collection and Evaluations (anwendungsbegleitende Datenerhebung, AbD); FIX: Coagulation Factor IX; PICO: Patient-Intervention-Comparator-Outcome	

In addition to the PICO scheme, G-BA defined that either the German Haemophilia Registry (Deutsches Hämophilieregister, DHR) or a data platform set up for the purpose of AbD is to be used as the primary data source provided that the quality criteria mentioned in Table 3 are fulfilled.

The G-BA resolution of 12 May 2023 [11] further required CSL Behring to submit a study protocol and statistical analysis plan (SAP) to G-BA by 12 October 2023, in which information on a number of aspects depicted in Table 3 is to be provided. A consultation meeting was held between CSL Behring and G-BA on 9 August 2023. The aspects discussed were incorporated into the study protocol as well as the statistical analysis plan.

Table 3: Requirements on data source, study protocol, and SAP per G-BA resolution [11]

Aspect	Requirements as per G-BA resolution
Data Source	Data source requirement Use of registries or a data platform to be set up specifically for the present Routine Practice Data Collection as a data source, which meet the requirements of Routine Practice Data Collection and fulfil at least the following quality criteria: • Detailed registry description or description of the data platform (protocol) • Exact definition or operationalization of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints and confounders • Use of standard classifications and terminologies • Use of validated standard data collection tools (questionnaire, scales, tests) • Training courses on data collection and recording • Implementation of a consensus disease-specific core data set • Use of exact dates for the patient, the disease, important examinations and treatments/ interventions • Clearly defined inclusion and exclusion criteria for patients • Strategies to avoid selection bias in patient inclusion to achieve representativeness • Specifications to ensure completeness of data per data collection time point and completeness of data collection time points • Source data verification (SDV) for 100 % of patients per data collection site for the primary endpoint and for at least 10 % of randomly selected patients per data collection site for all other endpoints over the period since the start of data collection When using a registry: Ensuring scientific independence and transparency Use of a registry or a data platform to be set up specifically for the present routine

Aspect	Requirements as per G-BA resolution
	practice data collection, in which treatment of haemophilia B is carried out in accordance with German daily care or is sufficiently similar to care in Germany Primary data source and integration of further data sources For the study design in the form of a comparator registry study, the following specifications must be taken into account: • Use of the German Haemophilia Registry (DHR) as primary registry, provided that the quality criteria are fulfilled • It is also possible to integrate other registries, taking into account all the data source requirements
Duration & scope of data collection	At present, it cannot be estimated how long sufficient factor IX activity can be maintained under gene therapy. For gene therapy in haemophilia A, there is initial evidence that factor VIII activity wanes after 1 to 2 years following gene therapy. The present case also involves a gene therapy for the treatment of a congenital blood coagulation factor deficiency. Therefore, due to the limited data available, the following observation period should be implemented when collecting the data accompanying the application: • Observation period of at least 3 years As an approximation of the appropriate number of cases for the routine practice data collection, possible scenarios based on the endpoint annual bleeding rate (ABR) are assumed in the result of an orienting sample size estimate: • Assumption of a distribution of 1:5 between intervention and comparator group, ABR = 0.8 under the intervention and ABR = 3 under the comparator therapy: o 325 patients (intervention group n = 55, comparator group n = 270) • Assumption of a distribution of 1:5 between intervention and comparator group, ABR = 1 under the intervention and ABR = 3.6 under the comparator therapy: o 349 patients (intervention group n = 59, comparator group n = 290) On the basis of this orienting sample size estimate on the basis of estimated or theoretically established effect assumptions, exemplary case numbers result in an order of magnitude at which it can be assumed that Routine Practice Data Collection for the present research question is feasible in principle. The final sample size planning is part of the study documents to be prepared.
Evaluations of the data for the purpose of the benefit assessment	The pharmaceutical company shall submit the following evaluations to the G-BA: • Interim analyses Evaluations of 3 interim analyses shall be presented. The relevant times for the performance of the interim analyses shall be the times specified in section 2.3. The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan. In the process, a check for discontinuation due to futility must also be carried out for each interim analysis. On the 1st interim analysis: Based on this interim analysis, a final sample size estimate will be made using the more precise effect assumptions rendered possible. If necessary, this can also be carried out at this time on the basis of benefit endpoints other than those mentioned in the present resolution and taking into account a shifted

Aspect	Requirements as per G-BA resolution
	hypothesis boundary in accordance with the procedure in IQWiG's concept. The interim analyses shall be prepared on the basis of module 4 of the dossier template, providing the full texts and study documents. • Final evaluations for the purpose of the renewed benefit assessment The final evaluations shall be carried out according to the specifications in the study protocol and statistical analysis plan. For the transmission of the final evaluations to the G-BA, the time specified in section 3 applies. The final evaluations shall be prepared in a dossier in accordance with the provisions of Section 9 paragraphs 1 to 7 of the Rules of Procedure of the G-BA
Protocol & SAP	The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out Routine Practice Data Collection and Evaluations. When preparing the study protocol and statistical analysis plan, the pharmaceutical company shall address the necessary adaptations to the identified indication-specific registry. With regard to the implementation of the collection of patient-reported endpoints on health-related quality of life, for the approval of the study documents, it must be confirmed: • To what extent an adaptation of the identified indication registry to the present requirements regarding the recording of patient-reported health-related quality of life is possible and within what period of time this can be done. With regard to the evaluation of the data, the following information in particular must be presented in advance in the study protocol and statistical analysis plan: • Information on the statistical methods and models used, as well as naming the procedures and the criteria used in model selection and adaptation • Information on the expected scope and reasons for missing data, as well as measures to avoid missing data and evaluation strategies to deal with missing data • Information on dealing with implausible data and outliers • Prespecification of a sensitivity analysis for the separate evaluation of the data on etranacogene dezaparvovec versus the data on recombinant or human plasma-derived coagulation factor IX preparations • Information on patients with AAV5 antibodies and testing of the feasibility of a subgroup analysis for the evaluation of the patient population with known AAV5 antibody status. For subgroup analyses, a sufficient number of patients or events must be available; the specifications in section 4.3.1.3.2. of Module 4 must be observed. • Information on other planned sensitivity analyses • Information on the standardization of the start of patient observation • Information on the identification, as well as the adequate, pre-specified adjustment for confounders • Information on the investigation of potential effect modifiers • Information on interim analyses taking into account requirements and specifications • Information on discontinuation criteria due to futility
Abbreviation: AAV5: Adeno-Associated Virus serotype 5; ABR: Annualized Bleeding Rate; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); FIX: Coagulation Factor IX; G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss); IQWiG: Institute for Quality and Efficiency in Health Care; n: number of patients; SAP: Statistical Analysis Plan; SDV: Source Data Verification	

6.4 Compared treatments: mode of action, administration and dosage

6.4.1 Etranacogene dezaparvovec

Etranacogene dezaparvovec (Hemgenix®) is a gene therapy medicinal product that allows for the expression of human coagulation FIX. It is a non-replicating, recombinant adeno-associated virus serotype 5 (AAV5) based vector containing a codon-optimised (self-) complementary deoxyribonucleic acid (cDNA) of the human coagulation FIX variant R338L (FIX-Padua) gene under the control of a liver-specific promoter (LP1). Etranacogene dezaparvovec is produced in insect cells by recombinant DNA technology [1].

Prior to the treatment with etranacogene dezaparvovec, patients need to be tested for the titre of pre-existing FIX inhibitors. Etranacogene dezaparvovec should only be administered to patients who have demonstrated absence of FIX inhibitors, also in the past. In case of a positive test result for human FIX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive etranacogene dezaparvovec. In addition, patients should be tested for the titre of neutralizing anti-AAV5 antibodies because pre-existing neutralizing anti-AAV5 antibodies above a titre of 1:678 (using the 7-point-assay) may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of etranacogene dezaparvovec therapy [1].

Etranacogene dezaparvovec is administered as a single-dose IV infusion. The summary of product characteristics (SmPC) recommends a single dose of 2×10^{13} gene copies per kg body weight corresponding to 2 mL/kg body weight, administered as an IV infusion after dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection. As of now, Hemgenix® can be administered only once [1].

The onset of effect from etranacogene dezaparvovec treatment may occur within several weeks post-dose. Therefore, haemostatic support with exogenous human FIX may be needed during the first weeks after etranacogene dezaparvovec infusion to provide sufficient FIX coverage for the initial days post-treatment [1].

6.4.2 FIX concentrates

The primary goals of haemophilia B therapy are the prevention of bleeding episodes, rapid and definitive treatment of bleeding episodes (breakthrough bleeding episodes) that occur even while on a regular prophylactic regimen and provision of adequate haemostasis during surgery

and emergencies. Currently, these goals are essentially met for haemophilia B subjects by IV injections of commercially available recombinant- or plasma-derived FIX products, either at the time of a bleeding episode (on-demand) or by regular infusions up to several times a week (prophylactically). The recent approvals of extended half-life FIX products allow for reduced frequency of factor administration (once every 7 to 14, or even 21 days) and maintenance of a higher FIX trough level [2].

Prophylaxis with FIX concentrates is referred to as regular replacement therapy; as opposed to episodic replacement therapy (on-demand therapy) which is defined as the administration of CFCs only at times when bleeding occurs. Due to the severity of bleeding phenotype, haemophilia B patients with severe or moderately severe disease routinely receive a prophlylactic FIX replacement therapy, which is complemented by an on-demand FIX treatment if needed.

The definition of an ACT by G-BA for the mandated AbD includes all approved FIX concentrates in Germany, either plasma-derived or recombinant FIX (including normal-half-life as well as extended-half-life products). Hence, all approved FIX concentrates can be used for prophylactic treatment and no further definition is needed. Both mode of administration and dosage of FIX prophylaxis should be in line with the recommendations of the corresponding SmPC as shown in Table 4.

Table 4: Authorized FIX propylaxis products for FIX replacement in German health care

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
Recombinant FIX concentrates			
Nonacog alfa (BeneFIX®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Nonacog alfa can be used for all age groups.	Nonacog alfa is administered by IV infusion after reconstitution of the lyophilized powder with sterile 0.234 % sodium chloride solution. In most cases it is administered at an infusion rate of up to 4 mL/min. In general, it should be administered at a slow infusion rate and the rate should be determined by patient's individual comfort level. Nonacog alfa can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition. <u>Long-term prophylaxis:</u> In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days. <u>On-demand treatment:</u> The calculation of the required dose of nonacog alfa can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 0.8 IU/dL (range from 0.4 to 1.4 IU/dL) in patients 12 years and older. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg]\ \times desired\ FIX\ increase\ [\%]\ or\ \left[\frac{IU}{dL}\right] \times 1.3\frac{dL}{kg}$ $1.3\frac{dL}{kg}$: reciprocal of observed recovery ($1\frac{IU}{kg} \div 0.8\frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of haemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of haemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	[16]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
Nonacog gamma (Rixubis®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Nonacog gamma is indicated in patients of all age groups.	Nonacog gamma is administered by IV infusion after reconstitution of the powder with the supplied solvent. The solution should then be clear, colourless, free from foreign particles and has a pH of 6.8 to 7.2. The osmolality is greater than 240 mosmol/kg. It can be either self-administered or administered by a caregiver. In both cases appropriate training is needed beforehand. Administration should be performed using a rate that ensures the comfort of the patient, up to a maximum of 10 mL/min. Nonacog gamma can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition, age and pharmacokinetic parameters of FIX (e.g., incremental recovery, half-life). <u>Long-term prophylaxis:</u> Usually doses of 40 to 60 IU of FIX per kg body weight are administered at intervals of 3 to 4 days for patients 12 years and older. <u>On-demand treatment:</u> The calculation of the required dose of nonacog gamma can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 0.9 IU/dL (range from 0.5 to 1.4 IU/dL) in patients 12 years and older. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg] \times desired\ FIX\ increase\ [\%\ ]\ or\ \left[\frac{IU}{dL}\right] \times 1.1\frac{dL}{kg}$ $1.1\frac{dL}{kg}$: reciprocal of observed recovery ($1\frac{IU}{kg} \div 0.9\frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of haemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of haemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	[17]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
Albutrepenonacog alfa (Idelvion®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Albutrepenonacog alfa can be used for all age groups.	Albutrepenonacog alfa is administered by IV infusion after reconstitution of the powder with the supplied solvent. Administration should be performed slowly using a rate that ensures the comfort of the patient, up to a maximum of 5 mL/min. Albutrepenonacog alfa can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition. <u>Long-term prophylaxis:</u> Usually doses of 35 to 50 IU/kg once weekly are administered. Well-controlled patients on a once-weekly regimen might be treated with up to 75 IU/kg at intervals of 20 to 14 days. Depending on patient's age dose intervals may be extended (> 18 years) or shortened (younger patients). After a bleeding episode during prophylaxis, patients should maintain their prophylaxis regimen as closely as possible, with 2 doses of albutrepenonacog alfa being administered at least 24 hours apart but longer if deemed suitable for the patient. <u>On-demand treatment:</u> The calculation of the required dose of albutrepenonacog alfa can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 1.3 IU/dL in patients 12 years and older. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg]\ \times desired\ FIX\ increase\ [\%\ ]\ or\ \left[\frac{IU}{dL}\right] \times 0.77\frac{dL}{kg}$ $0.77\frac{dL}{kg}$: reciprocal of observed recovery ($1\frac{IU}{kg} \div 1.3\frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of haemorrhage and surgery vary within a range from 30 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of haemorrhage and type of surgical	[18]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
		procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	
Nonacog beta pegol (Refixia®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Nonacog beta pegol can be used for all age groups.	Nonacog beta pegol is administered by IV bolus injection over several minutes after reconstitution of the powder for injection with the histidine solvent. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 mL/min. It can be either self-administered or administered by a caregiver. In both cases appropriate training is needed beforehand. Noncog beta pegol can be used as prophylaxis or as on-demand treatment. <u>Long-term prophylaxis:</u> Usually doses of 40 IU/kg body weight are administered once weekly. Adjustments of doses and administration intervals may be considered based on achieved FIX levels and individual bleeding tendency. <u>On-demand treatment:</u> Dose and duration of the substitution therapy depend on the location and severity of the bleeding. General recommendations on dosage in case of haemorrhage and surgery vary within a range from 40 to 80 IU/kg which corresponds to the required FIX level and depends on the degree of haemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	[19]
Eftrenonacog alfa (Alprolix®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Eftrenonacog alfa can be used for all age groups.	Eftrenonacog alfa is administered by IV injection over several minutes after reconstitution of the powder for injection with the suppied solvent (sodium chloride solution). The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 10 mL/min. It can be either self-administered or administered by a caregiver. In both cases appropriate training is needed beforehand. Eftrenonacog alfa can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient’s clinical condition. <u>Long-term prophylaxis:</u>	[20]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
		Recommended starting regimens are either: • 50 IU/kg once weekly, adjust dose based on individual response or • 100 IU/kg (highest recommended dose) once every 10 days, adjust interval based on individual response. Some patients who are well-controlled on a once every 10 days regimen might be treated on an interval of 14 days or longer. <u>On-demand treatment:</u> The calculation of the required dose of eftrenonacog alfa can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 1.0 IU/dL. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg] \times desired\ FIX\ increase\ [\%]\ or\ \left[\frac{IU}{dL}\right] \times 1.0\frac{dL}{kg}$ $1.0\frac{dL}{kg}$: reciprocal of observed recovery ($1\frac{IU}{kg} \div 1.0\frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of haemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of haemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	
Human plasma-derived FIX concentrates			
FIX (Alphanine®, Octanine®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency).	FIX is administered by IV injection after reconstitution of the powder for injection with the suppied solvent. The rate of administration should be determined by the patient's comfort level: Alphanine®: maximum injection rate at 10 mL/min Octanine®: maximum injection rate at 2 to 3 mL/min Haemonine®: maximum injection rate at 2 to 3 mL/min Immunine®: maximum injection rate at 2 mL/min FIX can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency,	[21, 22]
FIX (Haemonine®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency).		[23]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
	FIX is indicated in adults, adolescents and children aged 6 years and older.	on the location and extent of bleeding, and on the patient's clinical condition.	
FIX (Immunine®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). FIX can be used for all age groups - from children older than 6 years up to adults. The use of FIX in children under 6 years of age cannot be recommended as insufficient data are available for this purpose.	<u>Long-term prophylaxis:</u> Usually doses of 20 to 40 IU/kg body weight are administered at intervals of 3 to 4 days. <u>On-demand treatment:</u> The calculation of the required dose can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 1.0-2.0 IU/dL. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg] \times desired\ FIX\ increase\ [\%]\ or\ \left[\frac{IU}{dL}\right] \times x\frac{dL}{kg}$ $x\frac{dL}{kg}$: reciprocal of observed recovery ($\frac{IU}{kg}$ per $\frac{IU}{dL}$) Alphanine®: $x\frac{dL}{kg} = 0.8\frac{dL}{kg}$ Octanine®: $x\frac{dL}{kg} = 0.8\frac{dL}{kg}$ Haemonine®: $x\frac{dL}{kg} = 0.8\frac{dL}{kg}$ Immunine®: $x\frac{dL}{kg} = 0.9\frac{dL}{kg}$ The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of haemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of haemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	[24]

Abbreviations: FIX: Coagulation Factor IX; IU: International Units; IV: intravenous; pH: potential of Hydrogen; PTP: Previously Treated Patients; SmPC: Summary of Product Characteristics; WHO: World Health Organization

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
[1]The number of units of FIX administered is expressed in International Units (IU), in accordance to the current WHO standard for FIX products. FIX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FIX in plasma). One IU of FIX activity is equivalent to the quantity of FIX in one mL of normal human plasma.			

7 Research Question and Objectives

7.1 Research Question

The objective of this study is to evaluate the overall effectiveness and tolerability in FIX pre-treated adults with severe and moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors treated with gene therapy etranacogene dezaparvovec (Hemgenix®) compared to FIX prophylaxis.

The effectiveness and tolerability will be assessed based on patient-relevant endpoints. An endpoint is considered patient-relevant if it depicts how a patient feels, can perform his or her functions and activities, or whether he or she survives [25]. The endpoints depicted in this study are based on the PICO-scheme included in the G-BA resolution mandating this study [11].

Effectiveness covers the topics:

- Survival
- Bleeding
- Pain
- Joint Status
- Health-related quality of life (HRQoL)

Tolerability covers the topics:

- Adverse events (AE)
- Serious adverse events (SAE) approximated as AE leading to hospitalization or death
- Adverse events of special interest (AESI)
- Serious adverse events of special interest (SAESI) approximated as AESI leading to hospitalization or death

Exploratory endpoints cover the following:

- FIX utilization:

- Annualized infusion rate of prophylactic FIX concentrates (number of infusions), Annualized infusion rate of on-demand FIX concentrates (number of infusions), Time to return to prophylactic FIX therapy (etranacogene dezaparvovec only)

The outcomes of this study are to be used in a future benefit assessment according to § 35a SGB V in Germany. It is acknowledged that G-BA recommended the formulation of a formal hypothesis using a shifted null hypothesis building on IQWiG's proposed effect thresholds [11, 25]. However, decisions on an additional benefit are the sole responsibility of G-BA's decision-making processes in the benefit assessment procedures and have always been independent from any potential hypotheses formulated in confirmatory clinical studies. In the setting of this non-interventional, non-confirmatory study, all endpoints will thus be analyzed and reported to G-BA for its decision-making without formulation of a formal hypothesis.

7.2 Primary Objective(s)

The primary objective of this study is to evaluate the effectiveness of etranacogene dezaparvovec compared to FIX prophylaxis, as measured by the annualized bleeding rates of all treated bleeding (ABR_all treated bleeding), in FIX pre-treated adults with severe and moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors.

7.2.1 Effectiveness: Annualized Bleeding Rate (ABR)

ABR_all treated bleeding is defined as the cumulative number of all bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.

In clinical trials ABR is usually defined as the cumulative number of all bleeding events that require FIX treatment as well as those not requiring FIX treatment. However, G-BA has mandated the collection of data explicitly for treated bleeding in its resolution from 12 May 2023 [11] and thus the primary endpoint is determined as ABR of all treated bleeding.

7.3 Secondary Objective(s)

The secondary objectives of this study are to evaluate additional effectiveness and tolerability aspects of etranacogene dezaparvovec compared to FIX prophylaxis in FIX pre-treated adults with severe and moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors.

7.3.1 Effectiveness: Survival

Overall Survival (OS) is defined as the time (in months) from baseline to the date of death. Event is death from any cause and censored otherwise. Time for censored patients is defined as the time from the baseline to lost-to-follow-up or end of the study.

7.3.2 Effectiveness: Bleeding

ABR_severe bleeding is defined as the cumulative number of all severe bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.

ABR_life-threatening bleeding is defined as the cumulative number of all life-threatening bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.

ABR_joint bleeding is defined as the cumulative number of all joint bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.

The inclusion of severe and life-threatening bleeding as separate endpoints has been requested by G-BA. While a differentiation in the individual case might be possible at the discretion of the treating physician, a generally accepted definition for those endpoints is not available. However, the two bleeding endpoints need to be defined to ensure data comparability and outcome analysis. Therefore, those bleeding are defined in accordance to Pediatric Network on haemophilia management's (PedNET) definitions (used by DHR) on severe and life-threatening bleeding[3]. Within the DHR, these definitions are visible in the data entry mask for the documenting sites.

- Severe bleeding: Severe bleeding is a bleeding causing pain, swelling, and/ or mobility impairment which do not resolve within 24 hours

[3] Mild bleeding definition used by DHR: bleeding causing mild pain, mild swelling, and/ or mild mobility impairment which resolve within 24 hours.

- Life-threatening bleeding: Life-threatening bleeding is a severe bleeding which may present a particular risk to the patient

For joint bleeding, the DHR uses the definition by the International Society on Thrombosis and Haemostasis (ISTH). Hence, joint bleeding is defined in accordance to ISTHs´ definition [6] as the following:

- Joint bleeding: a joint bleeding is an unusual sensation 'aura' in the joint, in combination with any of the following: (a) increasing swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline.

7.3.3 Effectiveness: Pain

BPI-SF (Brief Pain Inventory – Short Form) is a validated, patient-reported instrument for the assessment of pain. The BPI-SF is a 9-item self-administered questionnaire used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning. The subject is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 11-point numerical rating scale (NRS) (0 = no pain, 10 = worst pain imaginable) [26, 27].

The present study aims for a patient-reported assessment of the symptom pain using the BPI-SF. Treatment centers are asked and trained to carry out BPI-SF assessments for patients included in this study at baseline and twice per year (every 6 months +/- 2.5 months) during follow up. Compared to clinical trials in which the BPI-SF is commonly used, there are significantly less frequent data points in the routine care [28, 15]. According to the manual, the evaluation of individual items on pain intensity in the questionnaire is possible [27]. Hence, item no. 5 of the BPI-SF is considered as appropriate to assess average pain in the context of this study setting in haemophilia as this item does not use a 24-hour recall period while all other scales of the BPI-SF explicitly do.

Financial compensation is provided to enhance documentation (see section 14.1.3). However, there are uncertainties about the actual points of assessment and documentation in 6-month intervals cannot be controlled in the non-interventional setting of the present study. The endpoints are thus evaluated as binary responder analyses over the entire observation period as recommended by IQWiG in the G-BA consultation [28].

BPI-SF_Worsening is defined as change from baseline in average pain (scale no. 5) and is analyzed as binary responder analysis. Patients showing an average pain rating two or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 10) at the end of observation period qualify as responders.

BPI-SF_Improvement is defined as change from baseline in average pain (scale no. 5) and is analyzed as binary responder analysis. Patients showing an average pain rating two or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 10) at the end of observation period qualify as responders.

7.3.4 Effectiveness: Joint Status

HJHS (Hemophilia Joint Health Score) is a validated, clinician-reported instrument for the assessment of joint status in haemophilia patients. The HJHS measures joint health, in the domain of body structure and function (i.e., impairment), of the joints most commonly affected by bleeding in haemophilia: the knees, ankles and elbows. Each index joint is assessed by 8 different items covering swelling (0-3), duration of swelling (0-1), muscle atrophy (0-2), crepitus on motion (0-2), flexion loss (0-3), extension loss (0-3), joint pain (0-2) and strength (0-4). Each index joint can reach a value of 20. In addition, global gait is assessed as an individual item on a 5-point scale (0-4). The total HJHS score is the sum of all 6 index joint scores and the global gait score and can reach a value of 124, with a higher score indicating worse joint health [29].

The present study aims for the assessment of the joint status using the HJHS (version 2.1). Treatment centers are asked and trained to carry out HJHS assessments for patients included in this study at baseline and twice per year (every 6 months +/- 2.5 months) during follow up. Financial compensation is provided to enhance documentation (see section 14.1.3). However, there are uncertainties about the actual points of assessment and documentation in 6-month intervals cannot be controlled in the non-interventional setting of the present study. The endpoints are thus evaluated as binary responder analyses over the entire observation period as recommended by IQWiG in the G-BA consultation [28].

HJHS_Worsening is defined as change from baseline in HJHS total score and is analyzed as binary responder analysis. Patients showing a HJHS total score 19 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 124) at the end of observation period qualify as responders.

7.3.5 Effectiveness: Health-Related Quality of Life (HRQoL)

The Haemophilia-specific Health-related Quality of Life Questionnaire for Adults (Haemo-QoL-A) is a specifically designed measure to capture aspects of health-related quality of life (HRQoL) for adult subjects with haemophilia. It consists of 41 items pertaining to 6 dimensions (physical functioning (9 items), role functioning (11 items), worry (5 items), consequences of bleeding (7 items), emotional impact (6 items) and treatment concerns (3 items)). Each item will be answered on a 6-point Likert scale ranging from 0 (never) to 5 (always) and the results of each sub-scale will be subsequently transformed on a scale from 0 to 100. The combination of scores of the sub-scales results in the total score, reaching values from 0 to 30 which will also be transformed on a scale from 0 to 100. A total score of 100 represents the highest quality of life [30–32].

The present study aims for a patient-reported assessment of the HRQoL using the Haemo-QoL-A. Treatment centers are asked and trained to carry out Haemo-Qol-A assessments for patients included in this study at baseline and twice per year (every 6 months +/- 2.5 months) during follow up. Financial compensation is provided to enhance documentation (see section 14.1.3). However, there are uncertainties about the actual points of assessment and documentation in 6-month intervals cannot be controlled in the non-interventional setting of the present study. The endpoints are thus evaluated as binary responder analyses over the entire observation period as recommended by IQWiG in the G-BA consultation[28].

Haemo-QoL-A: Total Score_Worsening is defined as change from baseline in Haemo-QoL-A total score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A total score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Total Score_Improvement is defined as change from baseline in Haemo-QoL-A total score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A total score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Physical Functioning_Worsening is defined as change from baseline in Haemo-QoL-A physical functioning domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A physical functioning domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Physical Functioning_Improvement is defined as change from baseline in Haemo-QoL-A physical functioning domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A physical functioning domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Role Functioning_Worsening is defined as change from baseline in Haemo-QoL-A role functioning domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A role functioning domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Role Functioning_Improvement is defined as change from baseline in Haemo-QoL-A role functioning domain score and is analyzed as binary responder analysis. Patients a Haemo-QoL-A role functioning domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Worry_Worsening is defined as change from baseline in Haemo-QoL-A worry domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A worry domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Worry_Improvement is defined as change from baseline in Haemo-QoL-A worry domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A worry domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Consequences of Bleeding_Worsening is defined as change from baseline in Haemo-QoL-A consequences of bleeding domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A consequences of bleeding domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Consequences of Bleeding_Improvement is defined as change from baseline in Haemo-QoL-A consequences of bleeding domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A consequences of bleeding domain score 15 or more

points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Emotional Impact_Worsening is defined as change from baseline in Haemo-QoL-A emotional impact domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A emotional impact domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Emotional Impact_Improvement is defined as change from baseline in Haemo-QoL-A emotional impact domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A emotional impact domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Treatment Concerns_Worsening is defined as change from baseline in Haemo-QoL-A treatment concerns domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A treatment concerns domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Treatment Concerns_Improvement is defined as change from baseline in Haemo-QoL-A treatment concerns domain score and is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A treatment concerns domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

7.3.6 Tolerability

Adverse events are entered into the DHR as a choice and/or free-text field. All tolerability endpoints are reported from baseline to censoring. For censoring reasons, please refer to SAP section 8.2.7.

7.3.6.1 Adverse Events (AE)

AE is a binary endpoint and defined as proportion of patients reporting an AE.

7.3.6.2 Serious Adverse Events (SAE)

SAE is a binary endpoint and defined as proportion of patients reporting a SAE. Seriousness is approximated via information on AE leading to hospitalization as well as death due to AE.

7.3.6.3 Adverse Events of Special Interest (AESI)

AESI_Thromboembolic is a binary endpoint and defined as proportion of patients reporting an AE that is classified as a thromboembolic event.

AESI_FIX_Inhibitor is a binary endpoint and defined as proportion of patients reporting an AE that is classified as development of FIX inhibitors.

AESI_Liver is a binary endpoint and defined as proportion of patients reporting an AE that is classified as symptomatic liver damage.

AESI_Neoplasms is a binary endpoint and defined as proportion of patients reporting an AE that is classified as malignant neoplasms.

7.3.6.4 Serious Adverse Events of Special Interest (SAESI)

SAESI_Thromboembolic is a binary endpoint and defined as proportion of patients reporting an AE that is classified as a thromboembolic event. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

SAESI_FIX_Inhibitor is a binary endpoint and defined as proportion of patients reporting an AE that is classified as development of FIX inhibitors. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

SAESI_Liver is a binary endpoint and defined as proportion of patients reporting an AE that is classified as symptomatic liver damage. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

SAESI_Neoplasms is a binary endpoint and defined as proportion of patients reporting an AE that is classified as malignant neoplasms. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

7.3.7 Exploratory endpoints

FIX_Utilization_Prophylaxis - Annualized infusion rate of prophylactic FIX concentrates (number of infusions) is defined as the cumulative amount of all consumed single doses

(number of infusions) of prophylactic FIX concentrates per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.

FIX_Utilization On-Demand - Annualized infusion rate of on-demand FIX concentrates (number of infusions) is defined as the cumulative amount of all consumed single doses (number of infusions) of on-demand FIX concentrates per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.

Return to prophylactic FIX therapy is defined exclusively for patients in the intervention arm of the study as the time between baseline and date of return to prophylactic FIX therapy based on therapy documentation.

8 Research Methods

8.1 Study Design

8.1.1 Research Design and Rationale

The study is a non-interventional, non-randomized, registry-based data collection in subjects with severe or moderately severe haemophilia B treated with the gene therapy etranacogene dezaparvovec (Hemgenix®) compared to a prophylaxis with either recombinant or plasma-derived FIX products. The study is based on secondary use of data from the DHR [33–35].

Subjects are enrolled until 1 January 2026. They are enrolled when they first meet the inclusion and exclusion criteria of the study, signed informed consent and have the first data submission to DHR following a number of changes that need to be implemented in the DHR case report form (CRF) (baseline). Patients are then observed until the date of data cut for final analysis (31 December 2028) or loss to follow-up.

Planned number of patients

All patients fulfilling inclusion while not fulfilling exclusion criteria (both for etranacogene dezaparvovec and FIX prophylaxis comparator) will be included in the study. As the study is conducted in a standard of care setting, the actual numbers of subjects per study population cannot be controlled. Also, as haemophilia B is a rare disease, there is a finite number of patients that can be enrolled.

Primary outcome variable

The study intends to capture the ABR_All treated bleeding as primary outcome. For details, refer to section 7.2.1.

Number and region of sites, countries involved

It is planned to conduct this trial in all study sites treating haemophilia B patients in routine practice in Germany.

Medicinal product(s)

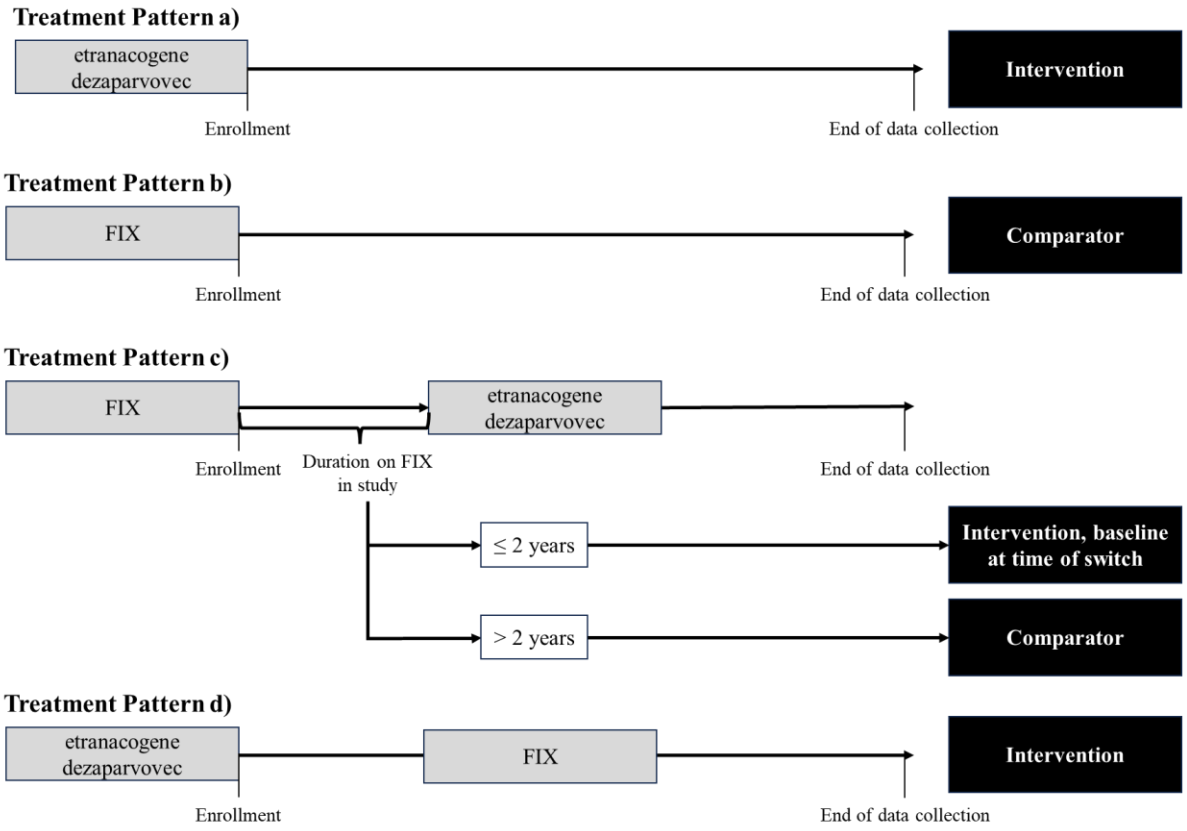
Etranacogene dezaparvovec (Hemgenix®): gene therapy, single-dose: dosing and IV administration according to SmPC

FIX products (plasma-derived or recombinant): prophylactic dosing and IV administration according to corresponding SmPC (please refer to section 6.4.2 for dosing details). In addition, on-demand treatment of bleeding as needed.

8.1.2 Other Important Design Features

It is expected that all subjects will be pre-treated with FIX products when enrolling in the study. Four types of treatment patterns regarding etranacogene dezaparvovec and FIX prophylaxis are possible (Figure 1). In addition to subjects who are (a) treated exclusively with etranacogene dezaparvovec or (b) exclusively with FIX prophylaxis from the time of enrollment to the end of observation, there will also be (c) patients who switch from FIX prophylaxis to etranacogene dezaparvovec at a given time point. Patients (d) treated with FIX for prophylaxis after receiving etranacogene dezaparvovec are theoretically also possible.

Figure 1: Treatment Patterns and Allocation to Intervention and Comparator



Due to the specific target population of this study being pre-treated with prophylactic FIX, the generally recommended framework of a new-user-design [15] cannot be implemented. Patients in groups a) and b) will be allocated to the intervention and comparator arm, respectively.

Per advice provided by IQWiG and G-BA [28], patients in group c) will be allocated to the intervention arm if they are treated with etranacogene dezaparvovec within the first two years after enrollment. In this case, baseline will be set at time of treatment with etranacogene dezaparvovec and previously collected data on treatment effects of FIX prophylaxis will be discarded. If treatment with etranacogene dezaparvovec happens more than two years after enrollment, patients are kept in the comparator arm and are not censored in main analysis to implement an intention-to-treat principle.

It is acknowledged that this approach can result in a minimum observation period of etranacogene dezaparvovec as well as FIX prophylaxis below the mandated three-year observation period. To generate insights on the effects of a shortened observation period, a sensitivity analysis will be performed that only includes patients with at least three years of

follow-up on their respective treatment. For details, please refer to SAP sections 6.4, 11.1.2 and 11.2.2.

8.1.3 Primary Endpoint(s)

The primary endpoint of this study is described in detail in section 7.2.

- Annualized bleeding rate (ABR) for all treated bleeding

8.1.4 Secondary Endpoint(s)

Secondary & exploratory endpoints are described in detail in section 7.3 and include the following:

Secondary endpoints:

- Survival**:** OS
- Morbidity**:**
    - Bleeding: ABR for
        - Severe bleeding
        - Life-threatening bleeding
        - Joint bleeding
    - Pain:
        - BPI-SF (scale no. 5) Worsening
        - BPI-SF (scale no. 5) Improvement
    - Joint status:
        - HJHS Worsening
- HRQoL:
  Haemo-QoL-A: Worsening and Improvement in
    - Total Score
    - Physical Functioning
    - Role Functioning
    - Worry

- Consequences of Bleeding
- Emotional Impact
- Treatment Concerns

- Tolerability:
  - AE
  - SAE (AE leading to death or hospitalization)
  - AESI and SAESI
    - Thromboembolic events
    - Development of FIX inhibitors
    - Symptomatic liver damage
    - Malignant neoplasms

- Exploratory endpoints:
  - FIX utilization:
    - Annualized infusion rate of prophylactic FIX concentrates (number of infusions)
    - Annualized infusion rate of on-demand FIX concentrates (number of infusions)
  - Return to prophylactic FIX therapy (etranacogene dezaparvovec only)

8.2 Selection of Subject Population

This is a non-interventional, non-randomized AbD using individual patient data documented by haemophilia sites that is routinely captured for reporting to DHR. The investigator will perform a screening with patients and examine the inclusion/exclusion criteria in this setting. Some of these inclusion/exclusion criteria are not depicted in DHR. Therefore, in consultation with the DHR, CSL Behring has compiled a list of modifications to the DHR dataset required to capture inclusion and exclusion criteria and other data necessary for the analysis of each of the requested endpoints. This proposal had been submitted to the DHR and was reviewed and discussed within the DHR steering committee. However, the required implementation of data fields to fully depict all inclusion and exclusion criteria were rejected by the steering committee due to legal considerations. Hence, the DHR steering committee proposed the following

procedure: The investigator who performed the patient screening will decide on the inclusion of the patient in the study. The inclusion of the patient is subsequently reflected via a respective data field in the DHR. Criteria that were already depictable via the current DHR CRF data fields will be collected as planned and depicted as patient characteristics (s. section 8.4.4). This specifically applies to inclusion criterion 1 to 3 and exclusion criterion 1 to 3. No data fields are currently available to capture the exclusion criteria 4 and 5. Table 5 to Table 6 in sections 8.2.1 and 8.2.2 show the inclusion and exclusion criteria of this study. During SDV, the full set of inclusion and exclusion criteria will be verified at the site.

8.2.1 Inclusion Criteria

Patients included in the study need to fulfill all inclusion criteria listed in Table 5.

Table 5: Inclusion criteria

#	**Inclusion criteria**
1	Adults with severe or moderately severe haemophilia B (congenital FIX deficiency; ≤ 5 % endogenous FIX activity[1])
2	Pre-treatment with either recombinant- or plasma-derived FIX concentrates
3	Signed informed consent

Abbreviations: FIX: Coagulation Factor IX

[1] The SmPC for etranacogene dezaparvovec does not specify a limit for endogenous FIX activity. According to current WFH guideline, severity is therefore described as ≤ 5 % endogenous FIX activity. This is consistent with the definition used in the DHR.

The first inclusion criterion listed in Table 5 is depicted in accordance with the population mandated for this study by G-BA [11] and disease severity definitions of World Federation of Hemophilia (WFH) Guidelines [8].
The EU marketing authorization for etranacogene dezaparvovec was granted for adult patients with severe or moderately severe haemophilia B (congenital FIX deficiency). Hence, patients under 18 years of age should not be included. The severity of FIX deficiency is characterized by residual endogenous FIX activity. Therefore, data on residual FIX activity will be collected for each patient at baseline in addition to severity. Moderately severe haemophilia B is characterized by a residual endogenous FIX activity of 1-5 % and severe haemophilia B is

characterized by a residual endogenous FIX activity of < 1 % according to WFH Guidelines [8]. As a result, patients with ≤ 5 % endogenous FIX activity will be included in the study.

The second criterion depicted in Table 5 is introduced to ensure that only patients eligible for a treatment with FIX concentrates are included in the study. A pre-treatment with FIX concentrates is routine practice in Germany for patients eligible for a switch to etranacogene dezaparvovec. As only adults are to be included, all participants should have been diagnosed years before study inclusion and hence are expected to be pre-treated with approved FIX concentrates.

The third criterion depicted in Table 5 serves to ensure compliance with all legal requirements of this study (see section 12).

8.2.2 Exclusion Criteria

Patients characterized by any of the criteria listed in Table 6 will not be included in the study.

Table 6: Exclusion criteria

#	**Exclusion criteria**
1	Currently participating in an interventional clinical trial
2	Known history of FIX inhibitors
3	Known advanced hepatic fibrosis or cirrhosis

4	Other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy. The following conditions may be included, but are not limited to[1]:
	
	• Disseminated intravascular coagulation[2]
	• Accelerated fibrinolysis[2]
	• Liver diseases:
	  • Profound liver fibrosis/ cirrhosis[2]
	  • Hepatic abnormalities on imaging and/or persistent elevations of liver enzymes
	  • Intake of hepatotoxic (active) substances
	  • Further pre-existing risk factors for hepatocellular carcinoma (e.g., uncontrolled hepatitis B/ C, non-alcoholic fatty liver disease)
	• Active/ chronic infections (e.g., HIV)
	• Immunodeficiency/ treatment with immunosuppressants
	• Pre-existing risk factors for thromboembolic events (e.g., history of cardiovascular/ cardiometabolic diseases, arteriosclerosis, hypertension, diabetes, higher age)

5	Known intolerance/hypersensitivity to any FIX concentrates and/or etranacogene dezaparvovec (active substance or to any of the excipients)

Abbreviations: FIX: Coagulation Factor IX; HIV: Human Immunodeficiency Virus

[1] The named medical conditions are just examples that may influence the decision for or against the gene therapy. The assessment of severity of these conditions and whether gene therapy can be prescribed in their presence is at the discretion of the documenting physician.
[2] The named medical condition may significantly impact the intended transduction of the vector and/or expression and activity of the protein.

The first criterion listed in Table 6 ensures that patients are not treated with any unauthorized drugs that were investigated for use in haemophilia B prior to their inclusion in the study.

The second criterion depicted in Table 6 is introduced to ensure that patients not eligible for a treatment with etranacogene dezaparvovec are excluded from the study. A documented history of FIX inhibitors formally precludes the use of etranacogene dezaparvovec as it is not authorized for haemophilia B patients with FIX inhibitors. This involves patients who are tested positively twice for FIX inhibitors irrespective of their titre level according to SmPC [1].

The third criterion depicted in Table 6 serve to ensure that patients with a contraindication for etranacogene dezaparvovec (according to SmPC) such as a known advanced hepatic fibrosis or cirrhosis are excluded from the study [1].

The fourth criterion listed in Table 6 is chosen to make sure all patients not eligible for a gene therapy due to other concomitant disorders or conditions are excluded from the study to ensure patient's safety and comparability of populations. The selection of medical conditions which, in the opinion of the investigator, render the patient unsuitable for gene therapy was based on first clinical knowledge derived from the 'Health Outcomes with Padua gene - Evaluation in Haemophilia B' (HOPE-B) study protocol [36] and the contraindications and special warnings and precautions for use listed in SmPC of Hemgenix® [1]. The presence of any of the medical conditions listed in Table 6 does not immediately exclude the patient from the study. The assessment of severity of these conditions and whether gene therapy can be prescribed in their presence is at the discretion of the documenting physician.

The fifth criterion in Table 6 was selected so that patients with an intolerance or hypersensitivity to the study drug (active substance or to any of the excipients) are not treated with the respective drug to ensure patient's safety. This includes treatment with etranacogene dezaparvovec as well as FIX preparations (recombinant or plasma-derived).

8.3 Discontinuation of Subjects

Subjects may be discontinued from this observational study at any time without personal disadvantages and without having to give a reason. For all discontinued patients the date of withdrawal/ discontinuation and the reason for withdrawal/ discontinuation should be noted in the CRF if available. Specific reasons for discontinuing a subject from the study can include the following:

1. Voluntary discontinuation by the subject: At any time during the study, a subject is free to discontinue his/ her participation, without prejudice to further treatment.
2. Protocol violations, e.g.: Did not meet inclusion/ exclusion criteria (coming to light after study enrollment)
3. Other reasons, e.g.: Lost to follow-up

8.4 Variables

8.4.1 Inclusion/ Exclusion criteria

Table 7: Inclusion criteria and and its depictability and operationalization in the DHR

Inclusion criteria	**Depictability and operationalization based on fields in DHR CRF**
Adults with severe or moderately severe haemophilia B (congenital FIX deficiency; ≤ 5 % endogenous FIX activity)	Depictability: Yes Operationalization: • "Date of birth" = mm.jjjj • "Diagnosis"" = Haemophilia B/ other • "Day of diagnosis" = tt.mm.jjjj/ unknown • "If haemophilia B: disease severity" = severe/ moderately severe/ mild/ subclinical • "Endogenous FIX activity [%]" = 0,0-200,0
Pre-treatment with either recombinant- or plasma-derived FIX concentrates	Depictability: Yes Operationalization: • "Has the patient received medication for the treatment of hemophilia in the past?" = yes/ no/ unknown • *"If yes, please specify type of medication" = Factor concentrate/ other*
Signed informed consent	Depictability: Yes Operationalization: • "Provision of signed informed consent (AbD) and fulfillment of all inclusion/ exclusion criteria " = yes/ no • "Date of enrollment (AbD)" = tt.mm.jjjj

	• "AbD is ongoing" = [tick box] • "Date of drop out or end of study (AbD)" = tt.mm.jjjj • "If drop out: reason for dropping out" = Regularly ended/ withdrawal of informed consent/ deceased/ lost to follow-up
Abbreviations: AbD: Routine Practice Data Collection and Evaluation (Anwendungsbegleitende Datenerhebung); CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); FIX: Coagulation Factor IX	

Table 8: Exclusion criteria and and its depictability and operationalization in the DHR

Exclusion criteria	**Depictability and operationalization based on fields in DHR CRF**
Currently participating in an interventional clinical trial	Depictability: Yes Operationalization: • "Current participation in an interventional clinical trial" = yes/ no • "Date of drop out/ end of trial" = tt.mm.jjjj
Known history of FIX inhibitors	Depictability: Yes Operationalization: • "Known history of FIX inhibitors" = yes/ no/ unknown • "If yes: amount of the max. inhibitor titre [BE/mL]" = [number] • "If yes: date of the max. inhibitor titre" = tt.mm.jjjj
Known advanced hepatic fibrosis or cirrhosis	Depictability: Yes Operationalization: • "Status liver disease" = No liver changes/ liver fibrosis (new diagnosis)/ liver fibrosis (chronic)/ liver cirrhosis Child A/ liver cirrhosis Child B/ liver cirrhosis Child C/ liver failure/ unknown

Other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy. The following conditions may be included, but are not limited to:
 	
• Disseminated intravascular coagulation
• Accelerated fibrinolysis
• Liver diseases:
  • Profound liver fibrosis/ cirrhosis[2]
  • Hepatic abnormalities on imaging and/or persistent
	Depictability: No[1]

elevations of liver enzymes • Intake of hepatotoxic (active) substances • Further pre-existing risk factors for hepatocellular carcinoma (e.g., uncontrolled hepatitis B/ C, non-alcoholic fatty liver disease) • Active/ chronic infections (e.g., HIV) • Immunodeficiency/ treatment with immunosuppressants • Pre-existing risk factors for thromboembolic events (e.g., history of cardiovascular/ cardiometabolic diseases, arteriosclerosis, hypertension, diabetes, higher age)	
Known intolerance/hypersensitivity to any FIX concentrates and/or etranacogene dezaparvovec (active substance or to any of the excipients)	Depictability: No[1]
Abbreviations: FIX: Coagulation Factor IX; HIV: Human Immunodeficiency Virus [1] As per the DHR steering committee's decision these data fields will not be added to the CRF of DHR due to legal considerations [37, 38].	

8.4.2 Outcomes

CSL Behring is currently in exchange with the DHR to discuss possibilities to implement changes related to data entry fields as well as SDV before the beginning of data collection. For SDV, please refer to section 14.1.1. Regarding outcomes, some data fields required for operationalization are already available in DHR. Other data fields (e.g. for the assessment of pain and quality of life) need to be introduced before the start of this study. Some data fields required for operationalization are already available in DHR as a one time assessment at timepoint of inclusion of the patient into the DHR, but need to be re-assessed at baseline and potentially again during the study e.g. if a patient switches treatment arms (and hence needs a new baseline).

In this section all planned outcomes are presented including their depictability and operationalization in the DHR.

Table 9: Annualized Bleeding Rate (ABR) and its depictability and operationalization in the DHR

Endpoint and definition	Depictability and operationalization based on fields in DHR CRF
ABR_all treated bleeding is defined as the cumulative number of all bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.	Depictability: Yes Operationalization: If number of EDs 0-50[1]: Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = Suspected bleeding/ spontaneous bleeding/ traumatic bleeding/ bleeding, cause unknown If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Reason for therapy" = Suspected bleeding/ spontaneous bleeding/ traumatic bleeding/ bleeding, cause unknown
Abbreviations: ABR: Annualized Bleeding Rate; CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); ED: Exposure Day [1] Category EDs 0-50 has been listed for completeness. However, as it can be assumed that patients with severe or moderately severe haemophilia have reached more than 50 EDs by the age of 18 years, it is not assumed that even a single patient is actually operationalized through this data field.	

Table 10: Overall Survival and its depictability and operationalization in the DHR

Endpoint and definition	Depictability and operationalization based on fields in DHR CRF
Overall Survival (OS) is defined as the time (in months) from baseline to the date of death. Event is death from any cause and censored otherwise. Time for censored patients is defined as the time from the baseline to lost-to-follow-up or end of the study.	Depictability: Yes Operationalization: • "Treatment status" = Currently on treatment/ drop out or treatment discontinued/ treatment pause • "If drop out: reason for drop out" = Deceased/ center switch (=drop out)/ withdrawal of consent • "If drop out: Date of drop out" = tt.mm.jjjj/ unknown
Abbreviations: CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); OS: Overall Survival	

Table 11: Bleeding endpoints and their depictability and operationalization in the DHR

Endpoint and definition	Depictability and operationalization based on fields in DHR CRF

ABR_severe bleeding is defined as the cumulative number of all severe bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring. DHR defines a severe bleeding as bleeding causing pain, swelling, and/ or mobility impairment which do not resolve within 24 hours. This definition is visible in the data entry mask for the documenting sites.	Depictability: Yes Operationalization: If number of EDs 0-50[1]: Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = spontaneous bleeding/ traumatic bleeding If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Reason for therapy" = spontaneous bleeding/ traumatic bleeding If reason "bleeding": • "Localisation" = Joint/ target joint/ muscle/ mucous membranes/ CNS/ gastrointestinal/ other/ unknown • *"If 'other': specify" = [free text]* • "Severity" = severe
ABR_life-threatening bleeding is defined as the cumulative number of all life-threatening bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring. DHR defines life-threatening bleeding as a severe bleeding which may present a particular risk to the patient. This definition is visible in the data entry mask for the documenting sites.	Depictability: Yes Operationalization: If number of EDs 0-50[1]: Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = spontaneous bleeding/ traumatic bleeding If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Reason for therapy" = spontaneous bleeding/ traumatic bleeding If reason "bleeding": • "Localisation" = Joint/ target joint/ muscle/ mucous membranes/ CNS/ gastrointestinal/ other/ unknown • *"If 'other': specify" = [free text]* • "Severity" = life-threatening
ABR_joint bleeding is defined as the cumulative number of all joint bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring. DHR defines joint bleeding as an unusual sensation 'aura' in the joint, in combination with any of the following: (a) increasing	Depictability: Yes Operationalization: If number of EDs 0-50[1]: Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = spontaneous bleeding/ traumatic bleeding If number of EDs > 50: Fill in therapy

swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline.	• "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Reason for therapy" = spontaneous bleeding/ traumatic bleeding If reason "bleeding": • "Localisation" = Joint/ target joint • "Severity" = Mild/ severe/ life-threatening/ unknown
Abbreviations: ABR: Annualized Bleeding Rate; CRF: Case Report Form; CNS: Central Nervous System; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); ED: Exposure Day [1] Category EDs 0-50 has been listed for completeness. However, as it can be assumed that patients with severe or moderately severe haemophilia have reached more than 50 EDs by the age of 18 years, it is not assumed that even a single patient is actually operationalized through this data field.	

Table 12: Pain endpoints and their depictability and operationalization in the DHR

Endpoint and definition	**Depictability and operationalization based on fields in DHR CRF**
BPI-SF_Worsening is defined as change from baseline in average pain (scale no. 5) and is analyzed as binary responder analysis. Patients showing at least two documentations of an average pain rating two or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 10) qualify as responders.	Depictability: (Yes)[1] Operationalization: • "Date of pain score" = tt.mm.jjjj • "Used score" = BPI-SF[2] • "Score pain scale no. 5" = [number]
BPI-SF_Improvement is defined as change from baseline in average pain (scale no. 5) and is analyzed as binary responder analysis. Patients showing at least two documentations of an average pain rating two or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 10) qualify as responders.	
Abbreviations: CRF: Case Report Form; BPI-SF: Brief Pain Inventory – Short Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister) [1] As per the DHR steering committee's decision, patient-related outcome (PRO) data will be collected in the DHR in the future. In case PRO questionnaires are collected electronically outside the DHR (e.g. via apps), it is currently under discussion how this data can be transferred to the DHR [37, 38]. To support the most complete data collection possible CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3). [2] PRO	

Table 13: Joint status endpoint and its depictability and operationalization in the DHR

Endpoint and definition	Depictability and operationalization based on fields in DHR CRF
HJHS_Worsening is defined as change from baseline in HJHS total score and is analyzed as binary responder analysis. Patients showing at least two documentations of a HJHS total score 19 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 124) qualify as responders.	Depictability: (Yes)[1] Operationalization: • "Date of joint score" = tt.mm.jjjj • "Used score" = Hemophilia Joint Health Score (HJHS)[2] • "Elbow left" = [number] • "Knee left" = [number] • "Ankle joint left" = [number] • "Elbow right" = [number] • "Knee right" = [number] • "Ankle joint right" = [number] • "Global Gait score:" = [number] • "Total score:" = [number]

Abbreviations: CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); HJHS: Hemophilia Joint Health Score

[1] As per DHR steering committee's decision all data fields required for operationalization are or will be available in CRF of DHR. However, it is currently unclear when the additional fields will be available for documentation by the centers. All these data fields will not be converted into mandatory fields but will remain optional [37, 38]. In order to support the most complete data collection possible, CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3).

[2] Assessment by a trained physician

Table 14: HRQoL endpoints and their depictability and operationalization in the DHR

Endpoint and definition	Depictability and operationalization based on fields in DHR CRF
Haemo-QoL-A: Total Score_Worsening is defined as change from baseline in Haemo-QoL-A total score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A total score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	Depictability: (Yes)[1] Operationalization: • "Date of HRQoL total score" = tt.mm.jjjj • "Used score" = Haemo-QoL-A[2] • "Physical functioning" = [number] • "Role functioning" = [number] • "Worry" = [number] • "Consequences of bleeding" = [number] • "Emotional impact" = [number] • "Treatment concern" = [number] • "HRQoL total score" = [number]
Haemo-QoL-A: Total Score_Improvement is defined as change from baseline in Haemo-QoL-A total score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A total	

score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Physical Functioning_Worsening is defined as change from baseline in Haemo-QoL-A physical functioning domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A physical functioning domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Physical Functioning_Improvement is defined as change from baseline in Haemo-QoL-A physical functioning domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A physical functioning domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Role Functioning_Worsening is defined as change from baseline in Haemo-QoL-A role functioning domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A role functioning domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Role Functioning_Improvement is defined as change from baseline in Haemo-QoL-A role functioning domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A role functioning domain score 15 or more	

points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Worry_Worsening is defined as change from baseline in Haemo-QoL-A worry domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A worry domain score 15 or more points below the baseline value (i.e. ≥ 15% of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Worry_Improvement is defined as change from baseline in Haemo-QoL-A worry domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A worry domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Consequences of Bleeding_Worsening is defined as change from baseline in Haemo-QoL-A consequences of bleeding domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A consequences of bleeding domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Consequences of Bleeding_Improvement is defined as change from baseline in Haemo-QoL-A consequences of bleeding domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A consequences of bleeding domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	

Haemo-QoL-A: Emotional Impact_Worsening is defined as change from baseline in Haemo-QoL-A emotional impact domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A emotional impact domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Emotional Impact_Improvement is defined as change from baseline in Haemo-QoL-A emotional impact domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A emotional impact domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Treatment Concerns_Worsening is defined as change from baseline in Haemo-QoL-A treatment concerns domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A treatment concerns domain score 15 or more points below the baseline value (i.e. ≥15% of the scale reaching from 0 to 100) qualify as responders.	
Haemo-QoL-A: Treatment Concerns_Improvement is defined as change from baseline in Haemo-QoL-A treatment concerns domain score and is analyzed as binary responder analysis. Patients showing at least two documentations of a Haemo-QoL-A treatment concerns domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) qualify as responders.	

Abbreviations: CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); Haemo-QoL-A: Haemophilia-specific Quality of Life Questionnaire for Adults; HRQoL: Health-related Quality of Life

[1] As per the DHR steering committee's decision, PRO data will be collected in the DHR in the future. In case PRO questionnaires are collected electronically outside the DHR (e.g. via apps), it is currently under discussion how this data can be transferred to the DHR [37, 38]. To support the most complete data collection possible CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3).

[2] PRO

Table 15: Tolerability endpoints and their depictability and operationalization in the DHR

Endpoint and definition	**Depictability and operationalization based on fields in DHR CRF**
AE is a binary endpoint and defined as proportion of patients reporting an AE.	Depictability: Yes[1] Operationalization: • "Other relevant events in this reporting period?" = Yes • "Other relevant events - Description" = Thromboembolic event/ malignant neoplasms/ other • *"Specify 'other' " = [free text]*[1] • "Serious consequences of relevant events" = Hospitalisation/ death/ no/ unknown
SAE is a binary endpoint and defined as proportion of patients reporting a SAE. Seriousness is approximated via information on AE leading to hospitalization as well as death due to AE.	Depictability: Yes Operationalization: • "Other relevant events in this reporting period?" = Yes • "Other relevant events - Description" = Thromboembolic event/ malignant neoplasms/ other • *"Specify 'other' " = [free text]*[1] • "Serious consequences of relevant events" = Hospitalisation/ death
AESI_Thromboembolic is a binary endpoint and defined as proportion of patients reporting an AE that is classified as a thromboembolic event. [2]	Depictability: Yes Operationalization: • "Other relevant events in this reporting period?" = Yes • "Other relevant events - Description" = Thromboembolic event • "Serious consequences of relevant events" = Hospitalisation/ death/ no/ unknown
AESI_FIX_Inhibitor is a binary endpoint and defined as proportion of patients reporting an AE that is classified as development of FIX inhibitors. [2]	Depictability: (Yes)[3] Operationalization: • "Is the patient to be classified as an inhibitor patient during the reporting period?" = Yes • "If yes: reason for the test" = Routine/ check-up/ reduced response to drug administration / no surgical hemostasis / other / unknown • "If yes: date of inhibitor test" = tt.mm.jjjj • "Treatment status" = Currently on treatment/ drop out or

	treatment discontinued/ treatment pause • "If drop out: reason for drop out" = Deceased/ center switch (=drop out)/ withdrawal of consent • "If drop out: Date of drop out" = tt.mm.jjjj/ unknown • "Days in hospital during the reporting period" = [number]
AESI_Liver is a binary endpoint and defined as proportion of patients reporting an AE that is classified as symptomatic liver damage. [2]	Depictability: Yes Operationalization: • "Status liver disease" = No liver changes/ liver fibrosis (new diagnosis)/ liver fibrosis (chronic)/ liver cirrhosis Child A/ liver cirrhosis Child B/ liver cirrhosis Child C/ liver failure/ unknown • "Serious consequences of selected liver disease" = Hospitalisation/ death/ no/ unknown
AESI_Neoplasms is a binary endpoint and defined as proportion of patients reporting an AE that is classified as malignant neoplasm. [2]	Depictability: Yes Operationalization: • "Other relevant events in this reporting period?" = Yes • "Other relevant events - Description" = Malignant neoplasms • "Serious consequences of relevant events" = Hospitalisation/ death/ no/ unknown
SAESI_Thromboembolic is a binary endpoint and defined as proportion of patients reporting an AE that is classified as a thromboembolic event. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI. [2]	Depictability: Yes Operationalization: • "Other relevant events in this reporting period?" = Yes "Other relevant events - Description" = Thromboembolic event • "Serious consequences of relevant events" = Hospitalisation/ death
SAESI_FIX_Inhibitor is a binary endpoint and defined as proportion of patients reporting an AE that is classified as development of FIX inhibitors. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI. [2]	Depictability: (Yes)[3] Operationalization: • "Is the patient to be classified as an inhibitor patient during the reporting period?" = Yes • "If yes: reason for the test" = Routine/ check-up/ reduced response to drug administration / no surgical hemostasis / other / unknown • "If yes: date of inhibitor test" = tt.mm.jjjj • "Treatment status" = Drop out or treatment discontinued • "If drop out: reason for drop out" = Deceased • "If drop out: Date of drop out" = tt.mm.jjjj/ unknown • "Days in hospital during the reporting period" = [number]
SAESI_Liver is a binary endpoint and defined as proportion of patients reporting an AE that is classified as symptomatic liver damage. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI. [2]	Depictability: Yes Operationalization: • "Status liver disease" = No liver changes/ liver fibrosis (new diagnosis)/ liver fibrosis (chronic)/ liver cirrhosis Child A/ liver cirrhosis Child B/ liver cirrhosis Child C/ liver failure/ unknown

	• "Serious consequences of relevant events" = Hospitalisation/ death
SAESI_Neoplasms is a binary endpoint and defined as proportion of patients reporting an AE that is classified as malignant neoplasm. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI. [2]	Depictability: Yes Operationalization: • "Other relevant events in this reporting period?" = Yes • "Other relevant events - Description" = Malignant neoplasms • "Serious consequences of relevant events" = Hospitalisation/ death
Abbreviations: AE: Adverse Event; AESI: Adverse Event of Special Interest; CRF: Case Report Form; CRO: Clinical Research Organization; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); MedDRA: Medical Dictionary for Regulatory Activities; SAE: Serious Adverse Event; SAESI: Serious Adverse Event of Special Interest; [1] AE and SAE are operationalized as a choice and/or free-text field. Seriousness is approximated via information on AE leading to hospitalization as well as death due to AE. [2] AESI and SAESI are operationalized as the proportion of patients reporting either TE, development of FIX inhibitors, symptomatic liver damage or malignant neoplasms. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI. [3] As per the DHR steering committee's decision, some of these fields will not be converted into mandatory fields but will remain optional [37, 38]. In order to support the most complete data collection possible, CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3).	

Table 16: Exploratory endpoints and their depictability and operationalization in the DHR

Endpoint and definition	**Depictability and operationalization based on fields in DHR CRF**
FIX_Utilization Prophylaxis is defined as the cumulative amount of all consumed single doses (infusions) of prophylactic FIX concentrates per patient-year of being at risk. Time at risk (in years) is defined as the time from baseline to censoring.	Depictability: (Yes)[1] Operationalization: If number of EDs 0-50:[2] Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = Prophylaxis If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Sum of ED in this treatment period" = [number][3] • "Reason for therapy" = Prophylaxis
FIX_Utilization On-Demand is defined as the cumulative amount of all consumed single doses (infusions) of on-demand FIX concentrates per patient-year of being at risk.	Depictability: (Yes)[1] Operationalization: If number of EDs 0-50:[2] Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = Suspected bleeding/ spontaneous bleeding/ traumatic bleeding/ bleeding, cause unknown/

Time at risk (in years) is defined as the time from baseline to censoring.	follow-up/ intensified on-demand treatment (=short-term prophylaxis)/ surgery + post-op/ ITT/ If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Sum of ED in this treatment period" = [number] [3] • "Reason for therapy" = Suspected bleeding/ spontaneous bleeding/ traumatic bleeding/ bleeding, cause unknown/ follow-up/ intensified on-demand treatment (=short-term prophylaxis)/ surgery + post-op/ ITT/
Return to prophylactic FIX therapy is defined exclusively for patients in the intervention arm of the study as the time between baseline and date of return to prophylactic FIX therapy based on therapy documentation.	Depictability: Yes Operationalization: If number of EDs 0-50:[2] Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = Prophylaxis If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Reason for therapy" = Prophylaxis

Abbreviations: CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); ED: Exposure Day; FIX: Coagulation Factor IX; IU: International Unit; ITI: Immune Tolerance Induction

[1] As per the DHR steering committee's decision, some of these fields will not be converted into mandatory fields but will remain optional [37, 38]. In order to support the most complete data collection possible, CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3).

[2] Category EDs 0-50 has been listed for completeness. However, as it can be assumed that patients with severe or moderately severe haemophilia have reached more than 50 EDs by the age of 18 years, it is not assumed that even a single patient is actually operationalized through this data field.

[3] FIX utilization will be operationalized via cumulative amount of ED in this treatment period under the assumption that only 1 infusion is administered per ED and per reason for therapy.

8.4.3 Covariates

The convergence to structural comparability in the study arms is achieved by appropriate adjustment methods for pre-specified confounders. Confounder pre-specification was conducted based on the methodological requirements of IQWiG which is described in the Rapid Report „Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V“ (Concepts for the generation and analysis of health-care-related data for the benefit assessment of drugs according to § 35a SGB V, version 1.1 of 13 May 2020 [15]) as well as in the recently updated “IQWiG Allgemeine Methoden” (IQWiG General Methods, version 7.0 of 19 September 2023

[25]. The methodology fundamentally consisted of a systematic literature review (SLR) to identify relevant national and international guidelines and recommendations and systematic reviews and meta-analyses for subsequent confounder extraction. In addition, clinical experts validated the clinical relevance of potential confounders for the target population of adult patients with haemophilia B. A detailed description of the methodology and the results is given in the 'Methodology of Confounder Identification' (see Annex A1). In response to the requests and recommendations of the G-BA in its resolution of 01 February 2024, further literature was searched for potential confounders not yet identified and the relevance of confounders was discussed with clinical experts and the result is included in this protocol (Annex A1_2 dated 28 March 2024).

Each confounder identified in the SLR was categorized into one of the following three categories by clinical experts:

- Very important: These parameters have a significant effect on patients' outcomes. If very important confounders are missing, the effect on the study results must be discussed in the study report.

- Less important: These confounders have a small effect on the results and should be controlled for in the statistical analysis, if possible. However, if confounders in this category cannot be controlled for, the results are still considered valid.

- Not important: These confounders are not considered relevant to this study, e.g., because they are captured as endpoints or because of the specific study setting.

The confounders listed in Table 17 have been identified as clinically very important and are thus potentially relevant for the included target population. These confounders are depictable in DHR and will be considered in study analyses. All confounders identified via SLR and considered not important in the context of this study are depicted in 'Methodology of Confounder Identification' (Annex A). In case of unavailability or missing data of very important confounders, potential biases will be discussed in the study report. Potential inhomogeneity between treatment arms with regards to the baseline confounders will be addressed by propensity score methods (PSM) (average treatment effect (ATE) fine stratification weights or inverse probability of treatment weights (IPTW)), as defined in the SAP (section 10).

Table 17: Overview of confounders, their clinical relevance, and their depictability and operationalization in the DHR

Confounder	Clinical relevance	Included in the study	Proposed operationalization by clinical experts	Depictability and operationalization based on fields in DHR CRF
Residual factor activity	Very important	Yes	The detection limit for residual factor activity is 1%. Therefore, clinical experts suggested an operationalization in 2 strata: • < 1 % (residual factor activity not measurable) • 1-5 % (residual factor activity measurable)	Depictability: Yes Operationalization: • "Residual factor activity [%]" = 0,0-200,0 • "Test used for residual activity measurement" = aPTT assay/ chromogenic assays/ other/ unknown • "Date of residual activity measurement" = tt.mm.jjjj/ unknown
Age	Very important	Yes	At the age of 50, the risk of comorbidities, further joint damage and the need for surgery increases. Therefore, clinical experts suggested an operationalization in 2 strata: • ≤ 50 years • > 50 years	Depictability: Yes Operationalization: • "Date of birth" = mm.jjjj
Dosage (intensity of prophylaxis) 12 months prior to study enrollment	Very important	Yes	Prophylactic dosing derived from the SmPC with tolerance limit ±25% shall be considered as normal range: • Low-dose therapy (below normal range) • In-label therapy (within normal range) • High-dose therapy (above normal range) Information on dosing and mode of administration of FIX preparations authorized by EMA can be found in section 6.4.2. All information was derived from the respective SmPCs and will be used as a reference to determine the normal range. The following formula will be used to determine patient's individual required units of FIX for each preparation/ medication as per SmPC:	Depictability: (Yes)[1] Operationalization: If number of EDs 0-50:[2] Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Weight [kg]" = [number] • "Preparation/ medication" = [Selection from list of drugs approved in Germany for the treatment of coagulation disorders in haemophilia] • "Other preparation/ medication" = [free text] • "Consumption/ dispension [IU]" = [number] If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj • "End of therapy" = tt.mm.jjjj • "Weight [kg]" = [number]

			$Required\ units\ of\ FIX\ [IU] = x\frac{IU}{kg} \times body\ weight\ [kg]$ $x\frac{IU}{kg}$: recommended dosage as per SmPC (s. Table 4) In-Label therapy is any therapy with a dosing within the range of: $Normal\ range = Required\ units\ of\ FIX\ [IU] \pm Required\ units\ of\ FIX\ [IU] \times 0.25$	• "Sum of ED in this treatment period" = [number] • "Preparation/ medication" = [Selection from list of drugs approved in Germany for the treatment of coagulation disorders in haemophilia] • "Other preparation/ medication" = [free text] • "Total dose per day" = [number] • "(Actual) consumption" = [number]
Joint status	Very important	Yes	HJHS (total score) at baseline	Depictability: (Yes)[3] Operationalization: • "Date of joint score" = tt.mm.jjjj • "Used score" = Hemophilia Joint Health Score (HJHS) • "Elbow left" = [number] • "Knee left" = [number] • "Ankle joint left" = [number] • "Elbow right" = [number] • "Knee right" = [number] • "Ankle joint right" = [number] • "Global Gait score" = [number] • "Total score:" [number]
ABR 12 months prior to study enrollment [4]	Very important	Yes	Record of the number of all bleeds requiring treatment 12 months prior to study enrollment and presentation of the results as a rate based on therapy documentation in CRF of DHR	Depictability: Yes Operationalization: If number of EDs 0-50[2]: Fill in therapy: • "Date of therapy" = tt.mm.jjjj • "Reason for therapy" = Suspected bleeding/ spontaneous bleeding/ traumatic bleeding/ bleeding, cause unknown If number of EDs > 50: Fill in therapy • "Start of therapy" = tt.mm.jjjj

				• "End of therapy" = tt.mm.jjjj • "Reason for therapy" = Suspected bleeding/ spontaneous bleeding/ traumatic bleeding/ bleeding, cause unknown

Abbreviations: CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); ED: Exposure Day; EMA: European Medicines Agency; HJHS: Hemophilia Joint Health Score; IU: International Unit; SmPC: Summary of Product Characteristics

[1] As per the DHR steering committee's decision, some of these fields will not be converted into mandatory fields but will remain optional [37, 38]. In order to support the most complete data collection possible, CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3).

[2] Category EDs 0-50 has been listed for completeness. However, as it can be assumed that patients with severe or moderately severe haemophilia have reached more than 50 EDs by the age of 18 years, it is not assumed that even a single patient is actually operationalized through this data field.

[3] As per DHR steering committee's decision all data fields required for operationalization are or will be available in CRF of DHR. However, it is currently unclear when the additional fields will be available for documentation by the centers. All these data fields will not be converted into mandatory fields but will remain optional [37, 38]. In order to support the most complete data collection possible, CSL Behring will be providing financial incentives to the study centers (s. section 14.1.3).

[3] ABR 12 months prior to study enrollment was suggested by the clinical experts. The evidence base mentioned was the publication Germini et al. which was excluded during the SLR of the confounder identification procedure because it refers mainly to evidence from haemophilia A studies. However, the clinical experts agreed that it is possible to extrapolate the evidence for this specific confounder to haemophilia B [39]. This confounder will be operationalized through all treated bleeding occurring 12 months prior to study enrollment.

In addition to the confounders identified and listed in Table 17, further parameters are needed with regard to planned subgroup and sensitivity analyses (see sections 8.7.5.1 and 8.7.5.2). This includes gender as well as AAV5 status. As presented in Table 18, both are depictable in the DHR and will be considered in further analyses. CSL Behring is currently in exchange with the DHR to discuss possibilities to implement changes related to data entry fields. This includes some data fields required for operationalization which are already available in DHR as one time assessment (e.g. at timepoint of inclusion of the patient into the DHR or at initiation of treatment with etranacogene dezaparvovec), but need to be re-assessed at baseline (especially for the comparator arm with FIX prophylaxis) and new data entry fields to be added for the comparator arm before the actual start of the study. In consultation with the DHR, CSL Behring has compiled a list of modifications to the DHR dataset required to capture inclusion and exclusion criteria and other data necessary for the analysis of each of the requested endpoints. This proposal has been submitted to the DHR and is awaiting final approval and implementation.

Table 18: Further parameters and their depictability and operationalization in the DHR

Parameter	Included in the study	Depictability and operationalization based on fields in DHR CRF
Gender	Yes	Depictability: Yes Operationalization: • "Gender" = male/ female/ diverse
AAV5 status	Yes	Depictability: Yes Operationalization: • „Was an AAV5 antibody test conducted?“ = yes/ no • "If yes: result" = positive/ negative • "If positive: amount of the max. antibody titre" = [number] • "Test used for antibody titre measurement" = [Selection from list of antibody tests for AAV5]
Abbreviations: AAV5: Adeno-Associated Virus serotype 5; CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister)		

8.4.4 Patient characteristics

The following patient characteristics will be obtained from DHR for the AbD:

Table 19: Patient characteristics

Patient characteristics	**Parameters assessed**
Patients demographics	• Age • Gender
Disease characteristics	• Diagnosis • Disease severity • Residual FIX activity [%]
Medical history	• History of FIX inhibitors • AAV5 status • ABR 12 months prior to study enrollment • Joint status • Known advanced hepatic fibrosis or cirrhosis
Treatment history	• Pre-treatment with either recombinant- or plasma-derived FIX concentrates • Dosage (intensity of prophylaxis) 12 months prior to study enrollment
Abbreviations: AAV5: Adeno-Associated Virus serotype 5; ABR: Annualized Bleeding Rate; FIX: Factor IX	

8.5 Data Source: German Haemophilia Registry (DHR)

The G-BA commissioned the IQWiG to develop a concept for the AbD of etranacogene dezaparvovec for the treatment of adult patients with severe or moderately severe haemophilia B without a history of FIX inhibitors. In this concept, the IQWiG identified the DHR via literature research as a potentially suitable registry for this study [40]. The suitability for the present AbD was evaluated by IQWiG in detail accroding to minimal quality criteria. These minimal criteria and their fulfillment by the registry (at timepoint of G-BA´s resolution) are shown in Table 20.

The DHR is an indication registry and has been active since 2008. It is a cooperation project of the German Haemophilia Society (DHG), the Society for Thrombosis and Haemostasis Research (GTH), the Haemophiliac Interest Group (IGH) and the Paul Ehrlich Institute (PEI) [40]. Treating physicians are legally obliged to report patients with haemophilia A or B, von Willebrand syndrome or factor I, II, V, VII, X, XI or XIII deficiency to the DHR [41]. By 2019, the DHR should primarily collect information on the care situation of patients with blood coagulation disorders. Due to the revised EMA guidelines for the clinical testing of recombinant and plasmatic FVIII and FIX products [42, 43] and the subsequent amendment of the Transfusion Act (TFG) in 2019, extensive adjustments were made to the DHR data set. The aim was, among others, to simplify the merging of different registry data and to also use the registry data for research through more comprehensive data sets [44].

There are 2 types of data reporting to the registry, the aggregated report *("Sammelmeldung")* and the extended data report (individual case report; *"Einzelmeldung"*). If patients do not give their consent to extended data reporting, doctors report aggregated data on patient numbers (differentiated by severity of illness and age groups) and consumption of coagulation preparations once a year (by 1 July of the following year at the latest) via a collective report [45]. If the patients have given their consent to individual case reporting, extended data on therapy, diagnosis and medically relevant events can be recorded in pseudonymised form. In this case, events can be reported as required, but at least once a year in accordance with the legal requirements [45, 46, 33]. In 2020, 140 institutions reported data on a total of 13912 patients with blood coagulation disorders in the registry, of which data for 2478 patients (18 %) were available in the form of individual reports [47]. A total of 860 patients with haemophilia B were registered, of which 420 had severe and 168 moderate haemophilia. For severe haemophilia B, individual case reports were available for 195 patients (46 %), and for moderate haemophilia B for 63 patients (38 %) [47]. Of the patients with haemophilia B (of any severity) included in the DHR, about 1 quarter are under 18 years of age [47], which should be subtracted

from the above figures. Thus, it can currently be assumed that there are approx. 450 adult patients in the relevant field of application in Germany.

For the purpose of this study, the data documented by haemophilia sites that is routinely captured for reporting to the DHR will be collected. Several adjustments are still needed in the DHR to meet IQWiG's minimal quality criteria. Due to several haemophilia AbDs being conducted in parallel and after extensive exchange with the DHR, an alternative study database is no longer a realistic option. CSL Behring is currently in dialogue with the DHR in order to discuss and implement all necessary modifications of the DHR for the collection of the required data as part of the AbD before the actual start of the AbD. A list of required modifications to the DHR dataset was compiled and the proposal was submitted to the DHR. Modifications were subject to the decision of DHR's steering committee who has made latest decisions in April 2024. While some requested adaptations were accepted and will lead to relevant adoptions to the DHR, the steering committee rejected further implementations of new data fields to fully depict all exclusion criteria as well as the conversion of optional data fields into mandatory data fields which were required for some endpoint or confounder analysis. The decision was prompted by the challenging technical feasibility within the DHR.

Table 20: Minimal Quality Criteria and Fulfillment by the DHR

#	**Minimal quality criteria as depicted in G-BA´s resolution of 12 May 2023 (IQWiG concept [40] Annex D)**	**Fulfillment by registry at timepoint of GBA´s resolution**
Systematics		
1	Detailed registry description	Yes (handbook and complete data set available)
Standardization		
2	Exact definition or operationalization of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints, and confounders	Yes
3	Current data plan/ coding manual	Yes
4	Use of standard classifications and terminologies	No
5	Use of validated standard instruments (questionnaires, scales, tests)	Partially
6	Training on data collection and recording	Yes
7	Implementation of an approved disease-specific core data set	Yes
8-11	Use of exact dates for the patient, the disease, important examinations, and treatments/interventions	Yes
Achievement of the recruitment target / sample acquisition		
12	Clearly defined inclusion and exclusion criteria for registry patients	Yes

#	**Minimal quality criteria as depicted in G-BA´s resolution of 12 May 2023 (IQWiG concept [40] Annex D)**	**Fulfillment by registry at timepoint of GBA´s resolution**
13	Completeness of the registry patients (full survey or representative sample)	Partially (not all patients in individual reporting)
14	Strategies to avoid unwanted selections during patient inclusion in order to achieve representativeness	For the entire registry: representativeness due to legal reporting obligation For individual reporting: Unclear
15	Specifications to ensure completeness of data per survey date	Not fully guaranteed (depending on individual or collective reporting and partly due to voluntary provision of different data)
16	Completeness of survey dates (loss-to-follow-up, drop-outs)	Unclear
17	Accuracy of data	With restriction (plausibility checks; no SDV)
18	Data consistency over time	Yes
19	SDV (e.g., for 10 % of randomly selected patients per survey center)	No[1]
20	Monitoring of registry via internal audits	Unclear
21	Monitoring of registry via external audits	No
22	QM system (if necessary with regular survey of quality indicators)	Unclear
23	Standard Operating Procedures for data collection	Yes
24 - 27	Assurance of scientific independence and transparency of the registry	Yes
28	Timeliness of registry documents (e.g., protocol, data plan, SAP, consent form etc.)	Unclear
29	Safeguarding patients' rights and data protection, taking ethical aspects into account	Yes
30	Timeliness (Up-to-dateness / rapid availability / punctuality of the required results)	No
31	Flexibility and adaptability (e.g., for embedding studies, for further data collection, in the event of a changed care situation)	Yes
32	Documentation trail – documentation of all process and definition changes in the registry	Partially
33	Audit trail – documentation and attributability of all data transactions	Unclear
34	Connectivity with other data sources	Unclear
Specific registry studies		
35-45	*Not applicable*	*Not applicable*
Other possible criteria from a regulatory perspective		

#	Minimal quality criteria as depicted in G-BA´s resolution of 12 May 2023 (IQWiG concept [40] Annex D)	Fulfillment by registry at timepoint of GBA´s resolution
46	Collection and handling of AEs according to regulatory requirements	No

Abbreviation: AE: Adverse Events; Federal Joint Committee (G-BA: Gemeinsamer Bundesausschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen); QM: Quality Management; SDV: Source Data Verification

[1] SDV was not (yet) fulfilled at timepoint of GBA´s resolution. However, SDV is possible according to the DHR and hence the implementation of SDV is planned. Please refer to section 14.1.1 for details.

8.6 Data Collection Methods and Management

8.6.1 Data Management

All clinical data for this project is intended to be collected and stored exclusively in the DHR. Study site personnel is responsible for patient data collection and data entry into DHR. Data will be entered into electronic Case Report Forms (eCRF) of the DHR. DHR uses a software provided by Adjumed Services AG as a custom application. According to the DHR office, a workflow is currently being developed that would allow external monitors a documented and efficient data review process. Validation of patient data in the software is currently performed through automated edit checks and may be performed in the future, following a positive decision by the steering committee, through manual checks performed by clinical research staff during routine on-site inspections. These clinical research staff members must be commissioned by the pharmaceutical company (see section 14.1.1 for details).

8.6.2 Data Transfer

Data for analysis will be transferred to a third party via a secure data transfer for statistical analysis. Data transfer will be strictly limited to the purpose of the study and as far as required for intended statistical analysis (see section 15).

8.7 Data Analyses

8.7.1 Sample Size Estimation

Since this study is a non-interventional, secondary use of data from the DHR registry, CSL Behring has no control over enrollment in the study. All patients fulfilling the inclusion while not fulfilling the exclusion criteria (see section 8.2) will be included in the study. Incentives to study center are expected to raise the number of patients consenting on individual

case reporting ("Einzelfallmeldung") or patients switching from aggregated reporting *("Sammelmeldung")* to individual case reporting.

In an effort to assess study feasibility in the context of the German care and registry structures, an orientational sample size estimation for various scenarios was performed by IQWiG [40] and two scenarios were depicted by G-BA in its resolution mandating the study [11]. All scenarios use the following assumptions:

- Endpoint used for sample size estimation: ABR
- $RR_0 = 0.5$ (shifted null-hypothesis)
- Power $\beta = 0.8$
- $\alpha = 0.05$, two-sided
- Negative binomial model with dispersion parameter $\phi = 1.5$
- Negligible censoring

The ABR inputs used for calculating the scenarios seem to have been chosen not based on the results of the HOPE-B trial. IQWiG describes "To obtain sample sizes that are realistically recruitable in an AbD, ABRs of 2.6 to 3.6 under the comparator therapy and ABRs of 0.6 to 1 for the intervention are assumed in the present design." [40].

All scenarios calculated by IQWiG also use the concept of a shifted null-hypothesis, i.e., a hypothesis threshold of rate ratio = 0.5 ($RR_0 = 0.5$). While not mandated by German Social law or G-BA code of procedure, it is acknowledged that this threshold and its application to the boundaries of the two-sided 95 % confidence interval (CI) has been requested by IQWiG both in its initial Rapid Report [15], its general methods [40] as well as consistently applied in all AbD concepts to date [40, 48–53].

The applied concept of a shifted null-hypothesis is derived from the established concept of a "dramatic effect" for naïve comparisons. While it is argued that effect thresholds can be reduced due to thorough confounder adjustment methods required in the context of an AbD, the thresholds are applied to the boundaries of the 95 % CI instead of the effect estimate (as is defined for the dramatic effect as well as the literature cited to derive these thresholds) [25].

While it is acknowledged that this approach guarantees a very high level of certainty, it is anticipated that it would also lead to patient numbers that cannot realistically be included in the context of an AbD in rare diseases. An alternative could be to follow the principle of the "dramatic effect", i.e., $p < 0.01$ but with reduced effect thresholds (rate ratio < 0.5).

Since actual patient numbers cannot be controlled by CSL Behring, an orientational sample size calculation was performed with two approaches [a) shifted null-hypothesis and b) dramatic effect criteria with modified effect threshold] based on both the scenarios calculated by IQWiG and selected by G-BA as well as the actual observed results from the HOPE B study. This dual approach is also motivated by the fact that the results generated by this study will meet interest of the scientific medical community that goes beyond the context and stakeholders involved in the German benefit assessment. While G-BA may choose to not consider any results not fulfilling the concept of a shifted null-hypothesis, CSL Behring anticipates that results showing a rate ratio < 0.5 at a significance level of $p < 0.01$ will meet significant interest in the scientific medical community.

For approach a) the same assumptions used by IQWiG were used:

- Endpoint used for sample size estimation: ABR
- $RR_0 = 0.5$ (shifted null-hypothesis)
- Power $\beta = 0.8$
- $\alpha = 0.05$, two-sided
- Negative binomial model with dispersion parameter $\phi = 1.5$
- Ratio of patient numbers intervention:comparator = 1:5
- Negligible censoring

The resulting sample sizes for the scenarios included in G-BA's resolution were replicated using PASS 2023 (Non-Inferiority Test for the Ratio of two Negative Binomial Rates) and subsequently the scenarios based on HOPE-B trial results were calculated. Results are illustrated in Table 21.

Assuming a patient ratio of 1:5 between intervention and comparator group, an ABR of 3.45 in the comparator group and 0.56 in the intervention group following a negative binomial

distribution with dispersion $\phi = 1.5$, 103 patients (intervention group n = 17, comparator group n = 86) are required under a shifted null hypothesis of rate ratio = 0.5 with power = 0.8 and $\alpha = 0.05$ two-sided (PASS 2023).

Considering the non-randomised comparison and the shifted null hypothesis boundaries, there is a high potential for bias, which will be discussed accordingly in the study report.

Table 21: Sample size estimation for shifted null-hypothesis approach

Scenario/ Endpoints	Event Rate Inter-vention	Event Rate Com-parator	Rate Ratio	Required Patients: Total	Required Patients: Inter-vention	Required Patients: Compa-rator
G-BA resolution 1	0.8	3.0	0.267	327	55	272
G-BA resolution 2	1.0	3.6	0.278	351	59	292
HOPE-B: ABR (FIX-treated and non-treated bleeding)	1.04	4.0	0.26	277	46	231
HOPE-B: FIX-treated bleeding	**0.56**	**3.45**	**0.16**	**103**	**17**	**86**
HOPE-B: severe bleeding	0.19	0.44	0.43	16 444	2 746	13 698
HOPE-B: life-threatening bleeding	0.02	0.13	0.16	1 008	168	840
HOPE-B: joint bleeding	0.33	2.2	0.15	113	19	94

Abbreviations: ABR: Annualized Bleeding Rate; FIX: Coagulation Factor IX; G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss); HOPE-B: Health Outcomes with Padua gene - Evaluation in Haemophilia B

For approach b), the following assumptions were used:

- Endpoint used for sample size estimation: ABR
- $RR_0 = 1$
- Power $\beta = 0.8$
- $\alpha = 0.01$, two-sided

- Negative binomial model with dispersion parameter $\phi = 1.5$
- Ratio of patient numbers intvervention:comparator = 1:5
- Negligible censoring

Calculation was also performed using PASS 2023. Results are illustrated in Table 22.

Assuming a patient ratio of 1:5 between intervention and comparator group, an ABR of 3.45 in the comparator group and 0.56 in the intervention group following a negative binomial distribution with dispersion $\phi = 1.5$, 53 patients (intervention group n = 9, comparator group n = 44) are required under a standard null hypothesis of rate ratio = 1.0 with power = 0.8 and $\alpha = 0.01$ two-sided (PASS 2023).

Table 22: Sample size estimation for approach derived from "dramatic effect" criteria with modified effect threshold

Scenario/ Endpoints	Event Rate Inter-vention	Event Rate Compa-rator	Rate Ratio	Required Patients: Total	Required Patients: Intervention	Required Patients: Compa-rator
G-BA resolution 1	0.8	3.0	0.267	98	16	82
G-BA resolution 2	1.0	3.6	0.278	101	17	84
HOPE-B: ABR (FIX-treated and non-treated bleeding)	1.04	4.0	0.26	89	15	74
HOPE-B: FIX-treated bleeding	**0.56**	**3.45**	**0.16**	**53**	**9**	**44**
HOPE-B: severe bleeding	0.19	0.44	0.43	395	66	329
HOPE-B: life-threatening bleeding	0.02	0.13	0.16	411	69	342
HOPE-B: joint bleeding	0.33	2.2	0.15	59	10	49

Abbreviations: ABR: Annualized Bleeding Rate; FIX: Coagulation Factor IX; G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss); HOPE-B: Health Outcomes with Padua gene - Evaluation in Haemophilia B

Based on the results of the HOPE-B trial, required patient numbers for ABR for FIX-treated bleeding and joint bleeding are the lowest among the endpoints included in this study and covered in sample size estimations. Based on this finding as well as the nature of FIX-treated bleeding representing the broadest bleeding definition that is anticipated to be captured in the DHR registry with good quality data, ABR for FIX-treated bleeding was chosen as the study's primary endpoint.

If effects observed in this study are comparable to those found in HOPE-B, a sufficient number of patients to reach required sample sizes for all treated bleeding and joint bleeding could likely be enrolled to show an effect using the concept of a shifted null-hypothesis as proposed by IQWiG. However, there is a substantial degree of uncertainty resulting from a number of factors.

1. CSL Behring expects significant differences in patient characteristics between the study's intervention and comparator arms. Given the novelty of gene therapy as a treatment approach and the well-established nature of FIX treatments for haemophilia B, it is likely that patients choosing gene therapy in the initial years of availability will be biased towards patients with relatively high bleeding rates on FIX or otherwise harder to manage conditions. Since patients in non-overlapping regions of the propensity score (PS)-distribution will be trimmed as part of the adjustment of covariates, it is expected that a significant portion of patients enrolled in the comparator arm of this study will not be eligible for adjusted outcome analyses. It is thus uncertain if the number of patients that can be included in adjusted analyses will meet the numbers calculated in the performed sample size estimations.

2. Interventional clinical trials and an AbD differ in terms of prioritizing internal vs. external validity. While internal validity tends to be a key priority for pivotal trials, external validity is of higher importance in the context of an AbD. It is thus uncertain if event rates for both intervention and comparator observed in this study will be comparable to those observed in HOPE-B. However, given the potential selection bias described above, bleeding rates observed in patients that are not trimmed from adjusted outcome analysis in this study may in fact be significantly higher than those observed in the overall population.

3. The willingness of patients and treatment centers to participate in this study cannot be anticipated at the time of study planning. Participation in the trial can be and was mandated by G-BA for treatment centers providing etranacogene dezaparvovec [14]

and while participation cannot be mandated on a patient level, CSL Behring expects a high willingness to enroll among patients treated with etranacogene dezaparvovec. In contrast, though, study participation cannot be mandated for treatment centers not providing etranacogene dezaparvovec and willingness of FIX patients to participate in the study is subject to significant uncertainty. As a result, both total patient numbers as well as the ratio of intervention-to-comparator patients is uncertain and may differ significantly from the assumptions used at time of study planning.

Due to the described uncertainties, G-BA has mandated a re-calculation of sample size after study commencement. The approach of sample size re-estimation is described in SAP section 4.5.2.

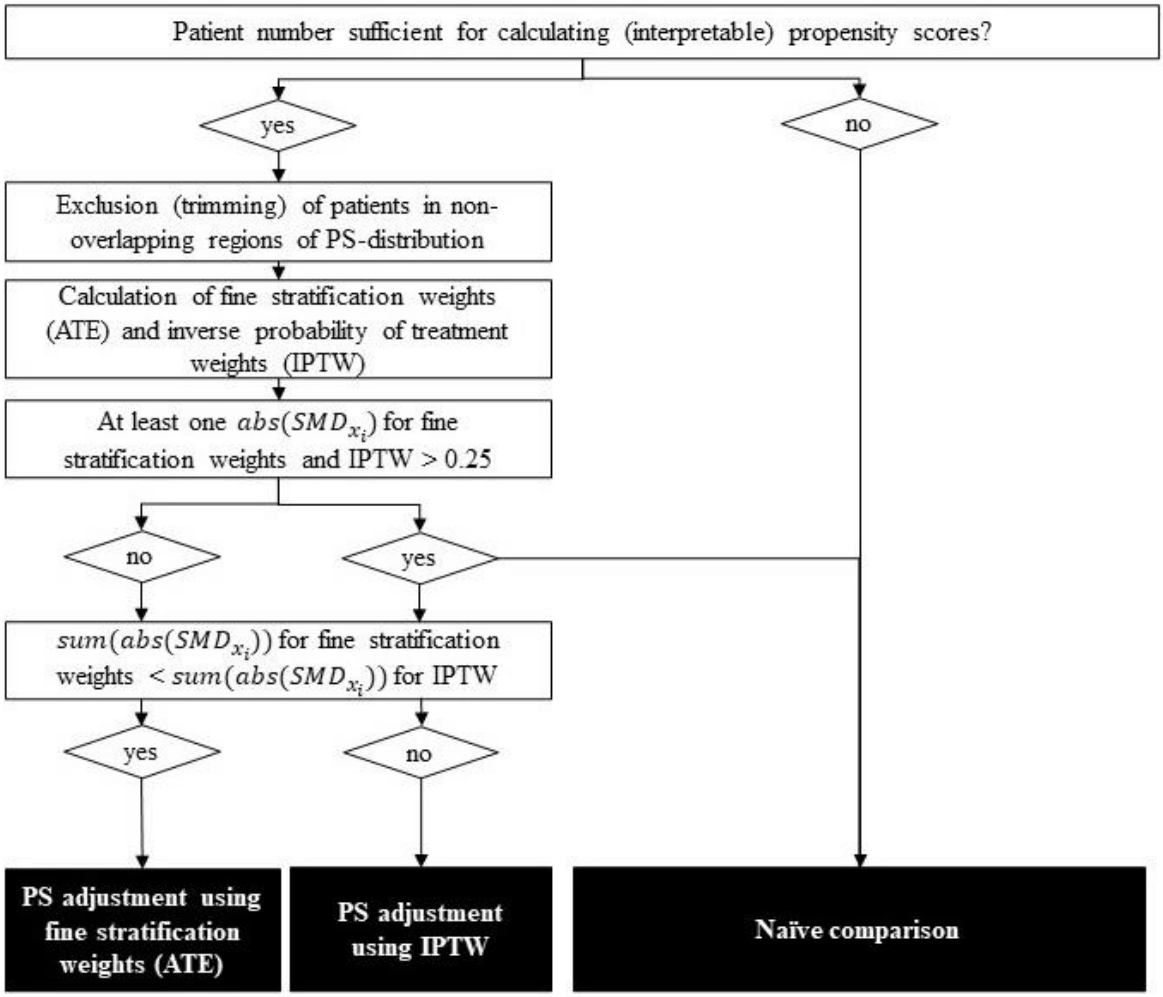
8.7.2 Statistical Methodology

The comparison of both interventions is carried out with appropriate statistical methods. Pre-specified confounders as well as patient characteristics are evaluated descriptively and standardized mean differences (SMD) are reported for all pre-specified confounders. Inhomogeneity between treatment arms with regard to pre-specified baseline confounders will be addressed by PSM (ATE fine stratification weights or inverse probability of treatment weights IPTW). The weighting approach will be selected by comparing confounder balance in terms of SMDs after weighting. Figure 2 illustrates the pre-specified decision tree for confounder adjustment.

The following confounders will be included in the analysis based on pre-specification via SLR and validation with clinical haemophilia experts:

- Residual factor activity
- Age
- Dosage (intensity of prophylaxis) 12 months prior to study enrollment
- Joint status
- ABR 12 months prior to study enrollment

Figure 2: Adjustment of confounders



Patient characteristics and SMDs for patients included in the analyses will be reported both weighted and unweighted. Patient characteristics and SMDs will be reported unweighted for patients trimmed from adjusted analyses.

TTE endpoints are estimated in the context of a Cox regression. For binary endpoints and count endpoints, a generalized linear model (GLM) is used. Scores will be analyzed as binary endpoints using pre-specified responder thresholds.

Survival curves and median survival time as well as hazard ratios are used for the representation of the TTE endpoints. Binary endpoints are analyzed using Risk Ratio as effect measure. Count endpoints will be evaluated using Rate Ratio as effect measure.

For all effect measures 95 % CI limits are presented. AE are summarized in terms of absolute and relative frequencies as well as time to first event by treatment episode.

Please refer to the SAP (section 11) for details.

8.7.3 Primary Analysis

A generalized linear models (GLM) for count data assuming a negative binomial distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion is performed, taking treatment as independent variable and PS weights as weighting variable.

8.7.4 Secondary Analysis

A GLM for count data assuming a negative binomial distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion is performed, taking treatment as independent variable and PS weights as weighting variable.

TTE endpoints are generally analyzed with weighted Cox proportional hazard regression, PS weight serves as weighting variable. Binary endpoints are generally analyzed using GLM for binary data assuming a binomial distribution with a link function appropriate for the intended effect measures (risk ratio: log, odds ratio: logit, risk difference: identity) and taking treatment as independent variable and PS weights as weighting variable.

In tolerability analyses, all kinds of AE are summarized in terms of absolute and relative frequencies by treatment. AE are analysed as binary endpoints accordingly.

8.7.5 Other Analyses

8.7.5.1 Subgroup Analyses

Subgroup analyses are planned for primary and secondary endpoints based on patient baseline characteristics, while no subgroup analyses will be performed for exploratory endpoints.

Subgroup analysis will only be performed in the context of main analysis (for primary and secondary analysis), while no subgroup analysis will be performed in the context of sensitivity analysis. Table 23 depicts subgroups derived from the requirements of the German benefit assessment dossier template as well as the confounders depicted in this study. Disease severity is described by the extent of residual endogenous FIX activity (< 1 % versus 1 - 5 %).

Subgroup analyses per region cannot be conducted because all patients are sourced from Germany.

Effect measures are calculated for each subgroup category as well as overall using the appropriate PS weights according to section 8.7.2. A p-value for the interaction treatment * subgroup is derived within the analytical framework for effectiveness and tolerability analyses, i.e. the Wald p-value of the regression coefficient for treatment * subgroup. Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients to mitigate convergence issues. Subgroup analyses for binary events per variable are conducted only if at least 10 events occurred in one of the subgroups to mitigate convergence issues.

Table 23: Overview of subgroups planned in the comparative analysis

Pre-defined subgroups	**Operationalization**
Age	≤ 50 years; > 50 years
Gender	Male; female
Dosage (intensity of prophylaxis) 12 months prior to study enrollment	Low-dose therapy (below normal range); In-label therapy (within normal range); High-dose therapy (above normal range)
Joint status	HJHS score at baseline[1]: < 21 HJHS ≥ 21 HJHS
ABR 12 months prior to study enrollment	ABR at baseline[2]: < 44 ABR (all treated bleeding) ≥ 44 ABR (all treated bleeding)
Residual FIX activity at enrollment	<1% (residual FIX activity not measurable); 1-5 % (residual FIX activity measurable)
AAV5 antibody titre at enrollment	positive; negative
Abbreviations: AAV5: Adeno-Associated Virus serotype 5; ABR: Annualized Bleeding Rate; HJHS: Hemophilia Joint Health Score; FIX: Coagulation Factor IX [1] If this operationalization is not feasible for the AbD study population, the mean HJHS will be used instead. [2] In case of problems with confounder adjustment, the mean ABR will be used instead.	

Rationale for operationalization of the confounder ABR 12 months prior study entry:

As the ABR 12 months prior study entry is unknown for the AbD study population, an exploratory search for a comparable population was conducted, but did not deliver any insights on practicable operationalizations for confounder adjustment. Therefore, the dossiers of

Hemgenix and any FIX products that underwent early benefit assessment have been searched for baseline values for the ABR 12 months prior study entry for the respective pivotal trial populations.

In the dossier of eftrenonacog alfa (ALPROLIX®), the mean ABR 12 months prior study entry (Min; Max) with a weekly dose-optimized prophlyaxis was 10.5 (0; 70) and with an individualized prophylaxis (interval) 10.0 (0; 100) [54]. In the dossier of albutrepenonacog alfa (IDELVION®) mean (SD) ABR 12 months prior study entry in the study B-LONG was 15.7 (15.83) with a weekly prophylaxis and 17.3 (21.87) with an interval based prophylaxis [55]. In the HOPE-B study, the mean (SD) [Max] ABR 12 months prior study entry for the safety population was 44.0 (81.5) [56].

In accordance with the HOPE-B study, the confounder ABR 12 months prior study entry will be operationalized as smaller than 44 and greater or equal to 44. However, it is unclear if this operationalization is feasible for the AbD study population. In case of problems with confounder adjustment, the mean ABR will be used instead.

Rationale for operationalization of the confounder HJHS:

The HJHS of the AbD study population is unknown, and an exploratory search did not deliver any results. Therefore, HJHS will be operationalized as smaller than 21 and greater or equal to 21. This is in line with the mean (SD) HJHS at screening of the HOPE-B study, which was 20.8 (17.1). If this operationalization is not feasible for the AbD study population, the mean HJHS will be used instead [57].

8.7.5.2 Sensitivity Analyses

To investigate the potential effects of unmeasured confounders, a before-after-comparison for patients treated with etranacogene dezaparvovec will be performed for bleeding endpoints. ABR will be determined for the 12 months prior to application of etranacogene dezaparvovec as well as for the time at risk after application of etranacogene dezaparvovec. Analysis of the number of reported bleeding events will be performed using a repeated measures generalized estimating equations (GEE) negative binomial regression model accounting for the paired design of the analysis with an offset parameter to account for the differential collection periods. An unstructured covariance matrix will be employed. If the model fails to converge, then a compound symmetry covariance structure will be used. The model will include the treatment (i.e. period) as a categorial variable. To allow time for etranacogene dezaparvovec to become fully active and to allow the subjects the opportunity to stop the treatment with prophylactic

FIX therapy, ABR counts beginning at day 21 of the post-treatment-period will be used in the analysis.

For further sensitivity analyses, please refer to SAP section 11.1.2, 11.2.2. and 12.1.2. No subgroup analyses are performed in the context of sensitivity analysis.

8.7.6 Feasibility Assessment

G-BA has mandated that study feasibility is assessed with each interim analysis. Given the challenges regarding data availability and possibility to perform adjusted interim analysis at the time of first interim analysis (SAP sections 4.5, 4.5.1.2), re-estimation of sample sizes was originally planned with the second interim analysis (SAP section 4.5.1.3). Following the decision of G-BA, dated 01. February 2024 re-estimation of sample size will also take place at the time of first interim analysis. Therefore, based on re-estimated sample sizes a feasibility assessment will be performed with all three interim analysis.

The assessment will be performed based on the following information:

- Updated sample size calculations based on interim analysis results
- Number of enrolled patients per study arm in the Safety Analysis Set and extrapolation of patient numbers per treatment arm based on study enrollment

Results will be reported to G-BA with the second and third interim analysis along with a recommendation on continuation or termination of the study. Any decision on actual termination of the study will only be made by CSL Behring after consultation with G-BA.

Sample sizes will be calculated using both the approach of a shifted null hypothesis as well as the approach derived from a standard null hypothesis. The approach derived from a standard null hypothesis will be used to assess study feasibility.

At the time of first interim analysis, updated sample sizes will still be subject to high uncertainty due to low patient numbers. Feasibility per patient population thus cannot be conclusively evaluated. No termination for infeasibility will take place at the time of first interim analysis but study feasibility will be discussed based on actual patient numbers.

8.8 Quality Control

To minimize the potential for bias in the use of registry data as part of the AbD, SDV will be performed. SDV as described in section 14.1.1 will significantly reduce the frequency of missing or implausible data. Sites will also be trained on the data requirements for this study.

8.9 Limitations of Research Methods

The present study is based on secondary use of data collected in DHR. Data collection in DHR is based on routine clinical practice and some information may be missing or unavailable, as information available in patient charts is restricted to the assessments performed and documented in clinical practice. Regarding effectiveness and tolerability endpoints, a limitation of observational studies conducted in routine clinical practice settings is that assessments are not done on a uniform schedule. While investigators and patients can and will be trained and incentivized to generate and document patient-reported outcomes given the non-interventional nature of this study it can not be guaranteed that data will be fully complete.

8.10 Other Aspects

N/A

9 Protection of Human Patients

This non-interventional, non-randomized, registry-based data collection will be performed in accordance with the ethical principles laid down in the Declaration of Helsinki and in consistence with applicable regulatory requirements.

According to the Professional Code for Physicians in Germany (Berufsordnung Ärzte, BO-Ä) Art 15, the final study protocol will be reviewed and approved by an Independent Ethics Committee before study start depending on the local requirements.

For informed consent, please refer to section 12.

10 Safety Reporting

This observational study is based on secondary use of data. In secondary collection of data in observational research it might not be feasible to collect individual serious and non-serious AE, pregnancy exposures, or incidents related to CSL Behring products because the minimum criteria required to report AEs, pregnancy exposures, and incidents might not be present in the

data source. Therefore, the individual case safety reporting will not be conducted for data extracted from the DHR as also recommended in GVP Module VI C1.2.1 b.

Physicians in Germany are obliged to report unintended drug reactions ("unerwünschte Arzneimittelwirkungen") that come to their attention in the context of their medical practice to the Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)) and incidents related to the use of medicinal products to the competent authority (§6 "Musterberufsordnung für Ärzte für die in Deutschland tätigen Ärztinnen und Ärzte - MBO-Ä 1997 - in der Fassung des Beschlusses des 124. Deutschen Ärztetages vom 5. Mai 2021 in Berlin"; https://www.bundesaerztekammer.de/fileadmin/user_upload/_old-files/downloads/pdf-Ordner/Recht/_Bek_BAEK_MBO-AE_Online_final.pdf).

It is assumed that the reporting of relevant safety data extracted/analyzed in this study has been already adequately performed in accordance with these local requirements and documented at the time of collection of these data through primary data collection mechanisms. These obligations will also be reiterated in the site training materials. In addition, source data verification during the on-site study monitoring visits will ensure that adverse events filed by the treating physician as (possibly) drug-related are also correctly and completely reported in the DHR.

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11 Implementation of a Protocol/ Protocol Amendment(s)

The final protocol of the observational study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Ethics Committee.

The Ethics Committee must also approve any amendment to the protocol and all advertising used to recruit patients for the study, according to local regulations.

12 Subject Informed Consent

Prior to any data collection under this protocol, a written informed consent form (ICF) and a privacy statement, if required, must be signed by the patient in accordance with local practice and regulations. Information about the registry will be explained to the patient. Confirmation of a patient's informed consent must be documented in the patient's medical records prior to any data collection under this protocol.

The investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of this observational study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated subject informed consent must be obtained before any specific procedure for the study is performed, including:

- Interview with the investigator
- Completion of questionnaires
- Completion of eCRF.

The investigator must store the original, signed Subject Informed Consent Form. If applicable, a copy of the signed Subject Informed Consent Form must be given to the subject.

13 Study Management

During the study, a CSL representative or delegate can implement different activities to assure compliance with CSL standards of quality. These activities could include but are not limited to:

- Confirm that the research team is complying with the protocol
- Confirm that data are being accurately recorded in the CRFs
- Ensure that the subject informed consent forms are signed and stored at the investigator's site, if applicable
- Ensure that the CRFs are completed properly

- Monitoring activities for:
    - Checking a sample of informed consent.

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, and number of sites.

14 Monitoring

14.1 General monitoring procedures

Monitoring and Source data verification will be performed by IQVIA. IQVIA will be granted access to a monitoring environment of the DHR and can only access patients that have enrolled in the AbD.

Site Initiation Visits (SIV) for the participating sites are carried out face to face by the IQVIA site manager (monitor) and is conducted prior to site activation. SIVs are carried out to confirm preparedness for protocol execution, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any training prior to activating the site for enrollment. To ensure high data quality for interim and final data analyses study sites will receive customized notifications by phone calls or emails to remind them to enter data in a timely manner before each data cut-off. The accuracy of patient clinical data is ensured through a combination of automated plausibility and completeness checks, as well as a thorough medical review. During the study, regular remote monitoring visits are executed. The focus of the remote monitoring visit is to evaluate the way the study is being conducted and to confirm that all issues are addressed in a timely manner. These visits will include review of queries, actions, site staff and patient enrollment. Visits do not take place until 1 patient has been enrolled at the site. Some sites may require more frequent regular monitoring contacts depending on issues noted at the site. Five remote monitoring visits will be conducted per site, however, visits might be shifted and frequency increased for some sites, while no remote monitoring visit will be conducted for other sites with low query rate or no patient enrollment. A close-out visit (COV) at each study site will be performed at the end of the study.

All relevant site contacts shall be documented.

14.1.1 Source Data Verification

To minimize the potential for bias in the use of registry data as part of the AbD and to ensure the patients fulfill the inclusion criteria and that the data from the patient medical records have been transferred correctly, 100 % on-site SDV will be performed for patient informed consent, inclusion and exclusion criteria, baseline confounders as well as the primary endpoint. In addition, for all secondary endpoints a minimum of 10% of randomly selected patients (at least one patient) per site will undergo SDV for the entire data collection period.

SDV will be performed by clinical monitors on the basis of all available patient records. Five on-site monitoring visits are planned per site. The exact scheduling will be determined based on number of enrolled patients. Prior to the visit the Monitor reviews all pertinent reference materials including but not limited to, previous monitoring report(s), enrollment status, eCRF completion and open action items. The conduct of the on-site monitoring visit follows the On-site Monitoring Visit Checklist developed for this purpose.

Issues identified and any questions left outstanding will be followed up with the site. Action items and timelines for resolution will be determined.

14.1.2 For-Cause Monitoring Visit

The purpose of the for-cause monitoring visit is to ensure the quality of the sites' data documentation, to verify if the patients fulfill the inclusion criteria and do not fulfill any of the exclusion criteria, if the data from the patient medical records have been transferred correctly and to address the issue that triggered the for-cause monitoring visit. For 4 sites (15 % of activated sites) a for-cause monitoring visit is planned.

The conduct of the for-cause monitoring visit follows the On-site Monitoring Visit Checklist.

A for-cause monitoring visit may include all routine monitoring activities or may be conducted to pinpoint/ address specific issues. This visit is done on-site. Criterion for determination of for-cause monitoring visit includes but is not limited to the following:

- First Patient In (FPI) for the site
- Number of patients enrolled
- High or low enrollment rate
- Data collection strategy not successful at capturing required data

- Electronic Medical Records (EMR) to Electronic Data Capture (EDC) issues, PRO issues
- High or low eCRF entry volume
- Number of outstanding findings from previous monitoring visits or contacts
- Improperly handled SAE/ SAESI.
- Number of outstanding open action items that have not been resolved
- Significant Site Staff changes and/or lack of site responsiveness

If necessary, changes to the possible extend of SDV will be depicted in an amendment to the study protocol.

14.1.3 Minimization of missing data

Due to the non-interventional nature of an AbD, complete avoidance of missing or implausible data is impossible. SDV as described in section 14.1.1 will significantly reduce the frequency of missing or implausible data. Sites will also be trained on the data requirements for this study. CSL will provide financial incentives to study center for documentation of information required for this study but not mandatory in the context of data provision to DHR. Financial compensation to study center is expected to support the regular collection of all required data (every 6 months +/- 2.5 months) and timely data entry into the DHR as well as to increase the completeness and quality of data. Incentives to study center are expected to raise the number of patients consenting on individual case reporting ("Einzelfallmeldung") or patients switching from aggregated reporting *("Sammelmeldung")* to individual case reporting. In addition, trainings will be conducted to study center to decrease missing data. Remaining missing data (including missing dates) will be addressed in statistical analysis (see section 11.5 and 12.1.4 of the SAP).

15 Plans for Disseminating and Communicating Study Results

Only aggregated data will be presented to CSL, no patient level data will be disclosed.

In addition to the final analysis, various interim analyses are planned (see section 5 for milestones). These have been scheduled based on the G-BA decision but also taking into account data availability at the respective points in time. See SAP section 4.5 for details.

A first status report will be submitted to G-BA 6 months after its resolution stating the study commencement expected in Q3 - Q4 2024, i.e., by March 2025. The report will be submitted using the template provided by G-BA. Even though no patient data for 2024 will be available from DHR by March 2025 (with the representative data cut of November 2024) due to annual reports (DHR data available in 2024 only covers patient data before study start as of 31 December 2023), CSL intends to submit the requested status report and baseline data (including a descriptive report on current status of the study) to the G-BA. Per the G-BA resolution of 12 May 2023 [11], a first interim analysis needs to be submitted to G-BA 18 months after study start in March 2026 (with the respective data cut of November 2025). The report will be submitted using the template provided by G-BA [58]. As it is expected that patient data available from DHR in 2025 will only cover approx. 3 months from study start, neither a first interim outcome analysis nor a sample size re-estimation is considered to be feasible at this timepoint. Nonetheless, CSL will follow G-BAs´ requirements and submit a first interim analysis covering baseline data, first interim outcome analysis, a sample size re-estimation, a feasibility assessment as well as a status report on current status of the study to the G-BA.

Per G-BA resolution of 12 May 2023 [11], a second interim analysis is due 36 months after study commencement in September 2027. The report will be submitted using the template provided by G-BA. At this point of time CSL intends to submit based on patient data from DHR with a data cut of Mid-May 2027 covering approx. 27 months of AbD (DHR data available until 31 December 2026). The submission to G-BA will include a status report, baseline data, second interim outcome analysis, sample size re-estimation, as well as a feasibility assessment.

CSL intends to submit the third interim analysis to G-BA in March 2029 (54 months after study commencement) based on patient data from DHR with a data cut of November 2028 (DHR data available until 31 December 2027), resulting in approx. 39 months of data from planned study commencement to end of available data. The report will be submitted using the template provided by G-BA and will cover a status report, baseline data, third interim outcome analysis as well as a feasibility assessment.

Results of final analysis will be submitted to G-BA in form of a value dossier for benefit assessment on 2 November 2029[4]. Upon completion of the study, a study report is prepared and serves as the basis for the description of the results that will be submitted to G-BA with the value dossier.

[4] Based on the current timelines, the time from study start to end of data collection would only allow for about 15 months of including patients in the etranacogene dezaparvovec arm to ensure sufficient observation time after the treatment switch. Postponing the final submission from November 2029 to November 2030 could allow for 2029 data from DHR to be included in the final analysis. This would increase the time to include patients in the etranacogene dezaparvovec arm from about 15 to about 27 months and thus likely increase the robustness of available evidence significantly. In case a G-BA resolution is passed to adjust timelines and postpone the final submission of the dossier, the timepoint of latest possible switch from FIX to etranacogene dezaparvovec would be adjusted accordingly to enable 3 years of data collection for all patients. The changes would be subject to an amendment and communicated to G-BA.

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17 Signature on Behalf of Marketing Authorization Holder

Study Title: Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Study Number: CSL222_5002

I have read the protocol CSL222_5002 titled "Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

18 Signature of Investigator

Study Title: Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Study Number: CSL222_5002

I have read the protocol CSL222_5002 titled "Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA".

By signing this protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from CSL Behring (CSL) and the Institutional Review Board or Independent Ethics Committee (as appropriate).

I will ensure that study staff fully understand and follow the protocol.

[redacted] Date

Annex 1 List of Standalone Documents

Number	Document Reference Number	Date	Title
CSL222_5002_A1	CSL222_5002_A1	September 2023	Confounder report 'Methodology of Confounder Identification
CSL222_5002_A2	CSL222_5002_A2	23 May 2024	SAP
CSL222_5002_A3	CSL222_5002_A3	28 March 2024	Addendum 1: Methodology of Confounder Identification: Discussion of relevance of confounders

STATISTICAL ANALYSIS PLAN (SAP)

Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Study Number:	CSL222_5002
Study Product	Etranacogene dezaparvovec (Hemgenix®)
Marketing authorisation holder:	CSL Behring GmbH (CSL) Emil-von-Behring-Strasse 76 35041 Marburg Germany
Version:	original v3.0
Version Date:	23 May 2024
Compliance:	This study will be conducted in accordance with standards of pharmacovigilance practices. Good Clinical Practice ICH guideline should serve as guidance document. Local (e.g. country specific) and regional (e.g. European Union directives) regulations may apply and must be followed.

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1 Modification History

Version	Effective Date	Author of modification	Summary of Change
1.0	9 October 2023		N/A – First Version
2.0	29 March 2024	CSL Behring	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
3.0	23 May 2024	CSL Behring	Modification due to decision of DHR's steering committee of 22 April 2024

Depicted changes introduced to version 1.0 in response to GBA's requirements mandated with its resolution dated 01 February 2024:

Section	Changes	Reason for Change
Title page; 3. Purpose	Version number and date were changed	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
4.1 Objectives and endpoints	The intended evaluation of AE, SAE and (S)AESI by MedDRA SOC/PT was removed after weighing up the effort and informative value for the Routine Practice Data Collection as suggested by G_BA. In consequence,	Implementation of G-BA´s suggestion

	abbreviations were removed from Table 1.	
4.1.2.3 Effectiveness: Pain	Responder analysis was adapted to qualify patients as responders who show an average rating of at least 15 % of the scale range above the baseline value at the end of observation period	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
4.1.2.4 Effectiveness: Joint status	Responder analysis was adapted to qualify patients as responders who show an average rating of at least 15 % of the scale range above the baseline value at the end of observation period	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
4.1.2.5 Effectiveness: Health-related Quality of Life	Responder analysis was adapted to qualify patients as responders who show an average rating of at least 15 % of the scale range above the baseline value at the end of observation period	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
4.4 Determination of sample size	Adjustments were introduced to clarify that all patients fulfilling the inclusion while not fulfilling the exclusion criteria are eligible for the study. A paragraph was added to re-emphasize the intended sample size which was already mentioned in other sections of the SAP. The mistake in the citation regarding ABR from HOPE B study results has been corrected by removal of EPAR as data source. ABR data has always been directly taken from HOPE B trial results.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

	Numbers in Table 3 and Table 4 for row "HOPE-B: major bleeding" were corrected due to calculation error.	
4.5.1 Interim Analyses Other Than Sample Size Re-estimation	The plans for the status reports as well as for the three interim analyses to be submitted to G-BA have been adjusted to strictly fit GBA's requirements in its resolution dated 12 May 2023. CSL Behring intends to submit all required reports and analyses as mandated on due time.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
4.5.2	It was clarified that re-estimation of sample size was originally planned with the second interim analysis for reasons elucidated in detail. However, in order to follow GBA´s requirements, CSL Behring will submit the sample size re-estimation with the first (and second) interim analysis.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
4.5.3 Feasibility assessment	More specific rules regarding feasibility assessment were added.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
8.1 Multiple Comparisions and multiplicity	A clarification was introduced. The Type I error rate will not be adjusted for multiplicity in primary, secondary or supporting analyses.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
8.2 Missing data and imputation	The original paragraph on missing data was adjusted to better fit requirements. Rules were specified for missing data	Implementation of G-BA requests and recommendations from

	(in dates, confounders, endpoints) and imputation strategies were added.	resolution dated 01 February 2024
8.3.1 Reference dates and study days	Corrections were made to align the paragraph on treatment switch with the study protocol.	Implementation of G-BA´s suggestion
8.3.2 Durations and TTE Data	Corrections were made to the calculation of durations and for elapsed time (TTE). The section on decimal numbers and the ignorance of actual number of days were removed.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
8.3.6 Actual treatment	Corrections were made to align the paragraph on treatment switch with the study protocol.	Implementation of G-BA´s suggestion
8.4.1 Confounding and baseline variables	A new paragraph on confounder methodology was added including the interaction between confounders.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
8.4.2 Subgroup definition, Table 8	The operationalisation of the predefined subgroups on “Joint status“ and “ABR 12 months prior to study enrollment” were both modified. For “Joint status” the operationalisation was modified to < 21 HJHS and ≥ 21 HJHS. For “ABR 12 months prior to study enrollment” the operationalisation was modified to < 44 ABR (all treated bleedings) and ≥ 44 ABR (all treated bleedings). The operationalisation of the predefined subgroups on “AAV5 status” were modified to positive and	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

	negative (instead of a fixed titer) to correspond to latest plans on DHR data fields.	
9.1 Subject Disposition, Demographic and baseline characteristics	A clarification was introduced to add that for each of the 100 imputed datasets the specified informations are provided. The intention for a discussion on the appropriateness of the resulting population included in the adjusted analysis has been removed, as it is not in the scope of the SAP but rather part of the study protocol to be submitted.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
10.2 Adjustment by PS methods	The paragraphy addressing the methodology for confounder adjustment and the use of PS was modified to clarify that confounder adjustment will be done in any case.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
10.4 Trimming	A new chapter on trimming methodology was added and the chosen methodology justified.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
10.5.3 Choice of PS weights: Figure 2	The mistake in the figure was corrected (SMWD once replaced by IPTW)	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
11.1.2 Sesitivity analyses of Primary endpoint	A paragraph was added to specify the intended methodology for analysis. The intended conduct of a prevalent new user design according to Webster-	Implementation of G-BA requests and recommendations from

	Clark has been added. Each patient is classified according to the treatment regimes he has undergone so far. time since general treatment initiation becomes an additional confounding variable. Each treatment regime pattern serves as stratum for the subsequent stratified analyses and confounders are updated at each stratum starting point. a stratified logistic regression using treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables is calculated to derive a PS. PS weights are calculated according to section 10.5 and the primary endpoint is analysed according to section 11.1.1.	resolution dated 01 February 2024
11.2.1.1 Analysis of rate endpoints	The use of an unstructured variance-covariance matrix for the repeated measures for a single patient will no longer be used and the section has thus been removed.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
11.2.1.2 Analysis of TTE Endpoints	A specification was introduced to TTE endpoints which are generally analyzed with weighted Cox proportional hazard regression, while PS weight serves as weighting variable. The section on treatment as independent variable to estimate the treatment effect approach has been removed.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
11.2.1.3 Analysis of binary endpoints	A new section was added to introduce Firth´s bias. As the sample size in this study is expected to be small and the	Implementation of G-BA requests and recommendations from

	events may be rare, Firth's bias correction should be applied to reduce the bias of maximum likelihood estimates and to avoid separation. From the model, estimates for risk ratio, odds ratio and risk difference instead of the least squares mean difference and standard error were chosen for etranacogene dezaparvovec relative to FIX. A modification to add the estimation of corresponding 95 % profile penalized likelihood CI was included.	resolution dated 01 February 2024
11.2.2 Sensitivity analyses of secondary endpoints	An unstructured variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of parameters of the model. Hedges'g and a 95% CI are computed according to the formulas provided in Goulet-Pelletier et al. for between treatment effects [1]. MMRM least square estimates of the mean difference, standard error and degrees of freedom are used to calculate a standard deviation as the denominator for Cohen's d. The intended conduct of a prevalent new user design according to Webster-Clark has been added. Each patient is classified according to the treatment	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

	regimes he has undergone so far. time since general treatment initiation becomes an additional confounding variable. Each treatment regime pattern serves as stratum for the subsequent stratified analyses and confounders are updated at each stratum starting point. a stratified logistic regression using treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables is calculated to derive a PS. PS weights are calculated according to section 10.5 and the primary endpoint is analysed according to section 11.2.1.	
11.4 and 11.5	Chapters have been replaced by the chapters 8.1 and 8.2 adressing missing values and imputations	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
12.1.1 Main analysis of tolerability endpoints	The intended analyses of tolerability analyses based on the evaluation by MedDRA SOC/PT was removed after weighing up the effort and informative value for the Routine Practice Data Collection as suggested by G_BA. AE are analysed as binary endpoints according to section 11.2.1.3. hence the redundant phrases were removed.	Implementation of G-BA´s suggestion as well as implementation of G-BA requests and recommendations from resolution dated 01 February 2024
12.1.2 Sensitivity analyses of	The intended conduct of a prevalent new user design according to Webster-Clark has been added. Each patient is	Implementation of G-BA requests and recommendations from

tolerability endpoints	classified according to the treatment regimes he has undergone so far. time since general treatment initiation becomes an additional confounding variable. Each treatment regime pattern serves as stratum for the subsequent stratified analyses and confounders are updated at each stratum starting point. a stratified logistic regression using treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables is calculated to derive a PS. PS weights are calculated according to section 10.5 and the primary endpoint is analysed according to section 12.1.1.	resolution dated 01 February 2024
12.1.3 Subgroup analyses of tolerability endpoints	Adjustments were made on the p-value for the interaction treatment * subgroup which is now derived from a likelihood ratio test.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
12.1.4	Chapter has been removed and replaced by sections 8.1 ad 8.2	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024
13	References were updated.	Implementation of G-BA requests and recommendations from resolution dated 01 February 2024

Depicted changes introduced to version 2.0 to reflect the limited approval of requested changes to the DHR by the DHR's steering committee decision of 22 April 2024:

Section	Changes	Reason for Change
Title page; 3. Purpose	Version number and date were changed	Modification due to decision of DHR's steering committee of 22 April 2024
4.5 Planned interim analyses 4.5.1 Interim Analyses Other Than Sample Size Re-estimation	Milestones were adjusted due to modifications in study protocol based on new DHR updates which lead to re-submission of study protocol to G-BA on 23 May 2024 and therefore a delay of study start. The timeframes for the status reports as well as for the three interim analyses to be submitted to G-BA have been adjusted accordingly.	Modification due to decision of DHR's steering committee of 22 April 2024
6 Study analysis sets	A footnote has been added to suggest an amendment in case G-BA changes its resolution regarding the submission timeline for the benefit assessment dossier currently due on 2 November 2029 to ensure a data collection for at least 3 years.	Delay in the timelines leading to delayed study commencement and hence restrictions in data availability until 2029.
8.4.1 Table 7	The reference dosage according to SmPC has been aligned and hence depicted for a once weekly dosing regimen of FIX products.	Need for clarification
14 Signature on behalf of the MAH	The list of responsibilities for the marketing authorisation holder has been adjusted to match with the	Responsibilities within CSL Behring have been changed

	changes made within the study protocol v3.0.	

2 List of Abbreviations

Abbreviation	Term
AAV5	Adeno-Associated Virus serotype 5
AbD	Routine Practice Data Collection and Evaluation (Anwendungsbegleitende Datenerhebung)
ABR	Annualized Bleeding Rate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATE	Average Treatment Effect
ATT	Average Treatment effect among Treated
BPI-SF	Brief Pain Inventory – Short Form
(c)DNA	(complementary) Deoxyribonucleic Acid
CFC	Clotting Factor Concentrate
CI	Confidence Interval
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CSR	Clinical Study Report
DBL	Database Lock
DHR	German Haemophilia Registry (Deutsches Hämophilieregister)
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EMA	European Medicines Agency
FIX	Coagulation Factor IX
G-BA	Federal Joint Committee, Germany (Gemeinsamer Bundesausschuss)
GCP	Good Clinical Practice
GCSP	Global Clinical Safety & Pharmacovigilance
GEE	Generalized Estimating Equations
GLM	Generalized Linear Model
Haemo-QoL-A	Haemophilia-specific Health-related Quality of Life Questionnaire for Adults
HJHS	Hemophilia Joint Health Score
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonization

Abbreviation	Term
IP	Investigational Product
IPTW	Inverse Probability of Treatment Weights
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
IU	International Units
IV	Intravenous
KM	Kaplan Meier
LP1	Liver-specific Promotor 1
MCAR	Missing Completely At Random
MMRM	Mixed Models for Repeated Measures
OS	Overall Survival
PASS 2023	Non-Inferiority Test for the Ratio of two Negative Binomial Rates
pH	Potential of Hydrogen
PS	Propensity Score
PTP	Previously Treated Patients
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAESI	Serious Adverse Event of Special Interest
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SGB V	Book Five of the Social Code
SLR	Systematic Literature Review
SMD	Standardized Mean Difference
SmPC	Summary of Product Characteristics
TTE	Time-To-Event
WHO	World Health Organization

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description of the planned statistical analyses of the study «Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in

severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA» (study number: CSL222_5002).

This SAP is based upon the following study documents:

- Clinical Study Protocol dated 23 May 2024

All decisions regarding the final analysis of the study results, as defined in this SAP, have been made before database lock (DBL) of the study data.

Deviations from the analyses in this SAP will be detailed in the clinical study report (CSR).

4 Study Design

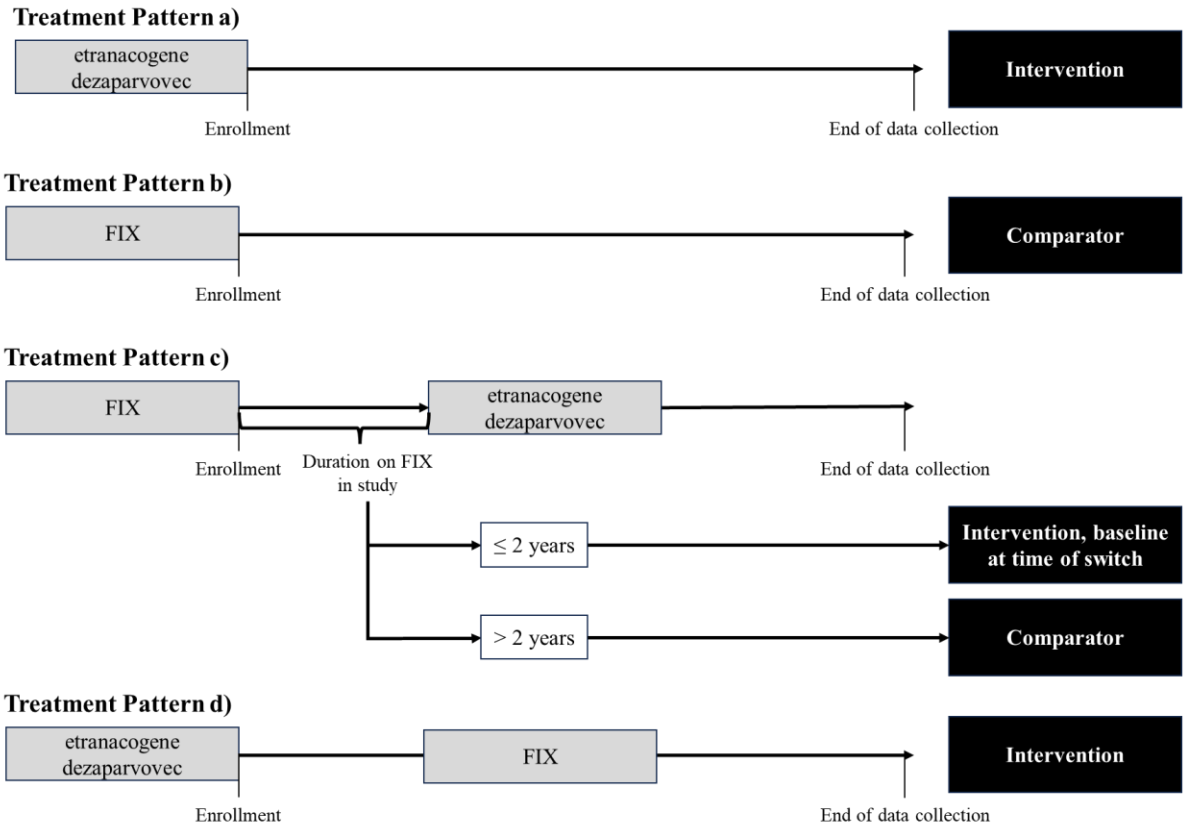
The study is a non-interventional, non-randomized, registry-based data collection in subjects with severe to moderately severe haemophilia B treated with the gene therapy etranacogene dezaparvovec (Hemgenix®) compared to a prophylaxis with recombinant or plasma-derived FIX products. The study is based on secondary use of data from the German Haemophilia Registry (Deutsches Hämophilieregister, DHR) [2].

Subjects are enrolled until 1 January 2026[1]. They are enrolled when they first meet the inclusion and exclusion criteria of the study, signed informed consent and have the first data submission to DHR following a number of changes that need to be implemented in the DHR case report form (CRF) (baseline). Patients are then observed until the date of data cut for final analysis (31 December 2028) or loss to follow-up.

It is expected that all subjects will be pre-treated with FIX products when enrolling in the study. Four types of treatment patterns regarding etranacogene dezaparvovec and FIX prophylaxis are possible (Figure 1). In addition to subjects who are (a) treated exclusively with etranacogene dezaparvovec or (b) exclusively with FIX prophylaxis from the time of enrollment to the end of observation, there will also be (c) patients who switch from FIX prophylaxis to etranacogene dezaparvovec at a given time point. Patients (d) treated with FIX on prophylaxis after receiving etranacogene dezaparvovec are theoretically also possible.

[1] In case a G-BA resolution is passed to adjust timelines and postpone the final submission of the dossier, the timepoint of latest possible switch from FIX to etranacogene dezaparvovec would be adjusted accordingly to enable 3 years of data collection for all patients. The changes would be subject to an amendment and communicated to G-BA.

Figure 1: Treatment Patterns and Allocation to Intervention and Comparator



Due to the specific target population of this study being pre-treated with prophylactic FIX, the generally recommended framework of a new-user-design [3] cannot be implemented. Patients in groups a) and b) will be allocated to the intervention and comparator arm, respectively.

Per advice provided by Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) and Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) [4], patients in group c) will be allocated to the intervention arm if they are treated with etranacogene dezaparvovec within the first two years after enrollment. In this case, baseline will be set at time of treatment with etranacogene dezaparvovec and previously collected data on treatment effects of FIX prophylaxis will be discarded. If treatment with etranacogene dezaparvovec is initiated more than two years after enrollment, patients are kept in the comparator arm and are not censored in main analysis to implement an intention-to-treat principle.

It is acknowledged that this approach can result in a minimum observation period of etranacogene dezaparvovec as well as FIX prophylaxis below the mandated three-year observation period. To generate insights on the effects of a shortened observation period, a

sensitivity analysis will be performed that only includes patients with at least three years of follow-up on their respective treatment.

4.1 Objectives and Endpoints

The effectiveness and tolerability will be assessed based on patient-relevant endpoints, which are derived from the G-BA resolution mandating this study [5].

Effectiveness covers the topics:

- Survival
- Bleeding
- Pain
- Joint status
- Health-related quality of life (HRQoL)

Tolerability covers the topics:

- Adverse events (AE)
- Serious adverse events (SAE) approximated as AE leading to hospitalization or death
- Adverse events of special interest (AESI)
- Serious adverse events of special interest (SAESI) approximated as AESI leading to hospitalization or death

Table 1: Study Objectives and Endpoints

Objectives	Endpoints	Summary Measure(s)
Primary	ABR: All treated bleeding	Rate Ratio
Secondary	OS	Hazard Ratio
	ABR: Severe bleeding	Rate Ratio
	ABR: Life-threatening bleeding	Rate Ratio
	ABR: Joint bleeding	Rate Ratio

Objectives	Endpoints	Summary Measure(s)
	Pain: BPI-SF: Worsening	Responder analysis over entire observation period, Risk Ratio
	Pain: BPI-SF: Improvement	Responder analysis over entire observation period, Risk Ratio
	Joint status: HJHS: Worsening	Responder analysis over entire observation period, Risk Ratio
	HRQoL: Haemo-QoL-A: Worsening	Responder analysis over entire observation period, Risk Ratio
	HRQoL: Haemo-QoL-A: Improvement	Responder analysis over entire observation period, Risk Ratio
	AE	Risk Ratio, overall
	SAE	Risk Ratio, overall Approximation of SAE as AE leading to hospitalization or death
	AESI: Thromboembolic events	Risk Ratio, overall
	SAESI: Thromboembolic events	Risk Ratio, overall Approximation of SAESI as AESI leading to hospitalization or death
	AESI: Development of FIX inhibitors	Risk Ratio, overall
	SAESI: Development of FIX inhibitors	Risk Ratio, overall Approximation of SAESI as AESI leading to hospitalization or death
	AESI: Symptomatic liver damage	Risk Ratio, overall
	SAESI: Symptomatic liver damage	Risk Ratio, overall Approximation of SAESI as AESI leading to hospitalization or death
	AESI: Malignant neoplasms	Risk Ratio, overall
	SAESI: Malignant neoplasms	Risk Ratio, overall Approximation of SAESI as AESI leading to hospitalization or death
Exploratory	Annualized infusion rate of prophylactic FIX concentrates (number of infusions): annualized amount of all consumed single doses (number of infusions) of prophylactic FIX concentrates	Rate Ratio

Objectives	Endpoints	Summary Measure(s)
	Annualized infusion rate of on-demand FIX concentrates (number of infusions): annualized amount of all consumed single doses (number of infusions) of on-demand FIX concentrates	Rate Ratio
	Time to resumption of prophylactic FIX therapy (etranacogene dezaparvovec patients only)	Only applicable to intervention arm, summary statistics (share of subjects with event, median, min/max TTE)
Abbreviations: ABR: Annualized Bleeding Rate; AE: Adverse Event; AESI: Adverse Event of Special Interest; BPI-SF: Brief Pain Inventory – Short Form; FIX: Coagulation Factor IX; Haemo-QoL-A: Haemophilia specific Quality of Life Questionnaire for Adults; HJHS: Hemophilia Joint Health Score; HRQoL: Health-Related Quality of Life; OS: Overall Survival; SAE: Serious Adverse Event; SAESI: Serious Adverse Event of Special Interest; TTE: Time-To-Event		

The operationalization of endpoints is shown in the following sections 4.1.1 to 4.1.3.

Reference date is the date of the first treatment with etranacogene dezaparvovec or FIX after enrollment and first data submission to DHR following a number of changes that need to be implemented in the DHR CRF unless otherwise noted.

4.1.1 Primary Endpoint: Annualized Bleeding Rate (ABR)

Annualized Bleeding Rate (ABR): all treated is defined as the cumulative number of all bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from reference date to censoring. For censoring events see section 8.3.7.

4.1.2 Secondary endpoints

4.1.2.1 Effectiveness: Survival

Overall survival (OS) is a time-to-event (TTE) endpoint.

OS is defined as

(Date of death/censor – reference date + 1) / 30.4375.

OS is defined as the time (in months) from the reference date to the *date of death*. Event is death from any cause and censored otherwise. Time for censored patients is defined as the time from the reference date to lost-to-follow-up or end of the study.

4.1.2.2 Effectiveness: Bleeding

ABR: Severe bleeding is defined as the cumulative number of all severe bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from reference date to censoring. For censoring events see section 8.3.7.

ABR: Life-threatening bleeding is defined as the cumulative number of all life-threatening bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from reference date to censoring. For censoring events see section 8.3.7.

ABR: Joint bleeding is defined as the cumulative number of all joint bleeding events that require treatment with at least one dose of factor concentrate across all patients per patient-year of being at risk. Time at risk (in years) is defined as the time from reference date to censoring. For censoring events see section 8.3.7.

4.1.2.3 Effectiveness: Pain

BPI-SF: Worsening

Brief Pain Inventory – Short Form (BPI-SF) is a validated, patient-reported instrument for the assessment of pain (refer to study protocol section 7.3.3 for details). Change from baseline in average pain (scale no. 5) is analyzed as binary responder analysis. Patients showing an average pain rating two or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 10) at the end of observation period qualify as responders.

BPI-SF: Improvement

BPI-SF is a validated, patient-reported instrument for the assessment of pain (refer to study protocol section 7.3.3 for details). Change from baseline in average pain (scale no. 5) is analyzed as binary responder analysis. Patients showing at least two documentations of an average pain rating two or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 10) at the end of observation period qualify as responders.

4.1.2.4 Effectiveness : Joint Status

HJHS: Worsening

Hemophilia Joint Health Score (HJHS) is a validated, clinician-reported instrument for the assessment of joint status in haemophilia patients (refer to study protocol section 7.3.4 for details). Change from baseline in HJHS total score is analyzed as binary responder analysis. Patients showing a HJHS total score 19 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 124) at the end of observation period qualify as responders.

4.1.2.5 Effectiveness: Health-Related Quality of Life

Haemo-QoL-A: Total Score Worsening

Haemophilia-specific Health-related Quality of Life Questionnaire for Adults (Haemo-QoL-A) measures health-related quality of life (HRQoL) in adults with haemophilia (refer to study protocol section 7.3.5 for details). Change from baseline in Haemo-QoL-A total score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A total score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Total Score Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A total score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A total score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Physical Functioning Worsening

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A physical functioning domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A physical functioning domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Physical Functioning Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A physical functioning domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A physical functioning domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Role Functioning Worsening

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A role functioning domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A role functioning domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Role Functioning Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A role functioning domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A role functioning domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Worry Worsening

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A worry domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A worry domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Worry Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A worry domain score is analyzed as binary responder analysis. Patients a Haemo-QoL-A worry domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Consequences of Bleeding Worsening

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A consequences of bleeding domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A consequences of bleeding domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Consequences of Bleeding Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A consequences of bleeding domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A consequences of bleeding domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Emotional Impact Worsening

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A emotional impact domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A emotional impact domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Emotional Impact Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A emotional impact domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A emotional impact domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Treatment Concerns Worsening

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A treatment concerns domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A treatment concerns domain score 15 or more points below the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

Haemo-QoL-A: Treatment Concerns Improvement

Haemo-QoL-A measures HRQoL in adults with haemophilia. Change from baseline in Haemo-QoL-A treatment concerns domain score is analyzed as binary responder analysis. Patients showing a Haemo-QoL-A treatment concerns domain score 15 or more points above the baseline value (i.e. ≥ 15 % of the scale reaching from 0 to 100) at the end of observation period qualify as responders.

4.1.2.6 Tolerability: Adverse Events (AE)

All tolerability endpoints are reported from baseline to censoring. For censoring reasons, please refer to section 8.3.7.

AE is a binary endpoint and defined as proportion of patients reporting an AE.

4.1.2.7 Tolerability: Serious Adverse Events (SAE)

SAE is a binary endpoint and defined as proportion of patients reporting a SAE. Seriousness is approximated via information on AE leading to hospitalization as well as death due to AE.

4.1.2.8 Tolerability: Adverse Events of Special Interest (AESI)

AESI: Thromboembolic is a binary endpoint and defined as proportion of patients reporting an AE that is classified as a thromboembolic event.

AESI: FIX Inhibitor is a binary endpoint and defined as proportion of patients reporting an AE that is classified as development of FIX inhibitors.

AESI: Liver is a binary endpoint and defined as proportion of patients reporting an AE that is classified as symptomatic liver damage.

AESI: Neoplasms is a binary endpoint and defined as proportion of patients reporting an AE that is classified as malignant neoplasms.

4.1.2.9 Tolerability: Serious Adverse Events of Special Interest (SAESI)

SAESI: Thromboembolic is a binary endpoint and defined as proportion of patients reporting an AE that is classified as a thromboembolic event. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

SAESI: FIX Inhibitor is a binary endpoint and defined as proportion of patients reporting an AE that is classified as development of FIX inhibitors. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

SAESI: Liver is a binary endpoint and defined as proportion of patients reporting an AE that is classified as symptomatic liver damage. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

SAESI: Neoplasms is a binary endpoint and defined as proportion of patients reporting an AE that is classified as malignant neoplasms. Seriousness is approximated via information on AESI leading to hospitalization as well as death due to AESI.

4.1.3 Exploratory Endpoints

FIX Utilization Prophylaxis - Annualized infusion rate of prophylactic FIX concentrates (number of infusions) is defined as the cumulative amount of all consumed single doses (number of infusions) of prophylactic FIX concentrates per patient-year of being at risk. Time at risk (in years) is defined as the time from reference date to censoring. For censoring events see section 8.3.7.

FIX Utilization On-Demand - Annualized infusion rate of on-demand FIX concentrates (number of infusions) is defined as the cumulative amount of all consumed single doses (number of infusions) of on-demand FIX concentrates per patient-year of being at risk. Time at risk (in years) is defined as the time from reference date to censoring. For censoring events see section 8.3.7.

Time to return to prophylactic FIX therapy is a TTE endpoint and defined exclusively for patients in the intervention arm of the study as:

(Date of resumption of prophylactic FIX therapy/censor – reference date + 1) / 30.4375.

For censoring events see section 8.3.7.

4.1.4 Primary Study Hypotheses

The outcomes of this study are to be used in a future benefit assessment according to § 35a Book V of the Social Code (SGB V) in Germany. It is acknowledged that G-BA mandated a final sample size estimation with the first interim analysis 18 months after study start using a shifted null-hypothesis building on IQWiG's proposed effect thresholds [6, 7, 3].

However, decisions on an additional benefit are the sole responsibility of G-BA's decision making processes in the benefit assessment procedures and have always been independent from any potential hypotheses formulated in confirmatory clinical studies. In the setting of this non-interventional, non-confirmatory study, all endpoints will thus be analyzed and reported to G-BA for its decision-making without formulation of a formal hypothesis.

All comparisons will be based on two-sided tests with alpha = 0.05, two-sided 95 % confidence intervals (CI) will be reported, all p-values are nominal without adjustment for multiplicity.

4.2 Study Treatments

4.2.1 Etranacogene Dezaparvovec

Etranacogene dezaparvovec (Hemgenix®) is a gene therapy medicinal product that allows for the expressiones ofthe human coagulation FIX. It is a non-replicating, recombinant adeno-associated virus serotype 5 (AAV5) based vector containing a codon-optimised (self-) complementary deoxyribonucleic acid (cDNA) of the human coagulation FIX variant R338L (FIX-Padua) gene under the control of a liver-specific promoter (LP1). Etranacogene dezaparvovec is produced in insect cells by recombinant DNA technology [8].

Prior to the treatment with etranacogene dezaparvovec, patients need to be tested for the titre of pre-existing FIX inhibitors. Etranacogene dezaparvovec should only be administered to patients who have demonstrated absence of FIX inhibitors. In case of a positive test result for human FIX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive etranacogene dezaparvovec. In addition, patients should be tested for the titre of neutralizing anti-AAV5 antibodies because pre-existing neutralizing anti-AAV5 antibodies above a titre of 1:678 (measured by 7-point-assay) may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of etranacogene dezaparvovec therapy [8].

Etranacogene dezaparvovec is administered as a single-dose intravenous (IV) infusion. The summary of product characteristics (SmPC) recommends a single dose of 2×10^{13} gene copies per kg body weight corresponding to 2 mL/kg body weight, administered as an IV infusion after dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection. Hemgenix® can be administered only once [8].

The onset of effect from etranacogene dezaparvovec treatment may occur within several weeks post-dose. Therefore, haemostatic support with exogenous human FIX may be needed during the first weeks after etranacogene dezaparvovec infusion to provide sufficient FIX coverage for the initial days post-treatment [8].

4.2.2 FIX concentrates

The primary goals of haemophilia B therapy are the prevention of bleeding episodes, rapid and definitive treatment of bleeding episodes (breakthrough bleeding episodes) that occur even while on a regular prophylactic regimen and provision of adequate haemostasis during surgery and emergencies. Currently, these goals are essentially met for haemophilia B subjects by IV injections of commercially available recombinant- or plasma-derived FIX products, either at

the time of a bleeding episode (on-demand) or by regular infusions up to several times a week (prophylactically). The recent approvals of extended half-life FIX products allow for reduced frequency of factor administration (once every 7 to 14, or even 21 days) and maintenance of a higher FIX trough level [9].

Prophylaxis with FIX concentrates is referred to as regular replacement therapy; as opposed to episodic replacement therapy (on-demand therapy) which is defined as the administration of clotting factor concentrates (CFC) only at times when bleeding occurs. Due to the severity of bleeding phenotype, haemophilia B patients with severe to moderately severe disease routinely receive a prophlylactic FIX replacement, which is complemented by an on-demand FIX treatment if needed.

The definition of an appropriate comparator treatment by G-BA for the mandated Routine Practice Data Collection (Anwendungsbegleitende Datenerhebung, AbD) includes all approved FIX products in Germany, either plasma-derived or recombinant FIX (including normal-halflife as well as extended-halflife products). Hence, all approved FIX products can be used for prophylactic treatment and no further definition is needed. Both mode of administration and dosage of FIX prophylaxis should be in line with the recommendations of the corresponding SmPC as shown in Table 2.

Table 2: Authorized FIX propylaxis products for FIX subtitution in German health care

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
Recombinant FIX preparations			
Nonacog alfa (BeneFIX®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Nonacog alfa can be used for all age groups.	Nonacog alfa is administered by IV infusion after reconstitution of the lyophilised powder with sterile 0.234 % sodium chloride solution. In most cases it is administered at an infusion rate of up to 4 mL per minute. In general, it should be administered at a slow infusion rate and the rate should be determined by patient's individual comfort level. Nonacog alfa can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition. <u>Long-term prophylaxis:</u> In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days. <u>On-demand treatment:</u> The calculation of the required dose of nonacog alfa can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 0.8 IU/dL (range from 0.4 to 1.4 IU/dL) in patients 12 years and older. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg]\ \times desired\ FIX\ increase\ [\%]\ or\ \left[\frac{IU}{dL}\right] \times 1.3\frac{dL}{kg}$ $1.3\frac{dL}{kg}$: reciprocal of observed recovery ($1\frac{IU}{kg} \div 0.8\frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of hemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of hemorrhage and type of surgical	[10]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
		procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	
Nonacog gamma (Rixubis®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Nonacog gamma is indicated in patients of all age groups.	Nonacog gamma is administered by IV infusion after reconstitution of the powder with the supplied solvent. The solution should then be clear, colourless, free from foreign particles and has a pH of 6.8 to 7.2. The osmolality is greater than 240 mosmol/kg. It can be either self-administered or administered by a caregiver. In both cases appropriate training is needed beforehand. Administration should be performed using a rate that ensures the comfort of the patient, up to a maximum of 10 mL/min. Nonacog gamma can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition, age and pharmacokinetic parameters of FIX (e.g. incremental recovery, half-life). <u>Long-term prophylaxis:</u> Usually doses of 40 to 60 IU of FIX per kg body weight are administered at intervals of 3 to 4 days for patients 12 years and older. <u>On-demand treatment:</u> The calculation of the required dose of nonacog gamma can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 0.9 IU/dL (range from 0.5 to 1.4 IU/dL) in patients 12 years and older. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg]\ \times desired\ FIX\ increase\ [\%\ ] or\ \left[\frac{IU}{dL}\right] \times 1.1\frac{dL}{kg}$ $1.1\frac{dL}{kg}$: reciprocal of observed recovery ($1\frac{IU}{kg} \div 0.9\frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of hemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of hemorrhage and type of surgical	[11]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
		procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	
Albutrepenonacog alfa (Idelvion®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Albutrepenonacog alfa can be used for all age groups.	Albutrepenonacog alfa is administered by IV infusion after reconstitution of the powder with the supplied solvent. Administration should be performed slowly using a rate that ensures the comfort of the patient, up to a maximum of 5 mL/min. Albutrepenonacog alfa can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition. <u>Long-term prophylaxis:</u> Usually doses of 35 to 50 IU/kg once weekly are administered. Well-controlled patients on a once-weekly regimen might be treated with up to 75 IU/kg at intervals of 20 to 14 days. Depending an patient's age dose intervals may be extended (> 18 years) or shortened (younger patients). After a bleeding episode during prophylaxis, patients should maintain their prophylaxis regimen as closely as possible, with 2 doses of albutrepenonacog alfa being administered at least 24 hours apart but longer if deemed suitable for the patient. <u>On-demand treatment:</u> The calculation of the required dose of albutrepenonacog alfa can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 1.3 IU/dL in patients 12 years and older. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg] \times desired\ FIX\ increase\ [\%\ ] or \left[\frac{IU}{dL}\right] \times 0.77 \frac{dL}{kg}$ $0.77 \frac{dL}{kg}$: reciprocal of observed recovery ($1 \frac{IU}{kg} \div 1.3 \frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of hemorrhage and surgery	[12]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
		vary within a range from 30 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of hemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	
Nonacog beta pegol (Refixia®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Nonacog beta pegol can be used for all age groups.	Nonacog beta pegol is administered by IV bolus injection over several minutes after reconstitution of the powder for injection with the histidine solvent. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 mL/min. It can be either self-administered or administered by a caregiver. In both cases appropriate training is needed beforehand. Noncog beta pegol can be used as prophylaxis or as on-demand treatment. <u>Long-term prophylaxis:</u> Usually doses of 40 IU/kg body weight are administered once weekly. Adjustments of doses and administration intervals may be considered based on achieved FIX levels and individual bleeding tendency. <u>On-demand treatment:</u> Dose and duration of the substitution therapy depend on the location and severity of the bleeding. General recommendations on dosage in case of hemorrhage and surgery vary within a range from 40 to 80 IU/kg which corresponds to the required FIX level and depends on the degree of hemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	[13]
Eftrenonacog alfa (Alprolix®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). Eftrenonacog alfa can be used for all age groups.	Eftrenonacog alfa is administered by IV injection over several minutes after reconstitution of the powder for injection with the suppied solvent (sodium chloride solution). The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 10 mL/min. It can be either self-administered or administered by a caregiver. In both cases appropriate training is needed beforehand. Eftrenonacog alfa can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient’s clinical condition.	[14]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
		Long-term prophylaxis: Recommended starting regimens are either: • 50 IU/kg once weekly, adjust dose based on individual response or • 100 IU/kg (highest recommended dose) once every 10 days, adjust interval based on individual response. Some patients who are well-controlled on a once every 10 days regimen might be treated on an interval of 14 days or longer. On-demand treatment: The calculation of the required dose of eftrenonacog alfa can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 1.0 IU/dL. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg]\ \times desired\ FIX\ increase\ [\%\ ] or\ \left[\frac{IU}{dL}\right] \times 1.0 \frac{dL}{kg}$ $1.0 \frac{dL}{kg}$: reciprocal of observed recovery ($1 \frac{IU}{kg} \div 1.0 \frac{IU}{dL}$) The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of hemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of hemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	
Human plasma-derived FIX preparations			
FIX (Alphanine®, Octanine®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency).	FIX is administered by IV injection after reconstitution of the powder for injection with the suppied solvent. The rate of administration should be determined by the patient's comfort level: Alphanine®: maximum injection rate at10 mL/min Octanine®: maximum injection rate at 2 to 3 mL/min Haemonine®: maximum injection rate at 2 to 3 mL/min Immunine®: maximum injection rate at 2 mL/min	[15, 16]
FIX (Haemonine®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency).		[17]

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
	FIX is indicated in adults, adolescents and children aged 6 years and older.	FIX can be used as prophylaxis or as on-demand treatment. In both cases dose and duration of substitution depends on the severity of FIX deficiency, on the location and extent of bleeding, and on the patient's clinical condition.	
FIX (Immunine®)	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). FIX can be used for all age groups - from children older than 6 years up to adults. The use of FIX in children under 6 years of age cannot be recommended as insufficient data are available for this purpose.	<u>Long-term prophylaxis:</u> Usually doses of 20 to 40 IU/kg body weight are administered at intervals of 3 to 4 days. <u>On-demand treatment:</u> The calculation of the required dose can be based on the finding that one unit of FIX activity per kg body weight is expected to increase the circulating level of FIX, an average of 1.0-2.0 IU/dL. The required dose is determined using the following formula: $Required\ units\ of\ FIX = body\ weight\ [kg] \times desired\ FIX\ increase\ [\%]\ or\ \left[\frac{IU}{dL}\right] \times x\frac{dL}{kg}$ $x\frac{dL}{kg}$: reciprocal of observed recovery ($\frac{IU}{kg}$ per $\frac{IU}{dL}$) Alphanine®: $x\frac{dL}{kg} = 0.8\frac{dL}{kg}$ Octanine®: $x\frac{dL}{kg} = 0.8\frac{dL}{kg}$ Haemonine®: $x\frac{dL}{kg} = 0.8\frac{dL}{kg}$ Immunine®: $x\frac{dL}{kg} = 0.9\frac{dL}{kg}$ The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. General recommendations on dosage in case of hemorrhage and surgery vary within a range from 20 to 100 IU/kg which corresponds to the required FIX level and depends on the degree of hemorrhage and type of surgical procedure. Further dosage guidance for bleeding episodes and surgery can be found in the respective SmPC.	[18]

Abbreviations: FIX: Coagulation Factor IX; IU: International Units; IV: intravenous; pH: potential of Hydrogen; PTP: Previously Treated Patients; SmpC: Summary of Product Characteristics; WHO: World Health Organization

Active substance (medicine name)	Therapeutic indication	Method of administration and dosage[1]	Reference
[1] The number of units of FIX administered is expressed in International Units (IU), which are related to the current WHO standard for FIX products. FIX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FIX in plasma). One IU of FIX activity is equivalent to that quantity of FIX in one mL of normal human plasma.			

4.3 Randomization and blinding

This is a non-interventional, non-randomized, open-label study with secondary use of data from the DHR. By nature of this study, no randomization and blinding applies. For details on adjustment of covariates, see section 10.

4.4 Determination of the Sample Size

Since this study is a non-interventional, secondary use of data from the DHR, CSL Behring has no control over enrollment in the study. All patients fulfilling the inclusion while not fulfilling the exclusion criteria (see protocol section 8.2) are eligible for the study.

Assuming a patient ratio of 1:5 between intervention and comparator group, an ABR of 3.45 in the comparator group and 0.56 in the intervention group following a negative binomial distribution with dispersion $\phi = 1.5$, 103 patients (intervention group n = 17, comparator group n = 86) are required under a shifted null hypothesis of rate ratio = 0.5 with power = 0.8 and $\alpha = 0.05$ two-sided (PASS 2023).

Further sample size considerations, including scenarios without a shifted null hypothesis, can be found in the following paragraphs.

In an effort to assess study feasibility in the context of the German care and registry structures, an orientational sample size estimation for various scenarios was performed by IQWiG [6] and two scenarios were depicted by G-BA in its resolution mandating the study [5]. All scenarios use the following assumptions:

- Endpoint used for sample size estimation: ABR
- $RR_0 = 0.5$ (shifted null-hypothesis)
- Power $\beta = 0.8$
- $\alpha = 0.05$, two-sided
- Negative binomial model with dispersion parameter $\phi = 1.5$
- Negligible censoring

The ABR inputs used for calculating the scenarios seem to not have been chosen based on the results of the HOPE-B trial. IQWiG describes *"To obtain sample sizes that are realistically*

recruitable in an AbD, ABRs of 2.6 to 3.6 under the comparator therapy and ABRs of 0.6 to 1 for the intervention are assumed in the present design."

All scenarios calculated by IQWiG also use the concept of a shifted null-hypothesis, i.e. a hypothesis threshold of rate ratio = 0.5 ($RR_0 = 0.5$). While not mandated by German Social law or G-BA code of procedure, it is acknowledged that this threshold and its application to the boundaries of the two-sided 95 % CI has been requested by IQWiG both in its initial Rapid Report [3], its general methods [7] as well as consistently applied in all AbD concepts to date [6, 19–25].

The applied concept of a shifted null-hypothesis is derived from the established concept of a "dramatic effect" for naïve comparisons. While it is argued that effect thresholds can be reduced due to thorough confounder adjustment methods required in the context of an AbD, the thresholds are applied to the boundaries of the 95 % CI instead of the effect estimate (as is defined for the dramatic effect as well as the literature cited to derive these thresholds) [7].

While it is acknowledged that this approach guarantees a very high level of certainty, it is anticipated that it would also lead to patient numbers that cannot realistically be included in the context of an AbD in rare diseases. An alternative could be to follow the principle of the "dramatic effect", i.e. $p < 0.01$ but with reduced effect thresholds (rate ratio < 0.5).

Since actual patient numbers cannot be controlled by CSL Behring, an orientational sample size calculation was performed with two approaches (a) shifted null-hypothesis and b) dramatic effect criteria with modified effect threshold) based on both the scenarios calculated by IQWiG and selected by G-BA as well as the actual observed results from the HOPE B study. This dual approach is also motivated by the fact that the results generated by this study will meet interest of the scientific medical community that goes beyond the context and stakeholders involved in the German benefit assessment. While G-BA may choose to not consider any results not fulfilling the concept of a shifted null-hypothesis, CSL Berhing anticipates that results showing a rate ratio < 0.5 at a significance level of $p < 0.01$ will meet significant interest in the scientific medical community.

For approach a) the same assumptions used by IQWiG were used:

- Endpoint used for sample size estimation: ABR
- $RR_0 = 0.5$ (shifted null-hypothesis)
- Power $\beta = 0.8$

- $\alpha = 0.05$, two-sided
- Negative binomial model with dispersion parameter $\phi = 1.5$
- Ratio of patient numbers intervention:comparator = 1:5
- Negligible censoring

The resulting sample sizes for the scenarios included in G-BA's resolution were replicated using PASS 2023 (Non-Inferiority Test for the Ratio of two Negative Binomial Rates) and subsequently the scenarios based on HOPE-B trial results were calculated. Results are illustrated in Table 3.

Table 3: Sample size estimation for shifted null-hypothesis approach

Scenario/Endpoints	Event Rate Inter-vention	Event Rate Comparator	Rate Ratio	Required Patients: Total	Required Patients: Intervention	Required Patients: Comparator
G-BA resolution 1	0.8	3.0	0.267	327	55	272
G-BA resolution 2	1.0	3.6	0.278	351	59	292
HOPE-B: ABR (FIX-treated and non-treated bleeding)	1.04	4.0	0.26	277	46	231
HOPE-B: FIX-treated bleeding	**0.56**	**3.45**	**0.16**	**103**	**17**	**86**
HOPE-B: major bleeding	0.19	0.44	0.43	16 444	2 746	13 698
HOPE-B: life-threatening bleeding	0.02	0.13	0.16	1 008	168	840
HOPE-B: joint bleeding	0.33	2.2	0.15	113	19	94
Abbreviations: FIX: Coagulation Factor IX						

For approach b), the following assumptions were used:

- Endpoint used for sample size estimation: ABR

- $RR_0 = 1$
- Power $\beta = 0.8$
- $\alpha = 0.01$, two-sided
- Negative binomial model with dispersion parameter $\phi = 1.5$
- Ratio of patient numbers intervention:comparator = 1:5
- Negligible censoring

Calculation was also performed using PASS 2023. Results are illustrated in Table 4.

Table 4: Sample size estimation for approach derived from "dramatic effect" criteria with modified effect threshold

Scenario/Endpoints	Event Rate Inter-vention	Event Rate Comparator	Rate Ratio	Required Patients: Total	Required Patients: Intervention	Required Patients: Comparator
G-BA resolution 1	0.8	3.0	0.267	98	16	82
G-BA resolution 2	1.0	3.6	0.278	101	17	84
HOPE-B: ABR (FIX-treated and non-treated bleeding)	1.04	4.0	0.26	89	15	74
HOPE-B: FIX-treated bleeding	**0.56**	**3.45**	**0.16**	**53**	**9**	**44**
HOPE-B: major bleeding	0.19	0.44	0.43	395	66	329
HOPE-B: life-threatening bleeding	0.02	0.13	0.16	411	69	342
HOPE-B: joint bleeding	0.33	2.2	0.15	59	10	49
Abbreviations: FIX: Coagulation Factor IX						

Based on the results of the HOPE-B trial, required patient numbers for ABR for FIX-treated bleeding and joint bleeding are the lowest among the endpoints included in this study and

covered in sample size estimations. Based on this finding as well as the nature of FIX-treated bleeding representing the broadest bleeding definition that is anticipated to be captured in the DHR with good quality data, ABR for FIX-treated bleeding was chosen as the study's primary endpoint.

If effects observed in this study are comparable to those found in HOPE-B, a sufficient number of patients to reach required sample sizes for all treated bleeding and joint bleeding could likely be enrolled to show an effect using the concept of a shifted null-hypothesis as proposed by IQWiG. However, there is a substantial degree of uncertainty resulting from a number of factors.

1. CSL Behring expects significant differences in patient characteristics between the study's intervention and comparator arms. Given the novelty of gene therapy as a treatment approach and the well-established nature of FIX treatments for haemophilia B, it is likely that patients choosing gene therapy in the initial years of availability will be biased towards patients with relatively high bleeding rates on FIX or otherwise harder to manage conditions. Since patients in non-overlapping regions of the PS distribution will be trimmed as part of the adjustment of covariates, it is expected that a significant portion of patients enrolled in the comparator arm of this study will not be eligible for adjusted outcome analyses. It is thus uncertain if the number of patients that can be included in adjusted analyses will meet the numbers calculated in the performed sample size estimations.

2. Interventional clinical trials and an AbD differ in terms of prioritizing internal vs. external validity. While internal validity tends to be a key priority for pivotal trials, external validity is of higher importance in the context of an AbD. It is thus uncertain if event rates for both intervention and comparator observed in this study will be comparable to those observed in HOPE-B. However, given the potential selection bias described above, bleeding rates observed in patients that are not trimmed from adjusted outcome analysis in this study may in fact be significantly higher than those observed in the overall population.

3. The willingness of patients and treatment centers to participate in this study cannot be anticipated at the time of study planning. Participation in the trial can be and was mandated by G-BA for treatment centers providing etranacogene dezaparvovec [26] and while participation cannot be mandated on a patient level, CSL Behring expects a high willingness to enroll among patients treated with etranacogene dezaparvovec. In contrast, though, study participation cannot be mandated for treatment centers not

providing etranacogene dezaparvovec and willingness of FIX patients to participate in the study is subject to significant uncertainty. As a result, both total patient numbers as well as the ratio of intervention-to-comparator patients is uncertain and may differ significantly from the assumptions used at time of study planning.

Due to the described uncertainties, G-BA has mandated that a re-calculation of sample size will take place after study commencement. The approach of sample size re-estimation is described in section 4.5.2.

4.5 Planned Interim Analyses

Multiple analyses are planned for this study and described in the following sections. In addition to statistical analyses performed for the described submissions, analyses defined in this SAP may be performed at any time based on data cuts supplied by DHR in order to develop and update statistical analysis programs.

Per G-BA's resolution mandating this study [5], specific times and extends of interim analyses are currently mandated. These are depicted in Table 5 with their exact mandated time relative to the G-BA resolution determining the study commencement as well as anticipated dates assuming a study commencement in Q3 to Q4 2024 and a required time of 4 months from data cut to submission for interim analyses and 6 months for final dossier submission.

Table 5: Schedule of interim and final analyses per G-BA mandating resolution

Type of analysis per G-BA resolution	Time relative to study commencement	Anticipated date of submission to G-BA
First status report	Submission: 6 months after study commencement (as issued by GBA resolution date) Data cut: December 2024 (DHR data available in 2024 only covers time before study commencement)	Submission: Mid-March 2025 Data cut: Mid-November 2024

Type of analysis per G-BA resolution	Time relative to study commencement	Anticipated date of submission to G-BA
First interim analysis incl. • Status report • Interim outcome analysis • Sample size re-estimation	Submission: 18 months after study commencement Data cut: 15 months after study commencement (DHR data available until 31 December 2024 – approx. 3 months after study commencement)	Submission: Mid-March 2026 Data cut: Mid-November 2025
Second interim analysis incl. • Status report • Interim outcome analysis	Submission: 36 months after study commencement Data cut: 33 months after study commencement (DHR data available until 31 December 2026 – approx. 27 months after study commencement)	Submission: Mid-October 2027 Data cut: Mid-June 2027
Third interim analysis incl. • Status report • Interim outcome analysis	Submission: 54 months after study commencement Data cut: 51 months after study commencement (DHR data available until 31 December 2027 – approx. 39 months after study commencement)	Submission: Mid-March 2029 Data cut: Mid-November 2028

Type of analysis per G-BA resolution	Time relative to study commencement	Anticipated date of submission to G-BA
Final analysis and dossier submission for benefit assessment[2]	Submission: 2 November 2029 Data cut: 55 months after study commencement	Submission: 2 November 2029 Data cut: 1 May 2029
Abbreviations: G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss)		

While CSL Behring acknowledges that the schedule set forth in the G-BA resolution mandating this study reflects G-BA's code of procedure [27], it does not seem adequate in the context of the established data submission scheduled for the DHR, which was mandated as the primary data source of this study [5].

Data is submitted to DHR on a yearly basis with a submission due date of 1 July of each year for the data collected in the previous year. This concerns both individual data submissions as well as yearly collective submissions, of which only the former can be used for this study. While it is theoretically possible to submit data to DHR at other points in time for other time periods, it was stated by DHR during the public consultation procedure for this study that the general process is a yearly reporting period submitted by 1 July for the following year [28]. This is also reflected in DHR's manual, which states*: "You can only select a period within the reporting year, but not across the turn of the year, and reporting periods of partial reports may not overlap within one annual report"* [29].

As such, the following challenges result:

- The status report currently mandated for submission 6 months after study commencement cannot contain any data from DHR that covers the time from study

[2] In case a G-BA resolution is passed to adjust timelines and postpone the final submission of the dossier, the timepoint of latest possible switch from FIX to etranacogene dezaparvovec would be adjusted accordingly to enable 3 years of data collection for all patients. The changes would be subject to an amendment and communicated to G-BA.

start in Q3 to Q4 2024, which is the earliest possible time patients can consent to participate in the study.

- The first interim analysis currently mandated for submission 18 months after study commencement can only contain about approx. 3 months of data (Q3 to Q4 to December 2024). Patient numbers as well as observation times will be very low, possibility of performing adjusted outcome analyses is thus very questionable and observation times will be very short. The anticipated data base at the time of first interim analysis thus does not seem to be adequate for (final) sample size estimation based on robust interim results.

- The currently mandated submission date of the value dossier for a new benefit assessment on 2 November 2029 would warrant a data cut in May 2029 to allow at least 6 months to perform data transfer, data processing, statistical analyses, quality assurance and drafting of the actual value dossier. The duration of 6 months was previously acknowledged by G-BA [30] and is already much less than standard practice for the creation of value dossiers (usually about 12-18 months preparation time). At current, there is thus uncertainty if the data year 2028 can be utilized for final analysis.

In light of these challenges, CSL Behring originally proposed modifications to the schedule and contents of submissions that are depicted in the following sections and could be implemented by G-BA by means of a declaratory resolution following the submission of the study protocol and this SAP.

However, CSL Behring will follow G-BA's requirements in response to its resolution dated 01 February 2024 and stick to the originally mandated content for all status reports and interim analyses.

4.5.1 Interim Analyses Other Than Sample Size Re-estimation

4.5.1.1 Status Report 6 Months after Study Commencement

G-BA's resolution mandating this study [5] currently mandates a report on status of recruitment that should contain the following information:

- The number and the respective medicinal treatment of the patients included so far
- Patient-related observation periods
- Any deviations regarding the expected number of recruits

As described in section 4.5, there will be no data available from DHR for the time period from and after study commencement for this report. However, in light of GBA's requirements in its resolution dated 01 February 2024, CSL Behring intends to submit all required reports and analyses. The status report 6 months after study commencement will thus contain the following information:

- The number and recruitment status of treatment centers participating in the study (e.g. contract signed, ethics committee (EC) approval granted, site initiation completed)
- The number of patients enrolled in the study per informed consent forms signed and supplied by the study sites to the clinical research organization (CRO) in charge of executing the study
- The status of technical implementation of changes to the DHR as well as implementation of source data verification (SDV) (see study protocol section 14.1.1)
- Any further relevant developments, insights, and general information regarding the study conduct as well as potential needs for adapting the study protocol and SAP based on such developments and insights
- The number and the respective medicinal treatment of the patients included so far (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)
- Patient-related observation periods (based on available DHR data)
- Any deviations regarding the expected number of recruits (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)

4.5.1.2 Baseline characteristics for both interventions including extend of missing valuesInterim Analysis and Status Report 18 Months after Study Commencement

G-BA's resolution mandating this study [5], currently mandates a first interim analysis to be submitted 18 months after study commencement. It would contain the following information:

- The number and the respective medicinal treatment of the patients included so far
- Patient-related observation periods

- Any deviations regarding the expected number of recruits
- Outcome analysis per sections 11 and 12 of this SAP
- Re-estimation of sample sizes based on results of interim outcome analyses following the methodology described in section 4.4
- Assessment of study feasibility based on results of sample size re-estimation and study recruitment

As described in section 4.5, data from DHR available for the first interim analysis will only cover approx. 3 months from time of study commencement in Q3 to Q4 2024 to the end of the data collection period (31 December 2024). Patient numbers as well as observation times will be very low and likely not allow for calculation of propensity scores (PS) to perform adjusted analyses (model non-convergence for PS estimation anticipated). Only naïve comparisons will thus likely be possible.

In addition, observation times will be from 0 to 2 months and thus too short to calculate robust ABRs. Calculation of data on pain, joint status and HRQoL will likely not be possible at all as these require at least two documentations after baseline, which would not be available given the short observation times.

The anticipated data base at the time of first interim analysis thus does not seem to be adequate for sample size estimation based on interim results. Consequently, a feasibility assessment does not seem possible at this time.

However, in light of GBA's requirements repeated in its resolution dated 01 February 2024, CSL Behring intends to submit all required reports and analyses on time. The interim analysis 18 months after study commencement will thus contain the following information:

- The number and recruitment status of treatment centers participating in the study (e.g. contract signed, EC approval granted, site initiation completed)
- Description of assumptions and key steps of data processing used for generating the submission
- The number and the respective medicinal treatment of the patients included so far (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)

- Patient-related observation periods (based on available DHR data)
- Any deviations regarding the expected number of recruits (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)
- The status of technical implementation of changes to the DHR as well as implementation of SDV (see study protocol section 14.1.1)
- Any further relevant developments, insights, and general information regarding the study conduct as well as potential needs for adapting the study protocol and SAP based on such developments and insights
- Baseline characteristics for both interventions including extend of missing values
- Standardized mean differences (SMD) per confounder
- In case patient numbers and confounder data should allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
    - Graphical illustration of overlap per patient population before adjustment using density plots
    - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis
    - Baseline characteristics for patients included in adjusted analysis after applying PS weights
    - SMDs after applying PS weights
- Re-estimation of sample sizes based on results of interim outcome analyses following the methodology described in section 4.4
- Assessment of study feasibility based on results of sample size re-estimation and study recruitment

Due to the foreseeable limitations in observation times, interim outcome analyses, re-estimation of sample size and feasibility assessment is performed with the first and second interim analysis scheduled for submission 18 and 36 months after study commencement (section 4.5.1.3).

4.5.1.3 Interim Analysis and Status Report 36 Months after Study Commencement

G-BA's resolution mandating this study [5] currently mandates a second interim analysis to be submitted 36 months after study commencement. It should contain the following information:

- The number and the respective medicinal treatment of the patients included so far
- Patient-related observation periods
- Any deviations regarding the expected number of recruits
- Outcome analysis per sections 11 and 12 of this SAP
- Assessment of study feasibility based on study recruitment

Per sections 4.5 and 4.5.1.2, it can be assumed that adjusted and robust interim outcome cannot be performed based on the data available at the time of first interim analysis 18 months after study commencement. For the second interim analysis 36 months after study commencement, though, complete data until 31 December 2026 will be available, resulting in 27 months of data from planned study commencement to end of available data. At the time of second interim analysis, patient numbers and observation times could allow for adjusted outcome analysis and thus and feasibility assessment.

However, in light of GBA's requirements in its resolution dated 01 February 2024, CSL Behring intends to submit all required reports and analyses. The interim analysis 36 months after study commencement will thus contain the following information:

- The number and recruitment status of treatment centers participating in the study (e.g. contract signed, EC approval granted, site initiation completed)
- Description of assumptions and key steps of data processing used for generating the submission
- The number and the respective medicinal treatment of the patients included so far (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)
- Patient-related observation periods (based on available DHR data)

- Any deviations regarding the expected number of recruits (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)
- Any further relevant developments, insights, and general information regarding the study conduct as well as potential needs for adapting the study protocol and SAP based on such developments and insights
- Baseline characteristics both interventions including extend of missing values
- SMDs per confounder
- In case patient numbers and confounder data should allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
    - Graphical illustration of overlap per patient population before adjustment using density plots
    - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis along with a discussion on appropriateness of the resulting population included in adjusted analysis for the initial question
    - Baseline characteristics for patients included in adjusted analysis after applying PS weights
    - SMDs after applying PS weights
    - Results of main and sensitivity analyses for all endpoints
    - Results of subgroup analyses
- Re-estimation of sample sizes based on results of interim outcome analyses following the methodology described in section 4.4
- Assessment of study feasibility based on results of sample size re-estimation and study recruitment

4.5.1.4 Interim Analysis and Status Report 54 Months after Study Commencement

G-BA's resolution mandating this study [5] currently mandates a third interim analysis to be submitted 54 months after study commencement. It should contain the following information:

- The number and the respective medicinal treatment of the patients included so far
- Patient-related observation periods
- Any deviations regarding the expected number of recruits
- Outcome analysis per sections 11 and 12 of this SAP
- Assessment of study feasibility based on results study recruitment

For the third interim analysis 54 months after study commencement, complete data until 31 December 2027 will be available, resulting in 39-40 months of data from planned study commencement to end of available data. At the time of third interim analysis, patient numbers and observation times is expected to allow for adjusted outcome analysis and feasibility assessment.

The Interim analysis 54 months after study commencement will thus contain the following information:

- The number and recruitment status of treatment centers participating in the study (e.g. contract signed, EC approval granted, site initiation completed)
- Description of assumptions and key steps of data processing used for generating the submission
- The number and the respective medicinal treatment of the patients included so far (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)
- Patient-related observation periods (based on available DHR data)
- Any deviations regarding the expected number of recruits (both based on available DHR data as well as information on study enrollment per signed informed consent forms and supplied by the study sites to the CRO in charge of executing the study)

- Any further relevant developments, insights, and general information regarding the study conduct as well as potential needs for adapting the study protocol and SAP based on such developments and insights
- Baseline characteristics both interventions including extend of missing values
- SMDs per confounder
- In case patient numbers and confounder data should allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
    - Graphical illustration of overlap per patient population before adjustment using density plots
    - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis along with a discussion on appropriateness of the resulting population included in adjusted analysis for the initial question
    - Baseline characteristics for patients included in adjusted analysis after applying PS weights
    - SMDs after applying PS weights
    - Results of main and sensitivity analyses for all endpoints
    - Results of subgroup analyses
- Assessment of study feasibility based on results of sample size re-estimation from second interim analysis and study recruitment

4.5.2 Interim Sample Size Re-estimation

Due to the uncertainties described in section 4.4, G-BA has mandated that a re-calculation of sample size estimates is performed with the first interim analysis submitted 18 months after study start. Given the challenges regarding data availability and possibility to perform adjusted interim analysis at this point in time (see sections 4.5, 4.5.1.2), re-estimation of sample sizes was originally planned with the second interim analysis (section 4.5.1.3).

The second interim analysis is expected to allow for adjusted outcome analysis that will be reported to G-BA. Based on these results, sample size calculations as described in section 4.4 can be performed using the event rates and effect estimates generated from interim analysis as well as insights on patient shares included in adjusted analyses after trimming of patients in non-overlapping regions of the PS distribution.

However, in order to follow GBA´s requirements, CSL Behring will submit the sample size re-estimation with the first and the second interim analysis.

For the most appropriate and feasible endpoint (which not necessarily need to be ABR of all treated bleeding), sample size calculation is conducted while considering adjustments of the alpha error.

The results of sample size re-estimation will be depicted in an amendment and serve as the basis for the feasibility assessment that will be reported to G-BA. Results will also be included in the submission of module 4 of the dossier template to G-BA.

4.5.3 Feasibility Assessment

G-BA has mandated that study feasibility is assessed with each interim analysis. Given the challenges regarding data availability and possibility to perform adjusted interim analysis at the time of first interim analysis (see sections 4.5, 4.5.1.2), re-estimation of sample sizes was originally planned with the second interim analysis (section 4.5.1.3). Based on re-estimated sample sizes a feasibility assessment will however be performed with all three interim analysis.

The assessment will performed based on the following information:

- Updated sample size calculations based on interim analysis results
- Number of enrolled patients per study arm in the Safety Analysis Set and extrapolation of patient numbers for per treatment arm based on study enrollment

Results will be reported to G-BA with the second and third interim analysis along with a recommendation on continuation or termination of the study. Any decision on actual termination of the study will only be made by CSL Behring after consultation with G-BA.

Sample sizes will be calculated using both the approach of a shifted null hypothesis as well as the approach derived from a standard null hypothesis. The approach derived from a standard null hypothesis will be used to assess study feasibility.

At the time of first interim analysis, updated sample sizes will still be subject to high uncertainty due to low patient numbers. Feasibility per patient population thus cannot be conclusively evaluated. No termination for infeasibility will take place at the time of first interim analysis but study feasibility will be discussed based on actual patient numbers fulfilling inclusion and exclusion criteria.

5 Changes from the Protocol Planned Analyses

There are no changes to the analyses planned in the study protocol.

6 Study Analysis Sets

6.1 Screened Analysis Set

The Screened Analysis Set consists of all subjects who provided written informed consent.

6.2 Enrolled Analysis Set

The Enrolled Analysis Set consists of all subjects in the Screened Analysis Set who entered the study. In the context of this study, the Enrolled Analysis Set consists of all subjects who signed informed consent.

6.3 Safety Analysis Set

The Safety Analysis Set consists of all subjects in the Enrolled Analysis Set who received any investigational product (IP) and for whom individual data submissions were performed to the DHR. This safety analysis set will be analyzed using the treatment the subject actually received. Patients, who initially received FIX at time of enrollment but are switched to etranacogene dezaparvovec on or before 1 January 2026[3] are analyzed in the intervention arm (see section 4).

[3] Based on the current timelines, the time from study start to end of data collection would only allow for about 15 months of including patients in the etranacogene dezaparvovec arm to ensure sufficient observation time after the treatment switch. Postponing the final submission from November 2029 to November 2030 could allow for 2029 data from DHR to be included in the final analysis. This would increase the time to include patients in the etranacogene dezaparvovec arm from about 15 to about 27 months and thus likely increase the robustness of available evidence significantly. In case a G-BA resolution is passed to adjust timelines and postpone the final submission of the dossier, the timepoint of latest possible switch from FIX to etranacogene dezaparvovec would be adjusted accordingly to enable 3 years of data collection for all patients. The changes would be subject to an amendment and communicated to G-BA.

6.4 3-year Follow-up Analysis Set

The 3-year Follow-up Analysis Set consists of all all subjects in the Safety Analysis Set with an observation period of at least three years on their respective treatment.

6.5 Plasma-derived FIX Analysis Set

The Plasma-derived FIX Analysis Set consists of all subjects in the Safety Analysis Set who received etranacogene dezaparvovec or plasma-derived FIX as IP. For a classification of plasma-derived vs. recombinant FIX products see section 4.2.2. Patients, who initially received plasma-derived FIX at time of enrollment but are switched to etranacogene dezaparvovec on or before 1 January 2026[3] are analyzed in the intervention arm (see section 4).

6.6 Recombinant FIX Analysis Set

The Recombinant FIX Analysis Set consists of all subjects in the Safety Analysis Set who received etranacogene dezaparvovec or recombinant FIX as IP. For a classification of plasma-derived vs. recombinant FIX products see section 4.2.2. Patients, who initially received recombinant FIX at time of enrollment but are switched to etranacogene dezaparvovec on or before 1 January 2026[3] are analyzed in the intervention arm (see section 4).

7 General Considerations

Data for this study will be collected via the DHR and provided to an independent external vendor for analysis.

R version 4.1 or higher and other software as appropriate (e.g. SAS version 9.4 or higher, SPSS version 26 or higher) will be used to perform all data analyses.

Summaries of continuous variables will be in terms of the number of observations, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum.

Other descriptive statistics (e.g. standard error, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section.

All comparisons will be based on two-sided tests with alpha = 0.05, two-sided 95 % CI will be reported, all p-values are nominal without adjustment for multiplicity.

For all used adjustment methods, the estimated effect measures will be investigated by means of appropriate tables and figures.

All analyses will be performed for the Safety Analysis Set (section 6.3) unless specified otherwise.

8 Data Handling Conventions

8.1 Multiple Comparisons and Multiplicity

The Type I error rate will not be adjusted for multiplicity in primary, secondary or supporting analyses.

8.2 Missing Data and Imputation

SDV should have the consequence that all information on file at treatment centers is ultimately depicted in the DHR and available for analysis in this study. Nevertheless, the following rules are followed when dealing with missing values.

Missing values in dates

Missing values in dates are imputed with regard to a target date. The study start date serves as target date.

1) Dates restricted to occur before the study start date (e.g. previous medication, medical history) will be imputed as follows:

   a) if only the day part of the affected date is missing:

      If the date's month is not the month of study start, the missing day will be set to 15. If the affected date's month is equal to the month of study start, the day part to impute is the minimum of (15, day of study start – 1).

   b) if only the year part of the affected date is **not** missing:

      If the date's year is not the year of study start, the missing day part will be set to 1 and the missing month part to 7. If the affected date's year is equal to the year of study start, the missing day-month-component will be the minimum of (01JUL, day-month of treatment start – 1).

2) Dates restricted to occur after the study start date will be imputed as follows:

a) if only the day part of the affected date is missing:

   If the date's month is not the month of study start, the missing day will be set to 15. If the affected date's month is equal to the month of study start, the day part to impute is the maximum of (15, day of study start + 1).

b) if only the year part of the affected date is **not** missing:

   If the date's year is not the year of study start, the missing day part will be set to 1 and the missing month part to 7. If the affected date's year is equal to the year of study start, the missing day-month-component will be the maximum of (01JUL, day-month of study start + 1).

If only the month of treatment start is available, the day of treatment start is set to *sdd* + 1. If only the day of treatment start is available, the month of treatment start is set to *smm*. If both day and month are missing, the treatment start date is replaced by the study start date.

Missing values in confounders

Missing values in confounding, baseline and subgroup variables are reported as „n.a.“ in descriptive analyses.

If a statistical complete case analysis using all confounders would use more than 95 % of all patients, missing values are considered missing completely at random (MCAR) and ignored in statistical analyses. A complete case analysis is conducted.

If the proportion of missing values is higher than 5 %, missing values are considered MAR and imputed using R-package MICE. Following the MIte approach in Leyrat et al. [31], m = 100 datasets after 10 iterations are generated including the endpoint of interest, the treatment group as well as the confounding variables. Missing values in confounding variabes are imputed using method *pmm* (predictive mean matching). Analyses described in sections 10, 11 and 12 are conducted for each imputed dataset. Finally, Rubin's rules are applied to the weighted effect estimates in each of the 100 datasets to derive pooled estimates.

If the proportion of missing values is higher than 25% or differs between the treatment groups (> ±15%), the MAR assumption is highly unlikely. Since there is no established way to impute missing values in confounding variables under the MNAR assumption, confounder imputation is completely omitted in this case and endpoints are compared unadjusted/naively.

Missing values in endpoints

Missing values in endpoints are summarized by treatment arms. In statistical analyses, they are treated as follows:

- TTE endpoints: If an event has occurred but the date is partially missing, the date is replaced in accordance with the rules described above, otherwise patients are censored at the time of last observation
- Binary endpoints and rate endpoints: Missing values of a patient i are replaced with non-missing values of a patient j who is treated with FIX. In case of the availability of a PS, the FIX patient is chosen whose PS is closest to that of patient i, e.g. $abs(PS_j - PS_i)$ is minimal taking into account 15 decimal places. If no PS is available, a patient is randomly drawn from the FIX patients.

8.3 General Derived Variables

8.3.1 Reference Dates and Study Days

Reference date is the date of the first treatment with etranacogene dezaparvovec or FIX after enrollment and first data submission to DHR following a number of changes that need to be implemented in the DHR CRF unless otherwise noted. In case a subject initially enrolled in the comparator arm of the study receives etranacogene dezaparvovec within the first two years after enrolment, the subject is eliminated from the comparator arm, re-allocated to the intervention arm and reference date (baseline) is set to the date of treatment with etranacogene dezaparvovec.

The number of days until a study assessment or procedure is calculated as:

- Study day = assessment date – reference date + 1 if assessment date is after or on the reference date
- Study day = assessment date – reference date if assessment date is before the reference date

There will be no study day zero.

8.3.2 Durations and Time-To-Event Data

Durations (e.g. the duration of an AE) are calculated in days as:

- Event end date – reference date + 1.

For elapsed time (e.g. the TTE), use:

- Event date – reference date + 1.

To transform durations or elapsed times, which are calculated in days into weeks, divide the number of days by 7; to report in months, divide the number of days by 30.4375; to report in years, divide the number of days by 365.25.

Time of being at risk after treatment is defined as (Date of data cut/censoring date – reference date + 1). For censoring reasons, see section 8.3.7.

8.3.3 Baseline Definition

Baseline is defined as the most recent, non-missing value before the reference date unless otherwise stated.

8.3.4 Change from Baseline

Change from baseline is calculated as:

- Visit value – baseline value.

Percentage change from baseline is calculated as:

- (Change from baseline / baseline value) * 100.

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline is missing.

8.3.5 Multiple Assessments

All data will be reported according to the nominal visit date for which they were reported (that is, no visit windows will be applied during dataset creation).

If multiple assessments are reported on the same date, then the mean of multiple measurements reported for the same date will be analyzed.

Data from all assessments including multiple assessments, will be included in listings.

8.3.6 Actual Treatment

The subjects' actual treatment will be derived from exposure data captured in DHR. If a subject changes a study treatment within allowed comparator treatments in the comparator arm, no specific analytic procedures are applied. In case a subject initially enrolled in the comparator arm of the study receives etranacogene dezaparvovec within the first two years after enrolment, the subject is eliminated from the comparator arm, re-allocated to the intervention arm and reference date (baseline) is set to the date of treatment with etranacogene dezaparvovec.

8.3.7 Censoring events

Regarding the analysis of TTE endpoints except for OS, patients are censored at the following events for main analysis:

- Death of any cause (date of death)
- Loss-to-follow-up (date of last visit)
- Data cut (date of last visit before date of data cut)
- End of the study (date of last visit before end of study date)

For OS, censoring events for main analysis are:

- Loss-to-follow-up (date of last visit)
- Data cut (date of last visit before data cut)
- End of the study (date of last visit before end of study date)

Time of being at risk after treatment is censored at the following events for main analysis:

- Death of any cause (date of death)
- Loss-to-follow-up (date of last visit)
- Data cut (date of last visit before date of data cut)
- End of the study (date of last visit before end of study date)

Censoring events and reasons for censoring, if available, will be summarized by treatment and confounders.

8.4 Covariates

8.4.1 Confounding and baseline variables

According to the protocol, characteristics in Table 6 influence the course of haemophilia B and are considered clinically important confounders.

Confounding variables are recorded at baseline. Categorical confounding variables are dummy-coded in regression based approaches for PS calculation. Continuous confounding variables enter the regression based approaches for PS calculation without transformation, assuming a linear relationship with the dependent variable.

Taking dependencies between confounders into account to avoid multicollinearity, the following interaction terms are tested one after the other using a logistic regression with the two confounders concerned and their interaction term:

1. Dosage (intensity of prophylaxis) 12 months prior to study enrollment * ABR 12 months prior to study enrollment
2. Age * Joint status
3. Joint status * Residual factor activity
4. ABR 12 months prior to study enrollment * Residual factor activity

Significant interactions (Wald-Test) at an alpha-level of 5% are included in the PS regression model as additional fixed effects.

Table 6: Confounding variables

Confounder	Clinical relevance	Proposed operationalization by clinical experts
Residual factor activity	Very important	The detection limit for residual factor activity is 1 %. Therefore, clinical experts suggested an operationalization in 2 strata: • ***< 1 %*** (residual factor activity not measurable***)*** • 1-5 % (residual factor activity measurable)
Age	Very important	At the age of 50, the risk of comorbidities, further joint damage and the need for surgery increases. Therefore, clinical experts suggested an operationalization in 2 strata: • ***≤ 50 years*** • > 50 years
Dosage (intensity of prophylaxis) 12	Very important	Prophylactic dosing derived from the SmPC with tolerance limit ±25 % shall be considered as normal range: • Low-dose therapy (below normal range)

months prior to study enrollment		• ***In-label therapy (within normal range)*** • High-dose therapy (above normal range) Reference dosages for each EMA authorized FIX product and calculation for determination of the normal range can be found in Table 7.
Joint status[2]	Very important	HJHS (total score) at baseline
ABR 12 months prior to study enrollment[1, 2]	Very important	Record of the number of all bleeding requiring treatment with at least one dose of factor concentrate and presentation of the results as a rate based on therapy documentation in CRF of DHR

Abbreviations: CRF: Case Report Form; DHR: German Haemophilia Registry (Deutsches Hämophilieregister); EMA: European Medicines Agency; FIX: Coagulation Factor IX; HJHS: Hemophilia Joint Health Score; SLR: Systematic Literature Review; SmPC: Summary of Product Characteristics

[1]ABR 12 months prior to study enrollment was suggested by clinical experts. The evidence base mentioned was the publication Germini et al. which was excluded during the SLR of the confounder identification procedure because it refers mainly to evidence from haemophilia A studies. However, the clinical experts agreed that it is possible to extrapolate the evidence for this specific confounder to haemophilia B [32]. This confounder will be operationalized through all treated bleeding occuring 12 months prior to study enrollment.

[2]This is a metric confounder with no categories. Hence, no reference categories will be defined for this confounder.

All reference categories are highlighted in bold and italics.

Table 7: Reference dosages for calculation of the normal range (reference category of the confounder 'dosage (intensity of prophylaxis) 12 months prior to study enrollment')

FIX products	**Reference dosage according to SmPC (average for a once weekly dosing)**[1]	**Calculation of required units of FIX**
Recombinant FIX concentrates		More detailed information on dosing and mode of administration of FIX preperations authorized by EMA can be found in section 4.2.2. All information was derived from the respective SmPCs and will be used as a reference to determine the normal range. The following formula will be used to determine patient's individual required units of FIX for each preperation/ medication as per SmPC:
Nonacog alfa (BeneFIX®)	80 IU/kg	
Nonacog gamma (Rixubis®)	100 IU/kg	
Albutrepenonacog alfa (Idelvion®)	37.5 IU/kg[2]	

Nonacog beta pegol (Refixia®)	40 IU/kg	$Required\ units\ of\ FIX\ [IU] = x\frac{IU}{kg} \times body\ weight\ [kg]$ $x\frac{IU}{kg}$: reference dosage according to SmPC In-Label therapy is any therapy with a dosing within the range of: $Normal\ range = Required\ units\ of\ FIX\ [IU] \pm Required\ units\ of\ FIX\ [IU] \times 0.25$
Eftrenonacog alfa (Alprolix®)	50 IU/kg	
Human plasma-derived FIX concentrates		
FIX (Alphanine®, Octanine®)	60 IU/kg	
FIX (Haemonine®)		
FIX (Immunine®)		

Abbreviations: EMA: European Medicines Agency; FIX: Coagulation Factor IX; IU: International Unit; SmPC: Summary of Product Characteristics

[1] All reference dosages were determined based on the SmPC recommendations and normed to a once-weekly administration for better comparability and overview. Nevertheless, all administrations are carried out at product-specific and patient-individual intervals. This should be taken into account when calculating the normal range. More detailed information on the recommended reference dosages and product-specific intervals can be found in Table 2.

[2] Assuming that patients are well-controlled.

8.4.2 Subgroup Definition

Table 8 shows subgroups considered in this study.

Table 8: Overview of subgroup covariates

Predefined subgroups	Operationalization
Age	• ≤ 50 years • > 50 years
Gender	Male; female
Dosage (intensity of prophylaxis) 12 months prior to study enrollment	• Low-dose therapy (below normal range) • In-label therapy (within normal range) • High-dose therapy (above normal range)
Joint status	HJHS score at baseline[1]: • < 21 HJHS • ≥ 21 HJHS

ABR 12 months prior to study enrollment	ABR at baseline[2]: • < 44 ABR (all treated bleeding) • ≥ 44 ABR (all treated bleeding)
Residual FIX activity at enrollment	• < 1% (residual factor activity not measurable) • ≥ 1% (residual factor activity measurable)
AAV5 antibody titre at enrollment	• positive • negative
Abbreviations: AAV5: Adeno-Associated Virus serotype 5; ABR: Annualized Bleeding Rate; HJHS: Hemophilia Joint Health Score; FIX: Coagulation Factor IX [1] If this operationalization is not feasible for the AbD study population, the mean HJHS will be used instead. [2] In case of problems with confounder adjustment, the mean ABR will be used instead.	

Rationale for operationalization of the confounder ABR 12 months prior study entry:

As the ABR 12 months prior study entry is unknown for the AbD study population, an orientative search for a comparable population has been performed, but did not deliver any insights on practicable operationalizations for confounder adjustment. Therefore, the dossiers of Hemgenix and any FIX products that underwent early benefit assessment have been searched for baseline values for the ABR 12 months prior study entry for the respective pivotal trial populations.

In the dossier of eftrenonacog alfa (ALPROLIX®), the mean ABR 12 months prior study entry (Min; Max) with a weekly dose-optimated prophlyaxis was 10,5 (0; 70) and with an individualized prophylaxis (interval) 10,0 (0; 100). Mean (SD) ABR 12 months prior study entry in the study B-LONG [Quelle: Dossier Rekombinantes Fusionsprotein aus Blutgerinnungsfaktor IX und Albumin – rIX-FP (IDELVION®)] was 15,7 (15,83) with a weekly prophylaxis and 17,3 (21,87) with an interval based prophylaxis. In the HOPE-B study, the mean (SD) [Max] ABR 12 months prior study entry for the safety population was 44 (81,5) [215].

In accordance with the HOPE-B study, the confounder ABR 12 months prior study entry will be operationalized as smaller than 44 and greater or equal to 44. However, it is unclear if this operationalization is feasible for the AbD study population. In case of problems with confounder adjustment, the mean ABR will be used instead.

Rationale for operationalization of the confounder HJHS:

The HJHS of the AbD study population is unknown, and an orientative search did not deliver any results. Therefore, HJHS will be operationalized as smaller than 21 and greater or equal to

21. This is in line with the mean (SD) HJHS at screening of the HOPE-B study, which was 20.8 (17.1). If this operationalization is not feasible for the AbD study population, the mean HJHS will be used instead.

9 Study Population

Unless otherwise stated, all tables and listings in this section will be based on the Safety Analysis Set.

9.1 Subject Disposition, Demographic and Baseline Characteristics

The summaries will be provided by treatment group and total population using the Safety Analysis Set:

- The number and the respective medicinal treatment of the patients included
- Patient-related observation periods
- Any deviations regarding the expected number of recruits
- Baseline characteristics both interventions including extend of missing values

For each of the 100 imputed datasets the following informations are provided:

- SMDs per confounder listed in section 8.4.1
- In case patient numbers and confounder data allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
    - Graphical illustration of overlap per patient population before adjustment using density plots
    - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis along with a discussion on appropriateness of the resulting population included in adjusted analysis for the initial question
    - Baseline characteristics for patients included in adjusted analysis after applying PS weights
    - SMDs after applying PS weights

9.2 Protocol Deviations

A deviation occurs when an investigator site, or study subject, does not adhere to protocol stipulated requirements. Deviations will be assessed by CSL Behring as they are reported and then evaluated periodically during study conduct. Deviations will be categorized as either major or minor. Only major protocol deviations for subjects in the Safety Analysis Set population will be summarized, though all major and minor deviations will be listed.

10 Adjustment of Covariates

The following sections 10.1 - 10.5 are carried out and results reported for each of the 100 imputed datasets (see section 8.2).

10.1 (Im)balance of confounders

To get an impression of the extent of (im)balance of confounders x_i in the Safety Analysis Set, confounders in the treatment arms are described descriptively using SMDs between treatment arms for each confounder.

10.2 Adjustment by PS score methods

Assuming that there is a sufficient number of patients per confounder (≈ 10:1), the propensity to receive etranacogene dezaparvovec given the confounding variables is determined using a logistic regression with treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables. If the logistic regression doesn't converge due to an insufficient ratio of patients per confounder or highly correlated confounders, a naive comparison is performed.

Categorical confounding variables enter the logistic regression as dummy-coded variables using the respective reference category depicted in section 8.4.1. Scale confounding variables are entered without transformation assuming a linear influence on the logit of receiving etranacogene dezaparvovec.

The PS distribution is displayed as a histogram/density plot for each treatment group.

10.3 Overlap

Overlap is defined as the proportion of non-trimmed patients to all patients.

10.4 Trimming

Since the tails of the PS distribution indicate patients with an extreme preference for one of the two treatments and this may be due to unmeasured confounding [33, 34], the tails need appropriate trimming to reduce bias in effect estimates.

The common approach is to remove nonpositivity regions, i.e. the lower cutpoint is the lowest PS in the intervention group while the upper cutpoint is the highest PS in the comparator group. In Monte-Carlo studies with a-priori known ("true") treatment effect that deal with comparatively large patient cohorts of 10,000 and more patients and 1,000 and more replications, this type of trimming proved to be inferior to other variants [35, 36]. In fact, trimming the bottom 5% of the PS distribution in the intervention group and the top 5% of the PS distribution in the comparator group and then re-estimating the PS in the trimmed cohort showed better coverage of the true effect and lower variance and MSE (mean square error) of the estimates than other approaches investigated in the study.

Therefore, patients in the intervention group whose PS is below the 5% percentile of their PS distribution as well as patients in the comparator group whose PS is above the 95% percentile of their PS distribution are trimmed and the PS is re-estimated in the remaining patients to improve covariance structure.

All confounding variables of excluded and included patients are reported in terms of absolute and relative frequencies by treatment arm to display differences between trimmed and remaining patients and allow for characterization of the remaining population that can serve as a basis for determining a potential added benefit (see section 9.1) in a subpopulation.

10.5 PS weights

According to the analyses and decision scheme provided in Desai & Franklin [25], both average treatment effect among treated (ATT) and average treatment effect (ATE) weights can be used for confounder adjustment. In this study, the PS for remaining patients receiving etranacogene dezaparvovec or FIX is used to derive weights for ATE estimates.

ATE fine stratification weights as well as inverse probability of treatment weights (IPTW) are thus determined.

10.5.1 ATE fine stratification weights

The PS distribution for all patients is clustered into 5 approximately equal sized strata and ATE fine stratification weights are subsequently calculated using the following formula for each treatment arm and PS stratum:

$$\left({}^{N_{total\ in\ PS\ stratum}}/_{N_{total}}\right) \Big/ \left({}^{N_{treatment\ arm\ in\ PS\ stratum}}/_{N_{total\ treatment\ arm}}\right)$$

10.5.2 ATE inverse probability of treatment weights (IPTW)

Weights for patients receiving etranacogene dezaparvovec are calculated using the formula:

$${}^{1}/_{PS_i}$$

Weights for comparator patients are calculated as follow:

$${}^{1}/_{(1-PS_i)}$$

The distribution of IPTW weights will winsorized at the 1st and 99th percentile to prevent variance inflation for a reduced cost of bias.

10.5.3 Choice of PS weights

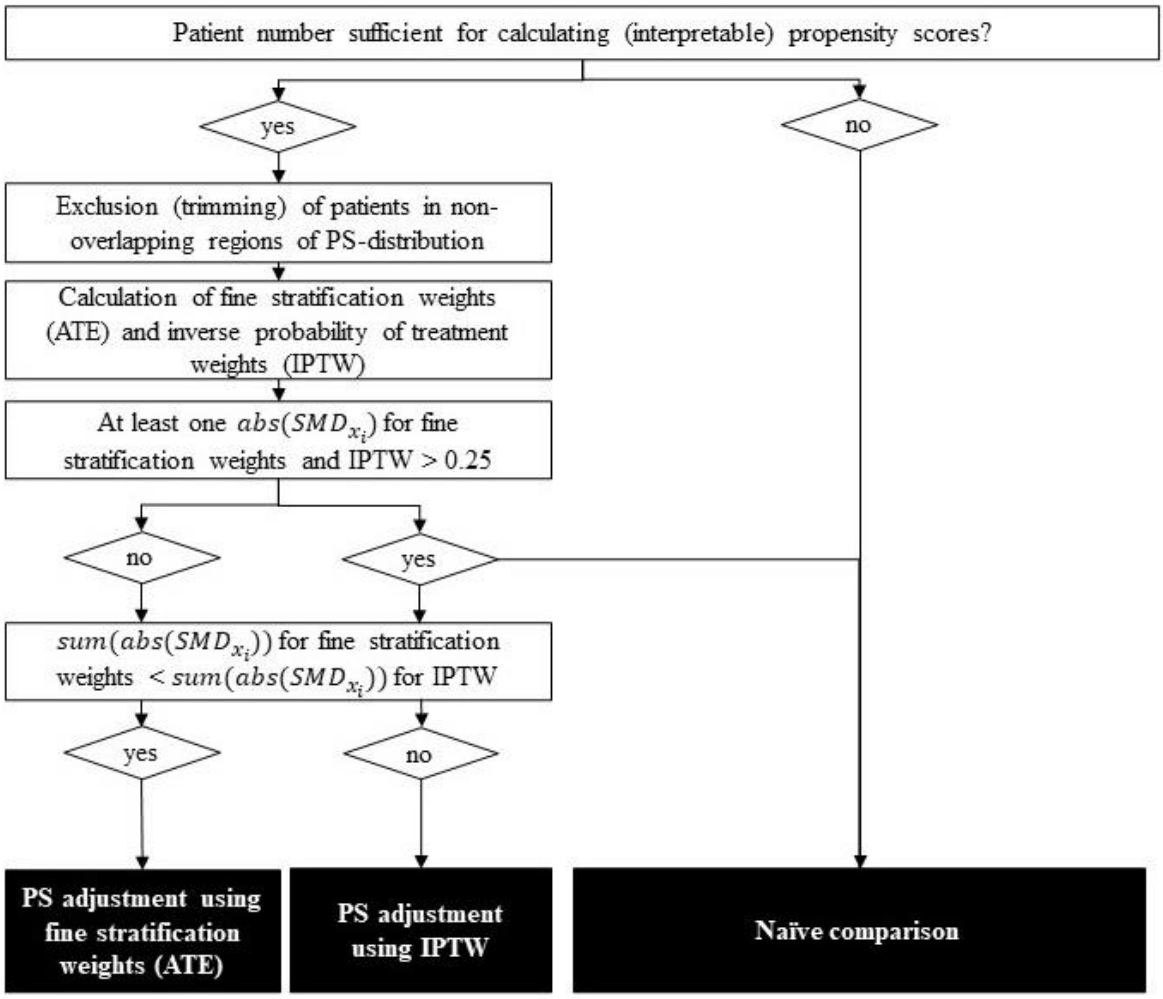
The weights that lead to $sum\left(abs(SMD_{x_i})\right) = min$ are used in continuation.

After PS weighting has been performed, the balance of all confounders is assessed in terms of $abs\left(SMD_{x_i}\right)$. Ideally, all confounders show $abs\left(SMD_{x_i}\right) < 0.1$.

Confounders with $abs\left(SMD_{x_i}\right) \leq 0.25$ are tolerated to allow PS-adjusted comparisons of endpoints, because otherwise only naïve comparison would remain. While no threshold is established in the literature, 0.25 was accepted by IQWiG and G-BA in the context of AbD studies in the past [37] and is thus used. If at least one confounder has $abs\left(SMD_{x_i}\right) > 0.25$ PS weighting is omitted and a naïve comparison of all endpoints is performed.

Figure 2 illustrates confounder adjustment for this study.

Figure 2: Adjustment of confounders



10.6 Adjustment in the setting of subgroup analysis

The same PS weights calculated for main analysis will be applied for subgroup analysis.

11 Efficacy Analyses

11.1 Analysis of Primary Endpoint

11.1.1 Primary Efficacy Analysis

A Generalized Linear Model (GLM) for count data assuming a negative binomial distribution with a log link function and Pearson chi-square scaling of standard errors to account for

potential overdispersion is performed, taking treatment as independent variable and PS weights as weighting variable. The logarithm of time in days each subject was observed until the time point of interest will be used as an offset variable in the model.

From the model, the least squares mean rate and standard error for etranacogene dezaparvovec as well as the mean rate ratio relative to FIX and corresponding 95 % CI will be estimated. These estimates will be reported as mean event rates per year by transforming the estimates using the exponential function and scaling by the unit of time (year).

11.1.2 Sensitivity Analyses of Primary Endpoint

To investigate potential differences in relative effectiveness and tolerability of etranacogene dezaparvovec compared to plasma-derived vs. recombinant FIX, analyses described in section 11.1.1 are repeated using the Plasma-derived FIX Analysis Set (section 6.5) as well as the Recombinant FIX Analysis Set (section 6.6).

To investigate the potential effects of etranacogene dezaparvovec administration after more than two years of FIX treatment, patients switching from FIX to etranacogene dezaparvovec that are analyzed in the comparator arm of the study are censored at time of treatment switch.

To investigate a potential change of effects over time, relative effectiveness and tolerability of etranacogene dezaparvovec compared to FIX, analyses described in section 11.1.1 are repeated using the 3-year Follow-up Analysis Set (section 6.4).

To investigate the potential effects of unmeasured confounders, a before-after-comparison for patients treated with etranacogene dezaparvovec will be performed. ABR will be determined for the 12 months prior to application of etranacogene dezaparvovec as well as for the time at risk after application of etranacogene dezaparvovec. Analysis of the number of reported bleeding events will be performed using a repeated measures generalized estimating equations (GEE) negative binomial regression model accounting for the paired design of the analysis with an offset parameter to account for the differential collection periods. An unstructured covariance matrix will be employed. If the model fails to converge, then a compound symmetry covariance structure will be used. The model will include the treatment (i.e. period) as a categorial variable. To allow time for etranacogene dezaparvovec to become fully active and to allow the subjects the opportunity to stop the treatment with prophylactic FIX therapy, ABR counts beginning at Day 21 of the post-treatment-period will be used in the analysis.

Assuming that current confounder values are available for each treatment switch, a "prevalent new-user design" according to Webster-Clark et al. [38] is conducted (if applicable).

a) Each patient is classified according to the treatment regimes he has undergone so far, e.g.

   - only FIX (prophylaxis)
   - only FIX (prophylaxis + on demand)
   - FIX – etranacogene dezaparvovec

b) time since general treatment initiation (first prescription of FIX therapy) becomes an additional confounding variable,

c) each treatment regime pattern serves as stratum for the subsequent stratified analyses and confounders are updated at each stratum starting point,

d) a stratified logistic regression using treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables is calculated to derive a PS.

e) PS weights are calculated according to section 10.5 and the primary endpoint is analysed according to section 11.1.1.

No subgroup analyses are performed in the context of sensitivity analysis.

11.1.3 Subgroup Analyses of Primary Endpoint

Subgroup analyses are conducted for all endpoints in main analysis for the subgroups listed in section 8.4.2. Patients with missing values in subgroup variables will be discarded from analyses as well as patients in subgroup categories that are only present in one treatment arm.

Effect measures are calculated for each subgroup category as well as overall. A p-value for the interaction treatment * subgroup is derived within the analytical framework as described in section 11.1.1, i.e. the Wald p-value of the regression coefficient for treatment * subgroup

Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients.

11.2 Analysis of Secondary Endpoints

11.2.1 Efficacy Analysis of Secondary Endpoints

11.2.1.1 Analysis of rate endpoints

A GLM for count data assuming a negative binomial distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion is performed, taking treatment as independent variable and PS weights as weighting variable. The logarithm of time in days each subject was observed until the time point of interest will be used as an offset variable in the model.

From the model, the least squares mean rate and standard error for etranacogene dezaparvovec as well as the mean rate ratio relative to FIX and corresponding 95 % CI will be estimated. These estimates will be reported as mean event rates per year by transforming the estimates using the exponential function and scaling by the unit of time (year).

11.2.1.2 Analysis of TTE Endpoints

TTE endpoints are generally analyzed with weighted Cox proportional hazard regression, PS weight serves as weighting variable.

The hazard ratio is determined by exponentiating the coefficients and presented along with a 95 % CI. A two-sided 95 % CI for median survival under each treatment is computed. Survival rates at fixed time points are presented along with their associated 95 % CIs as well as Kaplan Meier (KM)-Plots, if applicable.

11.2.1.3 Analysis of binary endpoints

Binary endpoints are generally analyzed using GLM for binary data assuming a binomial distribution with a link function appropriate for the intended effect measures (risk ratio: log, odds ratio: logit, risk difference: identity) and taking treatment as independent variable and PS weights as weighting variable.

As the sample size in this study is expected to be small and the events may be rare, Firth's bias correction should be applied to reduce the bias of maximum likelihood estimates and to avoid separation.

From the model, estimates for risk ratio, odds ratio and risk difference for etranacogene dezaparvovec relative to FIX and corresponding 95 % profile penalized likelihood CI are estimated.

11.2.2 Sensitivity Analyses of Secondary Endpoints

To investigate potential differences in relative effectiveness and tolerability of etranacogene dezaparvovec compared to plasma-derived vs. recombinant FIX, analyses described in section 11.2.1 are repeated using the Plasma-derived FIX Analysis Set (section 6.5) as well as the Recombinant FIX Analysis Set (section 6.6).

To investigate the potential effects of etranacogene dezaparvovec administration after more than two years of FIX treatment, patients switching from FIX to etranacogene dezaparvovec that are analyzed in the comparator arm of the study are censored at time of treatment switch.

To investigate a potential change of effects over time, relative effectiveness and tolerability of etranacogene dezaparvovec compared to FIX, analyses described in section 11.2.1 are repeated using the 3-year Follow-up Analysis Set (section 6.4).

Score endpoints are analyzed using mixed models for repeated measures (MMRM) and PS weights as weighting variable in the contect of sensitivity analysis. From the models, the least squares mean difference and standard error for etranacogene dezaparvovec relative to FIX and corresponding 95 % CI are estimated as well as Hedge's g.

An unstructured variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of parameters of the model.

Hedges'g and a 95% CI are computed according to the formulas provided in Goulet-Pelletier et al. for between treatment effects [1]. MMRM least square estimates of the mean difference, standard error and degrees of freedom are used to calculate a standard deviation as the denominator for Cohen's d.

Score endpoints are expected to be documented every six months. Patients with observations that are documented less than five or more than seven months apart will be excluded from MMRM analysis.

To investigate the potential effects of unmeasured confounders, a before-after-comparison for patients treated with etranacogene dezaparvovec will be performed for bleeding endpoints. ABR (for severe bleeding, life-threatening bleeding, and joint bleeding) will be determined for the 12 months prior to application of etranacogene dezaparvovec as well as for the time at risk after application of etranacogene dezaparvovec. Analysis of the number of reported bleeding events will be performed using a repeated measures GEE negative binomial regression model

accounting for the paired design of the analysis with an offset parameter to account for the differential collection periods. An unstructured covariance matrix will be employed. If the model fails to converge, then a compound symmetry covariance structure will be used. The model will include the treatment (i.e. period) as a categorial variable. To allow time for etranacogene dezaparvovec to become fully active and to allow the subjects the opportunity to stop the treatment with prophylactic FIX therapy, ABR counts beginning at Day 21 of the post-treatment-period will be used in the analysis.

Assuming that current confounder values are available for each treatment switch, a "prevalent new-user design" according to Webster-Clark et al. [38] is conducted (if applicable).

a) Each patient is classified according to the treatment regimes he has undergone so far, e.g.

   - only FIX (prophylaxis)
   - only FIX (prophylaxis + on demand)
   - FIX – etranacogene dezaparvovec

b) time since general treatment initiation (first prescription of FIX therapy) becomes an additional confounding variable,

c) each treatment regime pattern serves as stratum for the subsequent stratified analyses and confounders are updated at each stratum starting point,

d) a stratified logistic regression using treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables is calculated to derive a PS.

e) PS weights are calculated according to section 10.5 and the primary endpoint is analysed according to section 11.1.1.No subgroup analyses are performed in the context of sensitivity analysis.

11.2.3 Subgroup Analyses of Secondary Endpoints

Subgroup analyses are conducted for all endpoints in main analysis for the subgroups listed in section 8.4.2. Patients with missing values in subgroup variables will be discarded from analyses as well as patients in subgroup categories that are only present in one treatment arm.

Effect measures are calculated for each subgroup category as well as overall. A p-value for the interaction treatment * subgroup is derived within the analytical framework as described in section 11.2.1, i.e. the Wald p-value of the regression coefficient for treatment * subgroup in the case of rate and binary endpoints and the Likelihood-Ratio Test in the case of TTE endpoints.

Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients.

Subgroup analyses for binary events per variable are conducted only if at least 10 events occurred in one of the subgroups.

11.3 Analysis of Exploratory Endpoints

The endpoints FIX: Utilization Prophylaxis and FIX: Utilization On-Demand are rate endpoints and will be analyzed in the way as secondary rate endpoints as described in sections 11.2.1.1, 11.2.2 and 11.2.3.

Time to resumption of prophylactic FIX therapy is a TTE endpoint and exclusively defined for patients in the intervention arm of the study. It is thus analyzed descriptively for all subjects in the Safety Analysis Set that received etranacogene dezaparvovec as IP. Results will be summarized in terms of the number of patients, number of patients with event, median, Q1, Q3, minimum and maximum for observation times and TTE.

12 Tolerability Analyses

12.1 Analysis of Tolerability Endpoints

12.1.1 Main analysis of Tolerability Endpoints

All kinds of AE are summarized in terms of absolute and relative frequencies by treatment.

AE are analysed as binary endpoint according to section 11.2.1.3.

12.1.2 Sensitivity Analyses of Tolerability Endpoints

To investigate potential differences in relative effectiveness and tolerability of etranacogene dezaparvovec compared to plasma-derived vs. recombinant FIX, analyses described in section 12.1.1 are repeated using the Plasma-derived FIX Analysis Set (section 6.5) as well as the Recombinant FIX Analysis Set (section 6.6).

To investigate the potential effects of etranacogene dezaparvovec administration after more than two years of FIX treatment, patients switching from FIX to etranacogene dezaparvovec that are analyzed in the comparator arm of the study are censored at time of treatment switch.

To investigate a potential change of effects over time, relative effectiveness and tolerability of etranacogene dezaparvovec compared to FIX, analyses described in section 12.1.1 are repeated using the 3-year Follow-up Analysis Set (section 6.4).

Assuming that current confounder values are available for each treatment switch, a "prevalent new-user design" according to Webster-Clark et al. [38] is conducted (if applicable).

a) Each patient is classified according to the treatment regimes he has undergone so far, e.g.

    - only FIX (prophylaxis)
    - only FIX (prophylaxis + on demand)
    - FIX – etranacogene dezaparvovec

b) time since general treatment initiation (first prescription of FIX therapy) becomes an additional confounding variable,

c) each treatment regime pattern serves as stratum for the subsequent stratified analyses and confounders are updated at each stratum starting point,

d) a stratified logistic regression using treatment as dependent and the confounding variables and the statistically significant interactions (see section 8.4.1) as independent variables is calculated to derive a PS.

e) PS weights are calculated according to section 10.5 and the primary endpoint is analysed according to section 12.1.1.

No subgroup analyses are performed in the context of sensitivity analysis.

12.1.3 Subgroup Analyses of Tolerability Endpoints

Subgroup analyses are conducted for all endpoints in main analysis for the subgroups listed in section 8.4.2. Patients with missing values in subgroup variables will be discarded from analyses as well as patients in subgroup categories that are only present in one treatment arm.

Effect measures are calculated for each subgroup category as well as overall. A p-value for the interaction treatment * subgroup is derived from a likelihood ratio test.

Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients as well as at least 10 events occurred in one of the subgroups.

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14 Signature on Behalf of Marketing Authorisation Holder

Study Title: Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Study Number: CSL222_5002

I have read the protocol CSL222_5002 titled "Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

15 Signature of Investigator

Study Title: Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA

Study Number: CSL222_5002

I have read the protocol CSL222_5002 titled "Routine Practice Data Collection and Evaluation of etranacogene dezaparvovec (Hemgenix®) and prophylactic Factor IX (FIX) replacement in severe and moderately severe haemophilia B without a history of FIX inhibitors: a prospective, non-interventional study mandated by G-BA".

By signing this protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from CSL Behring (CSL) and the Institutional Review Board or Independent Ethics Committee (as appropriate).

I will ensure that study staff fully understand and follow the protocol.

Date

Annex 1 List of Standalone Documents

None.