VERTEX PHARMACEUTICALS INCORPORATED

PASS / Study 101 Information

Title	Long-term registry-based study of patients with transfusion-dependent β-thalassemia (TDT) or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel)
Protocol version identifier	VX22-290-101, Version 2.1
Date of last revision of protocol	15 November 2024
HMA-EMA Catalogue number	This study will be registered in the HMA-EMA Catalogue of RWD Studies following PRAC approval of the final protocol, and before study initiation.
Active Substance	exagamglogene autotemcel (exa-cel)
Medicinal Product	Casgevy®
Product Reference	EMEA/H/C/005763
Procedure Number	N/A
Marketing authorization holder(s)	Vertex Pharmaceuticals (Ireland) Limited
Joint PASS	No
Research Question and Objectives	*Primary* 1. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD 2. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT *Secondary* 1. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD 2. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT
Country(-ies) of Study	Germany, France, Italy, UK, US
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
allo-HSCT	allogeneic HSCT
ANC	absolute neutrophil count
Cas9	CRISPR-associated protein 9
CBC	complete blood count
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIC	cardiac iron concentration
CDM	Common Data Model
CPI	continuous process improvement
CRF	comprehensive research form (form type from CIBMTR)
CRISPR-Cas9	clustered regularly interspaced short palindromic repeats and CRISPR-associated 9 nuclease
EBMT	European Society for Blood and Marrow Transplantation
eGFR	estimated glomerular filtration rate
exa-cel	exagamglogene autotemcel (Casgevy), formerly known as CTX001
FU	follow-up
GDPR	General Data Protection Regulation
gRNA	guide RNA
Hb	hemoglobin
HbA	adult Hb
HBB	gene encoding the Hb beta subunit
HbF	fetal Hb
HbS	sickle cell Hb
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen
HMA-EMA Catalogue	Heads of Medicines Agencies and European Medicines Agency joint catalogue (former EU PAS Register)
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
ICH	International Council for Harmonization
IRB	institutional review board
LIC	liver iron concentration
MAH	Marketing Authorization Holder
MRI	magnetic resonance imaging
NI	non-interventional
NMDP	National Marrow Donor Program
OMOP	Observational Medical Outcomes Partnership
RBC	red blood cell
RNA	ribonucleic acid
RWD	real world data
SAE	serious AE
SCD	sickle cell disease
TDT	transfusion-dependent β-thalassemia

Abbreviation	Definition
TED	transplant essential data (form type from CIBMTR)
TNM	tumor, lymph node, metastasis classification system
UK	United Kingdom
US	United States
USA	United States of America
VOC	vaso-occlusive crisis

3 RESPONSIBLE PARTIES

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Registry Investigator(s)	[redacted] EBMT, Netherlands
	[redacted] CIBMTR, USA

4 ABSTRACT

Title

Long-term registry-based study of patients with transfusion-dependent β-thalassemia (TDT) or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel)

Rationale and Background

β-thalassemia is an inherited autosomal recessive blood disease characterized by reduced hemoglobin (Hb) production. Caused by mutations in the *HBB* gene, disease severity varies across a spectrum from intermedia to thalassemia major. β-thalassemia major, also called TDT, is fatal within the first few years after diagnosis if left untreated. Symptoms of TDT appear within the first 2 years of life and include severe anemia, splenomegaly, bone marrow expansion, failure to thrive and ultimately, death.

SCD is caused by a single nucleotide substitution in which a valine replaces a glutamic acid at position 6 of the β-globin chain leading to an abnormal or sickle Hb (HbS). HbS polymerizes in the deoxygenated state producing abnormal, sickle shaped red blood cells (RBCs) with limited flexibility and lifespan. These rigid cells are responsible for painful vaso-occlusive crisis (VOC), chronic anemia, inflammation, stroke, organ failure, and early mortality.

Exa-cel is a gene-edited cellular advanced therapy medicinal product administered through autologous hematopoietic stem cell transplantation (HSCT) to treat disorders caused by genetic defects that affect the production or function of Hb molecules, specifically β-thalassemia and SCD.

Information regarding long-term safety and effectiveness of therapy under the real-world conditions of use will be informative to patients, caregivers, and prescribers. Existing HSCT registries provide a mechanism to obtain these data.

Research Question and Objectives

Primary

1. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD
2. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allogeneic HSCT (allo-HSCT)

Secondary

1. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD
2. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT

Study Design

This will be a long-term, prospective observational cohort study using primary and secondary data collected by established international HSCT registries: the European Society for Blood and Marrow Transplantation (EBMT) Registry and the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry.

The study will follow patients who received exa-cel for treatment of TDT or SCD following approval of the therapy in Germany, France, Italy, and UK (via EBMT) and US (via CIBMTR). In addition, comparator populations of patients with TDT or SCD receiving an allo-HSCT from the same countries and same transplant centers will be invited to participate.

Data on a broad range of safety and effectiveness outcomes, as well as important covariates, will be collected within EBMT and CIBMTR via existing standard registry forms and custom, study-specific reporting forms.

The study enrolment period will continue for approximately 3 years following approval of exa-cel (in the respective region) and may be extended to up to 5 years enrollment. Eligible patients with TDT or SCD who are treated with exa-cel or receiving an allo-HSCT from the participating transplant centers and who consent to study participation will be included. Included patients will be followed for up to 15 years after the administration of exa-cel or allo-HSCT.

Measures to ensure long-term follow-up will include a combination of both transplant center and patient-specific interventions and will be applied to both exa-cel and allo-HSCT recipients.

In addition, participating EBMT and CIBMTR transplant centers will be trained to report directly to the Marketing Authorization Holder (MAH) information on all serious adverse events (SAEs), regardless of causality, among exa-cel recipients.

Should a hematologic malignancy be diagnosed in any patient receiving exa-cel in this study, participating centers will be instructed to contact the MAH to report the event and determine appropriate samples for analysis. The MAH will follow appropriate testing strategies to assess whether the malignancy developed as a result of off-target editing.

Population

All patients with TDT or SCD, treated at participating centers reporting data to EBMT or CIBMTR, and receiving exa-cel or allo-HSCT from the date of approval of exa-cel through the end of the enrolment period will be the source population for this long-term follow-up study.

All patients treated with exa-cel during the enrollment period will be eligible to enroll. Patients receiving allo-HSCT will only be eligible for comparator cohort inclusion if, at the time of enrolment, they are of an age approved for exa-cel.

Eligibility will further require patient's informed consent / assent to allow data collection for the purposes of this study.

To address the study objectives, the following longitudinal cohorts will be established within each registry:

1. Patients who received exa-cel for treatment of TDT (TDT Exa-cel Cohort)
2. Patients who received exa-cel for treatment of SCD (SCD Exa-cel Cohort)
3. Patients who received allo-HSCT for treatment of TDT (TDT Allo-HSCT Cohort)
4. Patients who received allo- HSCT for treatment of SCD (SCD Allo-HSCT Cohort)

Variables

Primary disease diagnosis and exposure variables will be collected at the time of patient enrolment. Safety and effectiveness outcomes will be collected during the post-transplant period; pre-transplant data corresponding to the key outcomes of interest will also be collected to allow assessment of disease status over time. Additional key variables will be collected at the time of patient enrolment and/or during the post-transplant period, as appropriate. All variables will be collected for each patient cohort, unless otherwise noted.

Category	Overview of Variables
Primary Disease Diagnosis	• β-thalassemia diagnosis and genotype • SCD diagnosis and genotype
Exposure	• HSCT date (as Day 0) • Autologous HSCT with exa-cel infusion • Allogeneic HSCT infusion
Safety Outcomes	• Neutrophil recovery • Platelet recovery • New malignancy, including hematologic • New or worsening hematologic disorder • Mortality, cause
Effectiveness Outcomes	• Primary disease severity measures* • Hemoglobin measures • Iron concentration measures • Disease-related end-organ damage / dysfunction • Iron overload management
Additional Key Variables	• Demographics • Health status • Mobilization and conditioning regimen • Transplant-related complications • Disease-related therapies • Additional laboratory measures, including CBC • Pregnancy (with outcome)

CBC: Complete Blood Count; SCD: sickle cell disease; HSCT: hematopoietic stem cell transplantation

*Includes red blood cell transfusions (TDT and SCD), vaso-occlusive crisis episodes (SCD only).

Data Sources

Data from 2 existing international registries covering countries with expected access to exa-cel will be used:

- EBMT Registry
- CIBMTR Registry

Both the EBMT and CIBMTR Registries have primary data collection capabilities for supporting pharmacoepidemiologic research studies. Primary and secondary data collected via these 2 registries will allow for the characterization of longitudinal patterns in a broad range of safety and effectiveness outcomes within cohorts of exa-cel treated patients and allo-HSCT comparator patients in EU, UK, and US.

Existing registry reporting forms and customized study-specific reporting forms jointly developed by the sponsor and registry operators will allow data to be collected on outcomes and other key variables essential to meet the objectives of this study. Data will be collected at standard timepoints following receipt of therapy for the first post-transplant year (100 days, 6 months, and 1 year), and annually thereafter. The data collection responsibilities of the participating transplant centers, including the efforts to ensure long-term patient follow-up as well as SAE reporting responsibilities, will be outlined in the site agreements, as applicable.

Study Size

Exa-cel enrollment targets include a minimum of 100 treated patients with TDT and 100 treated patients with SCD for a minimum of 200 exa-cel treated patients across all regions. It is expected that the enrollment period will be approximately 3 years,

though may be extended to up to 5 years enrollment. It is anticipated that there will be an approximately equal number of allo-HSCT comparator patients enrolled.

Data Analysis

To meet the study objectives, data will be analyzed separately for each registry and each cohort at pre-specified timepoints over the study duration (see Milestones Section). In addition to the separate analyses within each registry, pooled analyses of key safety outcomes are planned at pre-specified timepoints (after 5-, 10-, and 15-year duration of follow-up is accrued for all enrolled patients). The results of the interim and final analyses will be presented in interim and final study reports.

Descriptive statistics will be presented for all study endpoints. Continuous variables will be summarized using the following descriptive summary statistics where appropriate: the number of observations, mean, standard deviation, 95% CI, median, minimum value, maximum value, and 25^{th} and 75^{th} percentile values. Categorical variables will be summarized using counts, percentages, and 95% CIs as appropriate. Cumulative incidence curves will be provided for select outcomes.

Within the TDT and SCD Exa-cel Cohorts, comparisons of the post-transplant period to pre-transplant period will be performed, as appropriate.

Between cohort results (TDT Exa-cel versus TDT Allo-HSCT; SCD Exa-cel versus SCD Allo-HSCT) will also be evaluated within each registry separately.

Subgroup analyses will be performed by age group, genotype, and/or other patient characteristics, as appropriate. Subgroup analyses by country of transplant may be performed if sufficient patient counts are available to preserve patient anonymity. Additional ad hoc statistical analyses may be implemented, as applicable (e.g., modeling to adjust for differences in cohort characteristics in between-cohort analyses, time-to-event analyses for select outcomes). The details of the analyses will be included in the statistical analysis plan.

Findings from the analyses of TDT and SCD Exa-cel Cohorts will also be contextualized using published literature on the progression of TDT and SCD under the standard of care.

Milestones

Milestone	Planned Date
Start of data collection	2024
End of data collection	2042
Progress Report	31 August 2024
Progress Report	31 August 2025
Progress Report	31 August 2026
Interim Analysis 1	31 December 2027
Progress Report	31 December 2028
Progress Report	31 December 2029
Interim Analysis 2	31 December 2033
Interim Analysis 3	31 December 2038
Final report of study results	31 December 2043

5 AMENDMENTS AND UPDATES

None applicable.

6 MILESTONES

Study milestones are included in Table 1.

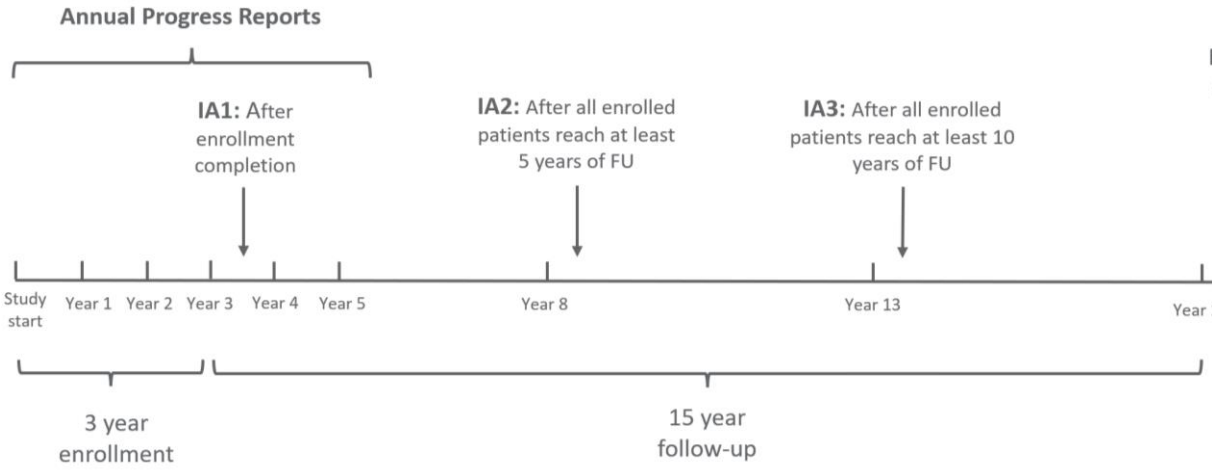
Table 1 Study Milestones

Milestone	Data Included	Planned Date
Start of data collection	NA	2024
End of data collection	NA	2042
Registration in the HMA-EMA Catalogue	NA	Following Protocol Approval
Progress Report	NA	31 August 2024
Progress Report	Tentatively through 31 August 2024	31 August 2025
Progress Report	Tentatively through 31 August 2025	31 August 2026
Interim Analysis 1	Tentatively through 31 December 2026 (anticipated end of enrollment period)	31 December 2027
Progress Report	Tentatively through 31 December 2027	31 December 2028
Progress Report	Tentatively through 31 December 2028	31 December 2029
Interim Analysis 2	Tentatively through 31 December 2032 (all enrolled patients anticipated to reach 5 years of follow-up)	31 December 2033
Interim Analysis 3	Tentatively through 31 December 2037 (all enrolled patients anticipated to reach 10 years of follow-up)	31 December 2038
Final Report	Tentatively through 31 December 2042 (all enrolled patients anticipated to reach 15 years of follow-up)	31 December 2043

HMA-EMA Catalogue: Heads of Medicines Agencies and European Medicines Agency joint catalogue (former EU PAS Register); NA: not applicable

Milestones depicted in Figure 1 assume a 3-year enrollment duration with a study closure after the final enrolled patient has been followed for 15 years (i.e., Year 18). Study milestones and analysis dates (Table 1, Figure 1) are estimated and may shift due to final approval dates, enrollment needs and/or data availability.

Figure 1 Planned Data Collection Milestones



FU: follow-up; IA: interim analysis
Note: Timelines may shift slightly if enrollment is extended to 5 years duration.

7 RATIONALE AND BACKGROUND

7.1 Background

β-thalassemia is an inherited autosomal recessive blood disease characterized by reduced hemoglobin (Hb) production. Caused by mutations in the *HBB* gene, disease severity varies across a spectrum from intermedia to thalassemia major. β-thalassemia major, also called transfusion-dependent β-thalassemia (TDT), is fatal within the first few years after diagnosis if left untreated. Symptoms of TDT appear within the first 2 years of life and include severe anemia, splenomegaly, bone marrow expansion, failure to thrive and ultimately, death.

Sickle cell disease (SCD) is caused by a single nucleotide substitution in which a valine replaces a glutamic acid at position 6 of the β-globin chain leading to an abnormal or sickle cell Hb (HbS). HbS polymerizes in the deoxygenated state producing abnormal, sickle shaped red blood cells (RBCs) with limited flexibility and lifespan. These rigid cells are responsible for painful vaso-occlusive crisis (VOC), chronic anemia, inflammation, stroke, organ failure, and early mortality.

Exagamglogene autotemcel (exa-cel) is a cellular product consisting of autologous $CD34^+$ human hematopoietic stem and progenitor cells modified by CRISPR-Cas9-mediated gene editing of the erythroid enhancer region of the *BCL11A* gene located on chromosome 2. *BCL11A* is a transcriptional silencer of γ-globin gene expression and hence a negative modulator of fetal Hb (HbF) production. Shortly before birth, *BCL11A* is turned on and there is a switch from HbF to adult Hb (HbA), which is made up of 2 α-globin chains and 2 β-globin chains. The switch from HbF to HbA is mediated by a transcriptional switch from γ-globin to β-globin expression within the β-globin gene cluster located on chromosome 11.

CRISPR-Cas9 is "clustered regularly interspaced short palindromic repeats and CRISPR-associated 9 nuclease". Cas9 is an enzyme that uses CRISPR guide RNA (gRNA) sequences to cleave a specific genomic locus that is complementary to the CRISPR gRNA. The goal of this genetic modification is to reactivate the expression of γ-globin messenger RNA in erythroid precursors, which in turn leads to an increase in HbF protein levels in adult erythroid cells.

Exa-cel is intended to treat disorders caused by genetic defects that affect the production or function of Hb molecules (β-thalassemia, SCD).

Information regarding long-term safety and effectiveness of therapy under the real-world conditions of use will be informative to patients, caregivers, and prescribers. Existing hematopoietic stem cell transplantation (HSCT) registries provide a mechanism to obtain these data.

7.2 Rationale

This 15-year observational, post-authorization, registry-based study will evaluate the long-term safety and effectiveness outcomes among patients with TDT and SCD who are treated with exa-cel in a real-world setting. This study will augment the exa-cel clinical program by enrolling and following both exa-cel-treated real-world patients as well as comparator patients receiving allogeneic HSCT (allo-HSCT) to treat TDT and SCD. While exact study cohort sizes are dependent upon commercial uptake and patient consent, it is expected that this study will enable data collection from a larger, more diverse sample of patients than included in the clinical trials. Collaboration with the European Society for Blood and Marrow Transplantation (EBMT) and Center for International Blood and Marrow Transplant Research (CIBMTR) patient registries allows access to the existing HSCT reporting platforms and minimization of excess reporting burden on the participating transplant centers.

8 RESEARCH QUESTIONS AND OBJECTIVES

8.1 Objectives

Primary

1. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD
2. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT

Secondary

1. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD
2. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT

8.2 Prior Hypotheses

This study will further characterize the effects of exa-cel treatment with real-world use, provide long-term follow-up of patients receiving treatment and provide descriptive analyses on specified safety and effectiveness outcomes using observational data. Because these analyses will be used

for active surveillance / hypothesis generation, no prior hypotheses are proposed. Though this is a hypothesis generating study, it is expected that the study results demonstrate that the safety profile of exa-cel in patients treated under real-world conditions is consistent with the clinical studies and that long-term treatment outcomes are not inferior to allo-HSCT outcomes.

9 RESEARCH METHODS

9.1 Study Design

This will be a multinational, long-term, prospective observational cohort study using primary and secondary data collected by established international HSCT registries: the EBMT Registry and the CIBMTR Registry. The justification for leveraging these existing registries as key sources of data for this study is provided in Annex 1. The assessment of the registries is provided in Annex 2 (EBMT) and Annex 3 (CIBMTR).

The study will follow patients who received exa-cel for treatment of TDT or SCD following approval of the therapy in Germany, France, Italy, and UK (via EBMT) and US (via CIBMTR). The representativeness of the EBMT and CIBMTR Registries for transplant-eligible TDT and SCD populations in their respective regions is discussed in Section 9.2. Data on a broad range of safety and effectiveness outcomes, as well as important covariates, will be collected within EBMT and CIBMTR Registries via existing and custom, study-specific reporting forms.

The study enrollment period will continue for approximately 3 years following approval of exa-cel, with potential for enrollment expansion to up to 5 years if the target sample size is not reached (see Section 9.5). Eligible patients with TDT or SCD who are treated with exa-cel at the participating transplant centers reporting data to EBMT or CIBMTR and who consent to study participation will be included in TDT and SCD Exa-cel Cohorts. If any patients from participating centers receive exa-cel infusion prior to the study protocol approval, such patients will be considered for study inclusion. Included patients will be followed for up to 15 years after the administration of exa-cel. In addition, comparator populations of patients with TDT or SCD receiving an allo-HSCT within the participating transplant centers will be identified and invited to participate. Included allo-HSCT comparator patients will also be followed for up to 15 years after transplant.

Measures to ensure long-term follow-up will include a combination of both transplant center and patient-specific interventions. In addition to standard patient-tracking routines, transplant centers participating in this sponsored study may receive additional education, patient tracking support, and/or tracking incentives based on annual patient follow-up.

For each included exa-cel-treated and allo-HSCT-treated patient, data will be captured for the baseline pre-transplant period, immediate peri-transplant period (pre-transplant conditioning regimen, cell infusion / Day 0, first 100 days), 6 months after transplant and annually thereafter throughout the 15-year post-transplant period (see schedule of data collection in Section 9.3.6). Long-term safety and effectiveness outcomes among exa-cel recipients will be evaluated within the TDT and SCD Exa-cel Cohorts comparing the post-transplant period to the pre-transplant period, as appropriate. Comparison of the key outcomes to the allo-HSCT-treated comparator groups will also be performed. Findings will be discussed in the context of available literature on the natural history of TDT and SCD under the medical standard of care, as appropriate.

Analyses will be performed by each registry separately (EBMT: data from Germany, France, Italy, UK; CIBMTR: US). Furthermore, within each registry, analyses will be performed separately for the TDT and SCD populations. In addition to the separate analyses within each registry, pooled analyses of key safety outcomes (Section 9.3.3) are planned at pre-specified timepoints (after 5-, 10-, and 15-year duration of follow-up is accrued for all enrolled patients).

In addition, participating EBMT and CIBMTR transplant centers will be trained to collect and report directly to the Marketing Authorization Holder (MAH) information on all serious adverse events (SAEs), regardless of causality, among exa-cel recipients starting at the time of exa-cel infusion and throughout the course of the study. All SAEs reported by the centers for the exa-cel treated study participants (Section 11) will be summarized in the study progress reports, interim analysis reports, and final study report.

Should a hematologic malignancy be diagnosed among any patient receiving exa-cel, participating centers will be instructed to contact the MAH to report the event and determine appropriate samples for analysis (Section 12). The MAH will follow the testing strategies described in Section 12 to assess whether the malignancy developed as a result of off-target editing.

9.1.1 Study Population

All patients with TDT or SCD treated in participating centers reporting data to EBMT or CIBMTR and receiving exa-cel or allo-HSCT will be the source population for this long-term follow-up study.

To address the study objectives, the following longitudinal cohorts will be established within each registry:

1. Patients who received exa-cel for treatment of TDT (TDT Exa-cel Cohort)
2. Patients who received exa-cel for treatment of SCD (SCD Exa-cel Cohort)
3. Patients who received allo-HSCT for treatment of TDT (TDT Allo-HSCT Cohort)
4. Patients who received allo-HSCT for treatment of SCD (SCD Allo-HSCT Cohort)

9.1.2 Inclusion and Exclusion Criteria

This study will have broad inclusion and minimal exclusion criteria. To be eligible for inclusion, patients must be:

- receiving an HSCT from a study-participating transplant center reporting data to the respective transplant registry; and
- receiving exa-cel or allo-HSCT for treatment of TDT or SCD from the date of approval of exa-cel through the end of the enrollment period.

For the Allo-HSCT Cohorts, patients must be of an age that corresponds with the exa-cel label current at the time of transplant.

All patients must additionally provide informed consent / assent for registry / study data collection.

For the Allo-HSCT Cohorts, patients receiving transplants with any donor type and cell source used during routine standard of care will be eligible for study enrollment.

Patients treated with alternative gene therapies or experimental therapies will not be included. No additional exclusion criteria will be implemented.

The inclusion criteria may be further modified as appropriate, e.g., to allow transplant centers from European countries other than Germany, France, Italy, or UK to be included if exa-cel becomes available during the proposed study enrollment period in those countries.

9.2 Setting

This is a study conducted in a real-world setting using primary and secondary data collected from the EBMT and CIBMTR patient registries. The registries provide robust coverage across their target regions, with the EBMT Registry estimated to capture data from 80% of all HSCT centers across Europe (Annex 2) and the CIBMTR estimated to capture all allo-HSCT and 85% of all autologous HSCT occurring within the US (Annex 3). The registry data sources are discussed further in Section 9.4 (Data Sources), Section 9.6 (Data Management), and Section 9.8 (Quality Control). All transplant centers participating in this study will report data directly to their respective transplant registry; SAEs, including hematologic malignancies, occurring among patients receiving exa-cel will additionally be reported directly to the MAH (Sections 11 and 12).

It is expected that patients recruited through both registries from both regions will be comparable because guidelines from organizations, such as the European Network for Rare and Congenital Anaemias, the American Society of Hematology, and the Thalassaemia International Federation, suggest that the standard of care across both Europe and the US for patients with SCD and TDT is similar.[1-4] Individuals with TDT receive regular transfusions and iron chelation with regular monitoring for iron accumulation in major organs and individuals with SCD are treated to reduce pain episodes, prevent stroke and other vaso-occlusive events, and monitor for potential organ damage. Though new medications are becoming available for these rare disease populations, hydroxyurea / hydroxycarbamide continues to be the standard of care, available globally and included on the World Health Organization List of Essential Medications.[5] With respect to exa-cel, in the post-approval setting it will be only available to individuals with severe forms of disease who are fit for transplant, suggesting that treated patients will have similar levels of disease severity and baseline comorbidity regardless of the region of transplant.

This study will include patients from Germany, France, Italy, UK, and US. Within Europe, Italy, France, and UK are among the top providers of HSCT to patients with TDT and SCD (EBMT data on file).[6] The US is among the top international providers of HSCT to patients with SCD (CIBMTR data on file). Within these 5 countries, study enrollment of both exa-cel-treated and comparator populations will take place from the participating transplant centers providing exa-cel commercially. Therefore, it is anticipated that patients receiving exa-cel post-authorization will be reflective of the eligible population in the target commercial regions and that the allo-HSCT comparators will similarly reflect the Exa-cel Cohorts' target age group for the region(s) and will receive comparable care. As indicated in Sections 9.1.1 and 9.1.2, all patients receiving exa-cel from participating transplant centers will be invited to enroll in the study. Patients receiving an allo-HSCT of any donor type or cell source and who are of an age that corresponds with the approved exa-cel label will also be invited to enroll and participate in the comparator group of the study.

All patients choosing to participate in the study will be enrolled by the transplant center at or before the time of transplant. The transplant centers have standardized forms and timepoints for reporting patient data to the patient registries. Baseline data and transplant specifics are collected

by transplant centers and entered into the registry at or near the time of transplant ("Day 0"). Follow-up reporting of each individual patient's status occurs by the transplant center to the registry at standardized time intervals: 100 days, 6 months, 1 year, and then annually post-transplant. Study-specific data collection will be integrated into the transplant center reporting timelines. Patient data may be sourced by transplant center personnel directly from the transplant site or via the patient's routine healthcare provider (HCP). Further information on the data to be collected and the schedule of data collection can be found in Section 9.3 (Variables).

9.3 Variables

All variables will be as reported to the transplant registries via either the standard existing registry forms or custom, study-specific reporting forms developed jointly with the registry operators:

Standard existing registry forms:

- EBMT Core Forms
- EBMT Extended Forms
- CIBMTR Pre-Transplant Transplant Essential Data (TED)
- CIBMTR Pre-Transplant Comprehensive Research Forms (CRF) and Post-Transplant CRF

Study-specific reporting forms for primary data collection:

- EBMT study-specific form
- CIBMTR study-specific form

All outcome variables specified in Sections 9.3.3 through 9.3.5 will be evaluated for both the exa-cel and allogeneic HSCT cohorts, including the TDT Exa-cel, TDT Allo-HSCT, SCD Exa-cel and SCD Allo-HSCT Cohorts, with a few exceptions which are noted below (e.g., VOC events are only applicable to SCD cohorts). . The study variables are summarized in Sections 9.3.1 through 9.3.5. The schedule of data collection is summarized in Section 9.3.6.

The current version of standard EBMT and CIBMTR data collection forms as well as mapping of study variables to these forms are provided in Annex 4. Study-specific forms are being developed with registry operators and will be finalized upon the protocol approval.

9.3.1 Primary Disease Diagnosis Variables

Variables described in this section are to allow classification of exposure and cohort allocation.

Primary disease diagnosis indicated for transplant will be as reported to the transplant registries and will include:

- β-thalassemia
- SCD

β-thalassemia or SCD genotype will also be recorded.

These variables will allow disease classification and may allow additional inference on disease severity.

9.3.2 Exposure Variables

Receipt of an autologous HSCT with exa-cel or an allo-HSCT, with the transplant date designated as Day 0, will be as reported to the transplant registries.

- Exa-cel HSCT
- Allo-HSCT

Additional transplant details for collection (e.g., conditioning regimen) are listed in Section 9.3.5.

9.3.3 Safety Outcome Variables

Variables described in this section are specifically to characterize the safety of the transplant procedure; collection and reporting of these safety outcomes encompass the primary objective of the study.

Neutrophil recovery information will allow assessment of the initial function of the graft and identify instances of neutrophil engraftment failure. Platelet recovery information will allow characterization of any instances of delayed platelet recovery; the threshold used for defining platelet recovery in patients with SCD is higher compared to patients with β-thalassemia to protect individuals with SCD from thrombocytopenia-associated hematologic complications.[7-11] New malignancy diagnosis information will allow assessment of the risk of secondary malignancies post-transplant.[12] New or worsening hematologic disorder is an exploratory variable to assess any indication of bone marrow compartment regeneration abnormality.

The following safety outcomes will be recorded as summarized in the schedule of data collection presented in Section 9.3.6:

- **Neutrophil recovery** will be defined as the achievement of an absolute neutrophil count (ANC) of $\geq 500/mm^3$ (or $\geq 0.5 \times 10^9/L$) for 3 consecutive measurements. Date of ANC recovery will be assigned as the date of the first of 3 consecutive measurements where the ANC is $\geq 500/mm^3$. Time to neutrophil recovery will be defined as number of days from the transplant date (Day 0) to the date of neutrophil recovery.
- **Platelet recovery** definition will differ based on the primary disease diagnosis:
  - For patients with β-thalassemia, platelet recovery will be defined as achievement of 3 consecutive measurements of platelets $\geq 20 \times 10^9/L$ after 7 days without platelet transfusion. Date of platelet recovery will be assigned as the first of the 3 consecutive measurements where platelets $\geq 20 \times 10^9/L$. Time to platelet recovery will be defined as number of days from the transplant date (Day 0) to the date of recovery.
  - For patients with SCD, platelet recovery will be defined as achievement of 3 consecutive measurements of platelets $\geq 50 \times 10^9/L$ after 7 days without transfusion. Date of platelet recovery will be assigned as the first of the 3 consecutive measurements where platelets $\geq 50 \times 10^9/L$. Time to platelet recovery will be defined as number of days from the transplant date (Day 0) to the date of recovery.
- **New malignancy**, including type and time to initial diagnosis, will be defined as any new malignancy, solid or hematologic, as reported to the transplant registry following the transplant date. Additional detail will be collected upon diagnosis, if available:

- TNM classification (for solid organ malignancies)
- Hematologic malignancy follow-up evaluation to be performed by the MAH as described in Section 12

- **New or worsening (non-malignant) hematologic disorder**, including time to diagnosis, may include the diagnosis of immune thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia, aplastic anaemia or other event, as reported to the transplant registry. Disorder status will be tracked at subsequent visits (e.g., stable, progressive, resolved), as applicable.
- **Mortality / Survival Status**, including time to event, will be based on the record in the respective registry:
  - Cause of death, as reported to the registries, will also be recorded
  - Date of last patient follow-up

9.3.4 Effectiveness Outcome Variables

Variables described in this section are to: (i) characterize disease status at baseline and (ii) allow direct and indirect assessment of the effectiveness and durability of the transplant. Characterization of the type and number of transfusions (among TDT and SCD patients) and/or severe VOC events (SCD patients only) pre- and post-transplant allows determination of whether overt disease symptomatology has been corrected with the transplant. Hb measures, including total Hb concentration as well as Hb fractionation (e.g., % HbS among patients with SCD), allows tracking of graft uptake and function at a more cellular level than the symptomatic measures. Iron concentration and iron overload management are secondary measures of graft function, as cessation of primary symptomology (transfusion dependence) should lead to measurable decreases in iron burden and a reduced need for iron overload therapies over time. Measures of organ dysfunction at baseline and over time are also secondary measures of graft function as successful correction of the underlying genetic deficiency is expected to prevent further accumulation of organ damage over time and/or prevent new disease-related organ damage events from occurring. These measures encompass the core effectiveness assessment for the transplant.

The following effectiveness outcomes will be recorded:

- **Primary disease severity measures** will be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6. Specifically, pre-transplant these events will be quantified for the 1 year (12 months) preceding initiation of the conditioning regimen:
  - RBC transfusion events (TDT and SCD) to be defined as the receipt of RBCs for the purpose of primary disease management (i.e., anemia). Number of RBC transfusions and number of units transfused will be recorded pre- and post-transplant (as available) as summarized in the schedule of data collection. Time from HSCT to most recent transfusion will be recorded.
  - Severe VOC events (SCD only): Number of severe VOC events will be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6. Time from HSCT to most recent severe VOC event will be recorded.

Severe VOC events will include any/all of the following events:

- Acute pain events, to be defined as an acute pain event that requires hospitalization or a visit to a medical facility for treatment
- Acute chest syndrome events, to be defined as clinical evidence of the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, cough or fever, and requiring hospitalization or a visit to a medical facility for treatment
- Priapism events, to be defined as a priapism event lasting >2 hours and requiring hospitalization or a visit to a medical facility for treatment
- Splenic sequestration event, to be defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥2 g/dL and requiring hospitalization or a visit to a medical facility for treatment

  - Hospitalization for any severe VOC event during the reporting period, to be recorded in the post-HSCT period only

- **Hb measures** will be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6:
  - Hb concentration, grams per deciliter (g/dL)
  - Hb fractionation measured to assess the relative proportion of Hb variants produced, including (at minimum): percent HbF, HbS (for SCD, only)
- **Iron concentration measures** will be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6:
  - Serum ferritin concentration, micrograms per liter (µg/L)
  - Liver iron concentration (LIC), measured by magnetic resonance imaging (MRI), milligrams per gram dry weight (mg/g)
  - Cardiac iron concentration (CIC), measured by obtaining MRI T2* (msec)
- **Disease-related end-organ damage or dysfunction** diagnoses, including approximate time to initial diagnosis if available, will be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6:
  - Anemia
  - Arrythmia
  - Central nervous system event (stroke, ischemic or hemorrhagic; transient ischemic attack)
  - Diabetes
  - Growth retardation / impairment
  - Heart failure, congestive
  - Hepatomegaly
  - Hypogonadism

- Hypothyroidism
- Liver cirrhosis
- Liver fibrosis
- Myocardial infarction
- Osteopenia or osteoporosis
- Osteonecrosis
- Pulmonary hypertension
- Retinopathy, SCD-related
- Renal failure
- Splenectomy, surgical
- Splenomegaly (among those with spleens)
- Ulcer(s) of the leg
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)

- **Iron overload management,** to be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6:
  - Chelation therapy agent (e.g., deferoxamine, deferiprone) use since last visit
  - Phlebotomy (for managing iron overload) use since last visit

9.3.5 Additional Key Variables

Additional key variables encompass general patient characteristics (e.g., demographics and health status), supporting transplant and laboratory measures (e.g., complete blood count [CBC]), and additional transplant-related complications (e.g., infection, bleeding, veno-occlusive liver disease) that may be of importance. The hematopoietic cell transplantation comorbidity index (HCT-CI) captures a wide range of co-existing diseases or organ impairments relevant to HSCT outcomes such as renal or hepatic impairment and prior history of malignancy. These variables may be considered as covariates for subgroup analyses and/or allow to further characterize the post-transplant outcomes.

Additional key variables will be recorded pre- and/or post-transplant as summarized in the schedule of data collection presented in Section 9.3.6 to assess patient demographics and general health status.

- **Demographics**
  - Age at initial disease diagnosis
  - Age at transplant
  - Sex
  - Race, Ethnicity (US only)
  - Country of transplant

- Payor type (US only)

- **Health status**
  - Performance score (Karnofsky for ages ≥16 years or Lansky for ages <16 years)
  - Hematopoietic cell transplantation comorbidity index (HCT-CI) items[13]
  - Height
  - Weight
  - Smoking history
- **Additional transplant details** will be recorded at the time of transplant, as available.
  - Preparative regimen (myeloablative, reduced-intensity, non-myeloablative, unknown)
  - Conditioning agent(s), including dose, start date, as available
  - $CD34^+$ cell infused dose, if available
  - Mobilization agent (Exa-cel Cohorts only)
  - Product identification (Exa-cel Cohorts only)
  - Donor type (Allo-HSCT Cohorts only)
  - Donor matching (Allo-HSCT Cohorts only)
  - Cell source (Allo-HSCT Cohorts only)
- **Disease-related therapy** use will be recorded pre- and post-transplant as summarized in the schedule of data collection presented in Section 9.3.6, to be defined as prescription or in-hospital use (i.e., for opioids) of the below agents or interventions at any time in the 1 year prior to HSCT (pre-transplant) or since the prior visit (post-transplant):
  - Crizanlizumab
  - Hydroxyurea / Hydroxycarbamide
  - L-glutamine
  - Luspatercept
  - Narcotics / Opioids (for indication-related pain, only)
  - Non-narcotic and/or nonsteroidal anti-inflammatory drug analgesics (for indication-related pain, only; if available)
  - Voxelotor
  - Other [with write-in field] to allow flexibility over time, a write-in field will be available to capture additional therapies not specified at the time of study initiation
- **Additional laboratory measures** will be recorded pre- and post-transplant, as available, as summarized in the schedule of data collection presented in Section 9.3.6:
  - CBC
    - RBC count

        - White blood cell count
        - Hb (included in Section 9.3.4)
        - Hematocrit
        - Mean corpuscular volume
        - Platelet count
    - Reticulocyte count
    - Erythropoietin
    - Soluble transferrin receptor
    - Lactate dehydrogenase
    - Liver function measures
        - Alanine transaminase / Alanine aminotransferase
        - Aspartate transferase / Aspartate aminotransferase
        - Bilirubin, Total
        - Bilirubin, Direct
        - Bilirubin, Indirect
    - Glomerular filtration rate, estimated (eGFR)
- **Transplant-related complications,** including time to initial diagnosis, to be recorded post-transplant as summarized in the schedule of data collection presented in Section 9.3.6:
    - Infection (including site, organism)
    - Bleeding events (including site)
    - Veno-occlusive disease / sinusoidal obstruction syndrome
    - Non-infectious interstitial pneumonitis / idiopathic pneumonia syndrome
    - Graft-versus-host disease (acute, chronic)
- **Pregnancy report**, including delivery date, for patient or partner (outcomes: live birth, stillbirth, spontaneous abortion, elective or therapeutic abortion, not yet delivered, other).
    - For live births, if available, to also collect instances of small for gestational age, intrauterine growth retardation, other.

9.3.6 Schedule of Data Collection

Data collection for each patient will occur on the following schedule: Baseline / Day 0 report, Day 100, 6-month and 1-year assessments, then annual assessments thereafter.

Data will be collected using registry standard and study-specific forms. Mapping of variables to standard collection or study-specific collection is included in Annex 4.

In addition to the data collection in the registry databases, all SAEs including hematologic malignancy, regardless of causality, among exa-cel recipients starting at the time of exa-cel

infusion and throughout the course of the study must be reported directly to the MAH (Sections 11 and 12).

Table 2 Data Collection Schedule

Registry Variable	Baseline / Day 0	Post-HSCT Follow-up			
		Day 100	Month 6	Year 1	Years 2 to 15 (annual)
Informed consent / assent	X				
Primary disease diagnosis					
β-thalassemia or SCD diagnosis	X				
Genotype	X				
Exposure					
Transplant date / Day 0 designation	X				
Exa-cel or allo-HSCT	X				
Safety outcomes					
Neutrophil recovery		X	X		
Platelet recovery		X	X	X	
New malignancy		X	X	X	X
New or worsening hematologic disorder		X	X	X	X
Mortality, cause		X	X	X	X
Effectiveness outcomes					
Primary disease severity events (RBC transfusion, VOC) [a]	X	X	X	X	X
Hb measures (total Hb, HbF) [a, b]	X	X	X	X	X
Iron concentration measures [a, b]	X	X	X	X	X
Disease-related end organ damage / dysfunction diagnoses [a]	X	X	X	X	X
Iron overload management [a]	X	X	X	X	X
Additional key variables					
Age at initial disease diagnosis	X				
Age (at transplant)	X				
Sex	X				
Race, ethnicity (US only)	X				
Country of transplant	X				
Payor type (US only)	X				
Performance score	X	X			
Comorbidity index	X				
Infused $CD34^+$ Dose [c]	X				
Donor type [d]	X				
Cell source [d]	X				
Mobilization and conditioning regimen	X				
Height [b]	X	X	X	X	X
Weight [b]	X	X	X	X	X
Disease-related therapies [a]	X	X	X	X	X
Additional laboratory measures [a, b]	X	X	X	X	X
Transplant-related complications		X	X	X	

Table 2 Data Collection Schedule

Registry Variable	Baseline / Day 0	Post-HSCT Follow-up			
		Day 100	Month 6	Year 1	Years 2 to 15 (annual)
Pregnancy, outcome		X	X	X	X

allo-HSCT: allogeneic HSCT; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; HbF: fetal Hb; HSCT: hematopoietic stem cell transplantation; RBC: red blood cell; SCD: sickle cell disease; US: United States; VOC: vaso-occlusive crisis

Note: Time to event will be captured for all variables, where specified in Section 9.3.

[a] Data on history pre-HSCT will be collected retrospectively at enrollment. This may include: transfusion (TDT and SCD) and/or severe VOC (SCD only) rates in the 1 year prior to preparative regimen initiation, historic diagnoses, pre-transplant therapies in the 1 year prior to HSCT, recent pre-transplant laboratory findings, etc.

[b] The non-missing measurement most proximal to the data report date.

[c] Exa-cel Cohorts only

[d] Allo-HSCT Cohorts only

9.4 Data Sources

Data from 2 existing international registries covering countries with expected access to exa-cel will be used:

- EBMT Registry
- CIBMTR Registry

Both the EBMT and CIBMTR registries have primary data collection capabilities for supporting pharmacoepidemiologic research studies. Primary and secondary data collected via these 2 registries will allow for the characterization of longitudinal patterns in a broad range of safety and effectiveness outcomes within cohorts of exa-cel-treated patients and allo-HSCT comparator patients in both Europe and the US. Each registry has data consistency checking and an auditing mechanism to verify the validity of the data reported (Sections 9.6 and 9.8). Each registry also has Committees / Working Parties that oversee the management and scientific integrity of registry operations (see Annex 2 and Annex 3).

Standard registry forms and customized study-specific reporting forms jointly developed by sponsor and registry operators will allow data to be collected on outcomes and other key variables essential to meet the objectives of the study. Data will be collected at standard timepoints following receipt of therapy for the first post-transplant year, and annually thereafter. The data collection responsibilities of the participating transplant centers, including the efforts to ensure long-term patient follow-up as well as SAE reporting responsibilities, will be outlined in the site agreements, as applicable.

Existing standard registry-specific data collection forms to be used for this study can be found in Annex 4.

9.4.1 EBMT

The EBMT is a non-profit organization registered in the Netherlands, first established in 1974. The EBMT registry holds data on patients given a HSCT or cellular therapy infusion procedure. The registry holds data on more than 680,000 patients that received a transplant procedure as well as data on more than 6,000 patients that received a chimeric antigen receptor T-cell therapy. The registry receives data from approximately 80% of European transplant centers and is the principal source of data in the field for clinical research for retrospective clinical studies,

epidemiological trends and feasibility studies for prospective clinical studies. In more recent years, the EBMT Registry has been used for regulatory purposes and represents a valuable research tool for future long-term studies of outcomes among recipients of gene therapies requiring an autologous HSCT procedure.

The EBMT full membership requires clinical transplant centers to commit to submit a minimum set of data on all patients treated in their center on an annual basis. The duty is to report all consecutive HSCT and other cellular therapies and follow-up data.

In August 2023, EBMT moved to a new platform for data collection called EBMT Registry (Section 9.6.1). This innovative platform replaces ProMISe and Castor, streamlining data management practices for a more cohesive user experience.

EBMT standard data collection forms can be divided into the Core Dataset Forms and the Extended Dataset Forms:

1. **Core Dataset Forms**: These forms collect the minimum essential data that must be provided by all member centers for their consenting patients.
2. **Extended Dataset Forms**: These forms collect additional information that can be provided by centers to keep more details on a patient's medical history, or if the EBMT working party requests this information for a specific study. It includes items with more detailed questions that are relevant to most studies conducted by EBMT Working Parties. Data from the extended dataset is collected through a number of additional forms and can only be entered in addition to the core dataset.

In addition, study-specific forms can be developed and implemented in close collaboration between the sponsors and EBMT to meet the needs of individual research studies and will contain those fields specific for a study that are not present in existing forms.

9.4.2 CIBMTR

The CIBMTR® is a non-profit research collaboration between the National Marrow Donor Program (NMDP)® / Be The Match® and the Medical College of Wisconsin in the US. The CIBMTR is now in the seventeenth year of a robust, collaborative affiliation and outcomes-focused research endeavor. The CIBMTR Coordinating Center is committed to supporting the highest level of clinical and health services research. The CIBMTR collaborates with the global scientific community to advance HSCT and other cellular therapy worldwide to increase survival and enrich quality of life for patients. Their prospective and observational research is accomplished through scientific and statistical expertise, a large network of transplant centers, and a clinical database of more than 600,000 patients.[14] CIBMTR has been successfully used for hundreds of clinical research studies positively impacting both clinical practice and transplant patients; this includes studies conducted as commitments to regulatory authorities.

CIBMTR standard data collection forms include:

- **Transplant Essential Data (TED) Forms:** These forms collect the core, transplant essential data. TED form completion is mandatory for allogeneic transplants occurring (or using donor material from) in the US; complete reporting, including autologous transplant activity, is requested for all centers that report allogeneic activity. Essential data forms include information on the indication for the procedure (including hemoglobinopathy), information on patient demographics, health status, and common comorbidities prior to transplant;

transplant type, preparative regimen, and recovery; plus, post-transplant secondary malignancies, vital status, and cause of death.

- **Comprehensive Report Forms (CRF):** The CRF-level data capture additional patient, disease, and treatment-related data. These are more extensive forms, completed regularly by a smaller fraction of the centers that have agreed to provide CRF-level data. The CIBMTR SCD and thalassemia pre-infusion data and SCD post-infusion data CRFs collect targeted information on disease diagnosis, disease-related organ damage accrued prior to the transplant, disease-related medication history, and disease status following transplant. Centers will collect CRF-level data for all enrolled study participants.

In addition, study-specific forms can be developed and implemented in close collaboration between the sponsors and CIBMTR to meet the needs of individual research studies and will contain those fields specific for a study that are not present in existing forms.

9.5 Study Size

Exa-cel is an advanced therapeutic medicinal product targeted for individuals with 1 or more severe manifestations of rare hematologic disorders. HSCT for SCD and TDT is a rare procedure, with allogeneic transplants for SCD and TDT representing only a small fraction of the total annual HSCT volume managed by transplant centers. In 2019, hemoglobinopathies were only 1.4% of the HSCT volume reported to the EBMT[15], and 1.1% of the reported volume in the US.[16, 17] The average number of transplants performed historically (2016 through 2019) in Germany, France, Italy, UK, and US for patients with SCD and TDT who are 12 years of age and older without a matched donor (equivalent to the population indicated for exa-cel) is approximately 70 patients per year (CIBMTR data on file, EBMT data on file).[16] It is expected that exa-cel will be available to only small numbers of patients in routine clinical practice.

As such, exa-cel enrollment targets include a minimum of 100 treated patients with TDT and 100 treated patients with SCD for a minimum of 200 exa-cel treated patients across all regions included in the study. It is expected that the enrollment period will be up to approximately 3 years, though may be extended to up to 5 years enrollment if the minimum sample size is not reached within 3 years.

It is anticipated that there will be an approximately equal number of allo-HSCT comparator patients enrolled. While eligibility for the Allo-HSCT Cohorts will be limited to patients aged 12 years and older, it will not be limited by donor type and may include patients from the larger pool of individuals receiving matched, mismatched or haploidentical donor transplants (see Section 9.1.2 for full inclusion / exclusion criteria).

Exa-cel uptake under real-world conditions is ultimately unknown and may be impacted by factors such as access and reimbursement, transplant center capacity to treat patients with newly available gene therapies, advances in allogeneic transplantation such as haploidentical transplant, potential availability of other gene or oral therapy products, and other unforeseen factors. Nevertheless, it is anticipated that approximately 1/3 of the final enrolled sample will be from European centers.

9.6 Data Management

Data management is maintained at each registry according to their internal processes.

9.6.1 EBMT

In August 2023, EBMT moved to a new electronic data capture platform for data collection which replaces ProMISe and Castor platforms. The EBMT Registry is a flexible data entry web application, connected to a fast and responsive live application database, enabling users to enter and retrieve data. The application database is then connected to the analytical database where all the data is restructured and organized according to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) (for more details on OMOP CDM please refer to https://ohdsi.github.io/CommonDataModel/).

To ensure the data entered into the database is complete, correct, accurate, allowable, valid, and consistent, the following data quality edit checks will be implemented where applicable:

- EBMT Registry system-generated edit checks
- Automated (SPSS/R programmed) edit checks
- Manual edit checks by EBMT Statisticians, data managers, clinical study coordinators, monitors, or any applicable user
- Medical review by the EBMT medical officer
- Study specific data retrieval is a verified process caried out by the qualified data managers and enabled by qualified information technology specialists. After data are extracted for a study-specific need, the datasets undergo an analyses dataset preparation process, which includes
    - data verification by qualified and experienced data managers and monitors at the EBMT Clinical Study Unit; and
    - study data file preparation: analyses dataset, by qualified and experienced statisticians and medical experts at the EBMT

The study data file preparation takes place in order to enable data analytics on the EBMT Registry collected data, study statistical analyses, site management, and study management.

9.6.2 CIBMTR

The FormsNet™ application is a secure clinical research management system for electronic submission of outcome data to the CIBMTR, in compliance with the Stem Cell Therapeutic Outcomes Database. Training is available through the CIBMTR.

Data extraction from the CIBMTR database and data transformation is performed by Master-level biostatisticians with relevant expertise. Data cleaning is performed in conjunction with the scientific director, who has in-depth knowledge of data collection by the CIBMTR and clinical expertise in transplantation and cellular therapies. The CIBMTR Data Operations Department assists with any queries to centers for clarifying data during the data cleaning process. The CIBMTR Master-level biostatisticians, in collaboration with Doctorate-level biostatisticians, perform the analyses. The CIBMTR has a unique partnership and close collaboration with the Division of Biostatistics at the Medical College of Wisconsin that includes PhD-level statistical support for studies.

9.7 Data Analysis

All analyses for this study will be performed by the respective statistical / programming teams using SAS, SPSS, R, or equivalent statistical software. All outcome variables specified in Sections 9.3.3 through 9.3.5 will be evaluated for both the exa-cel and allogeneic HSCT cohorts, including the TDT Exa-cel, TDT Allo-HSCT, SCD Exa-cel and SCD Allo-HSCT Cohorts. Patient-level data (pseudonymized) will additionally be available, for both exa-cel and allo-HSCT cohort participants, with patient consent / assent.

To meet the study objectives, data will be analyzed separately for each registry and each cohort at pre-specified timepoints over the study duration. Each interim report will include separate analyses of the data collected by each registry and will provide a descriptive comparison of the EBMT and CIBMTR patient populations in terms of (i) demographic and clinical characteristics, (ii) treatment(s) received, and (iii) outcomes. In addition to the separate analyses within each registry, pooled analyses of key safety outcomes (Section 9.3.3) will be performed at pre-specified timepoints (after a 5-, 10-, and 15-year duration of follow-up is accrued for all enrolled patients), unless substantial heterogeneity is observed between the two registries. Any potential issues precluding variable harmonization across the two registries will be discussed in the analysis reports. Pooled analysis of additional outcomes may be performed if feasible and warranted. The results of the interim and final analyses will be presented in interim and final study reports.

Descriptive statistics will be presented for all study outcomes:

- **Continuous variables** will be summarized using the following descriptive summary statistics, where appropriate: the number of observations, mean, standard deviation, 95% CI, median, minimum value, maximum value, and 25^{th} and 75^{th} percentile values.
- **Categorical variables** will be summarized using counts, percentages, and 95% CIs, as appropriate.

Crude risks, crude relative risks with 95% CI, and odds ratios with 95% CI will be calculated for outcomes, as appropriate. Cumulative incidence, treating death as a competing risk, will be calculated and presented for select safety outcomes. Overall survival curves will be produced.

Long-term safety and effectiveness outcomes among exa-cel recipients will be evaluated for the TDT Exa-cel and SCD Exa-cel Cohorts within each registry separately. Comparisons of the post-transplant period to pre-transplant period will be performed, as appropriate.

Between cohort results, comparing the Exa-cel Cohorts to their appropriate Allo-HSCT Cohort, will also be evaluated within each registry separately.

Subgroup analyses will be performed by age group, genotype, and/or other patient characteristics such as baseline disease severity, as appropriate. Subgroup analyses by country of transplant may be performed if sufficient patient counts are available to preserve patient anonymity. Additional ad-hoc statistical analyses may be implemented, as needed – this may include modeling to adjust for differences in cohort characteristics in between-cohort analyses and/or time to event analyses for select outcomes. A discussion of potential confounders associated with the key safety outcomes among patients with hematologic diseases is provided in Section 9.9.2.

Findings will be discussed in the context of available published literature on the natural history of TDT and SCD under the medical standard of care, as appropriate.

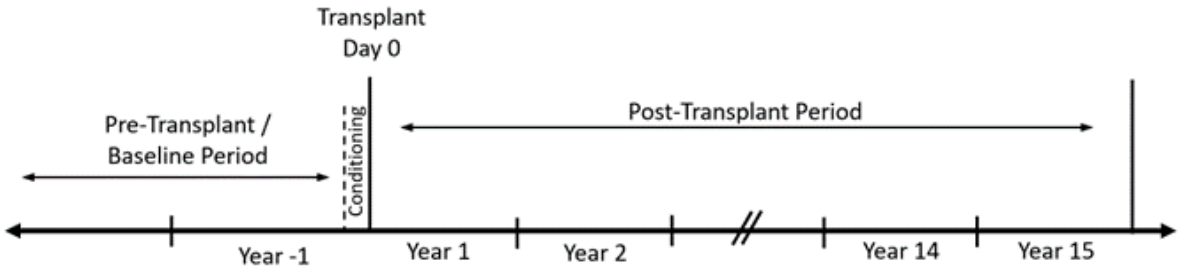
Further details will be provided within the statistical analysis plan.

9.7.1 Definition of Study Periods

For safety and effectiveness outcome analyses within the Exa-cel and Allo-HSCT Cohorts the pre-transplant and post-transplant periods will be defined as described below and illustrated in Figure 2:

- **Day 0 (transplant date)** is defined as the day of exa-cel product or allogeneic donor cell infusion, depending on cohort, as reported to the registries.
- **The pre-transplant / baseline period** will be broadly defined as the period prior to Day 0, with the length of the period varying depending on the study measures being evaluated:
  - For the *primary disease severity* measures (see Section 9.3.4 Effectiveness Outcome Variables) and *disease-related therapies* (see Section 9.3.5), the baseline period will be defined as 1 year prior to initiation of the conditioning regimen.
  - For *laboratory measures*, baseline will be defined as the non-missing measure most proximal, but prior to treatment initiation. This includes effectiveness measures such as total Hb, Hb fractionation (e.g., % HbS for SCD) and serum ferritin (see Section 9.3.4) as well other laboratory measures (see Section 9.3.5).
  - For pre-transplant *disease-related end-organ damage or dysfunction* (see Section 9.3.5) baseline will be defined as any time prior to the transplant.
  - Other variables such as patient demographics, pre-transplant height, weight and health status will be as reported at the most recent time point prior to transplant.
- **The post-transplant period** will continue for up to 15 years after the final enrolled patient's Day 0. For each patient, Year 1 will include events, new diagnoses or findings, and/or therapies initiated (or continued) within the first 365 days after Day 0; Year 2 will include the same occurring from patient day 366 to day 730, etc. Year 1 will further include the following time intervals based on existing transplant registry reporting: Day 0 to Day 100, Day 100 to 6 months, and 6-month to 1-year reporting. All patients, both exa-cel treated or comparator, will be followed for up to 15 years. Patients will be censored to last reported timepoint only after 2 years of loss to follow-up.

Figure 2 Study Periods



9.7.2 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for each cohort for the pre-transplant period:

- Primary disease diagnosis variables (Section 9.3.1)
- Baseline demographic measures (Section 9.3.5)
- Baseline health status measures (Section 9.3.5)
- Baseline disease severity measures (Section 9.3.4)
- Baseline Hb measures (Section 9.3.4)
- Baseline iron concentration measures (Section 9.3.4)
- Baseline disease-related end-organ damage or dysfunction diagnoses (Section 9.3.4)
- Baseline iron overload management (Section 9.3.4)
- Baseline disease-related therapies (Section 9.3.5)
- Baseline additional laboratory measures (Section 9.3.5)
- Additional transplant-related details (Section 9.3.5)

Any demographic or health differences between US and European patients will be summarized in the interim and final study reports.

The baseline demographic and clinical characteristics of the exa-cel and comparator patients will be compared descriptively. Any major differences identified between the cohorts will be accounted for using stratification or modelling, as needed and feasible based on patient counts.

9.7.3 Safety Analyses

Safety outcomes will be evaluated for each cohort from each registry at each time point of the post-transplant period. In addition to the separate analyses within each registry, pooled analyses of the safety outcomes listed below will be performed at pre-specified timepoints (after a 5-, 10-, and 15-year duration of follow-up is accrued for all enrolled patients), unless substantial heterogeneity is observed between the two registries. Any potential issues precluding variable harmonization across the two registries will be discussed in the analysis reports. Analyses will be performed overall and in subgroups by patient age group, genotype, country, and/or other category, as appropriate and if sufficient data are available. Additional analyses may be performed for outcomes deserving further investigation if sufficient data are available. Statistical testing may be performed comparing the frequencies or rates of outcomes from the TDT Exa-cel and TDT Allo-HSCT Cohorts, and the SCD Exa-cel and SCD Allo-HSCT Cohorts, if sufficient data are available.

- **Neutrophil Recovery**

  Proportion of patients reaching the neutrophil recovery threshold, with the corresponding 95% CI, will be calculated at each timepoint of the post-transplant period until all patients have reached neutrophil recovery.

Time to neutrophil recovery, in days, will be calculated for each patient from Day 0, as reported by the registries.

The proportion of patients who recovered neutrophils by specific timepoints of interest (for example, by Day 42) will also be calculated.

Cumulative incidence curves detailing time to neutrophil recovery may be produced.

- **Platelet Recovery**

  Platelet recovery threshold will vary for SCD and TDT cohorts.

  Proportion (with 95% CI) of patients reaching the platelet recovery threshold will be calculated at each timepoint of the post-transplant period until all patients have reached platelet recovery.

  Time to platelet recovery, in days, will be calculated for each patient from Day 0, as reported by the registries.

  Cumulative incidence curves detailing time to platelet recovery may be produced.

- **New Malignancy**

  Proportion (with 95% CI) of patients diagnosed with a new hematologic malignancy will be calculated for each timepoint of the post-treatment period.

  Proportion (with 95% CI) of patients diagnosed with a new solid malignancy will be calculated for each follow-up of the post-treatment period.

  Cumulative incidence of new malignancy over the entire post-HSCT period will also be reported.

  Specific malignancy types will be reported as the proportion(s) of all malignancies reported.

  TNM classification, where available, will be reported for the subset of solid tumors.

- **New or Worsening Hematologic Disorder**

  Proportion (with 95% CI) of patients diagnosed with a new (or worsening) hematologic disorder will be calculated for each timepoint of the post-treatment period.

  Cumulative incidence of new hematologic disorders over the entire post-HSCT period will also be reported.

- **Mortality / Survival Status**

  Proportion (with 95% CI) of deaths (overall and by cause) will be calculated for each timepoint of the post-treatment period.

  Overall survival over the entire post-HSCT period will also be reported.

Individual line listings will be provided for the key safety outcomes of hematologic malignancy diagnosis and mortality.

9.7.4 Effectiveness Analyses

Effectiveness analysis outcomes will be evaluated for each cohort from each registry for each post-transplant follow-up period. Analyses will be performed overall and in subgroups by patient age group, genotype, and/or other category, as appropriate and if sufficient data are available. Additional analyses may be performed for outcomes deserving further investigation if sufficient data are available. Statistical testing may be performed comparing the frequencies or rates of outcomes from the TDT Exa-cel and TDT Allo-HSCT Cohorts, and the SCD Exa-cel and SCD Allo-HSCT Cohorts, if sufficient data are available.

- **For the primary disease severity measures,** descriptive statistics for the number of events in the 1 year prior to the preparative regimen initiation and at each of the post-transplant follow-up periods will be reported:
  - Number of RBC transfusion events (TDT and SCD)
  - Number of severe VOC events (SCD only)

  Proportions of patients who are RBC transfusion-free, severe VOC-free or severe VOC hospitalization-free (as appropriate) will also be reported at each timepoint of the post-transplant periods.

  Time RBC transfusion-free or VOC-free, from Day 0 to the most recent event, will also be summarized.
- **Hb measures** (total Hb, % HbF, % HbS [where relevant]) will be summarized as continuous variables for each timepoint of the post-transplant period, with a 95% CI, among patients with an observation.
- **Iron concentration measures** (serum ferritin, LIC, CIC) will be summarized as continuous variables for each timepoint of the post-transplant period, with a 95% CI, among patients with an observation.

  Absolute change from baseline may be calculated for patients with non-missing baseline and post-transplant years.
- **New disease-related end-organ damage or dysfunction diagnoses** will be summarized for each timepoint of the post-transplant period as the proportion of patients with a new diagnosis (i.e., categorical variables), with a 95% CI.

  Cumulative diagnoses over the entire post-HSCT observation period may be reported for select diagnoses.
- **Use of iron overload management tools** (chelation therapy, phlebotomy) will be summarized for each timepoint of the post-transplant follow-up period as the proportion of patients receiving therapy (i.e., categorical variables).

9.7.5 Other Analyses

Additional key outcomes will also be evaluated for eachcohort from each registry for each time point of the post-transplant period. Findings will be summarized as categorical or continuous measures, as appropriate:

- Post-transplant complications

- Post-transplant health status measures
- Post-transplant disease-related therapies
- Post-transplant additional laboratory measures, including relevant CBC results at each available timepoint throughout the study duration
- Post-transplant pregnancies

In addition to all analyses of the pre-specified outcome variables (Section 9.3.3 through 9.3.5) for both the exa-cel and allogeneic HSCT cohorts, Serious Adverse Events (SAEs) among participating exa-cel recipients reported to the sponsor per Section 11 will be provided with each study report as a summary tabulation (proportion of exa-cel treated patients with SAE reports, by type) and in a listing format. Findings from the hematologic malignancy evaluation (Section 12) will also be provided, where available.

9.8 Quality Control

9.8.1 EBMT

The EBMT's quality control system relies primarily upon electronic data entry control triggers that promote consistency of the data and data quality / completion reports provided to the individual transplant centers. Data quality and completion reports may include information on percent of patients with annual reporting as well as individual missing data and statistical assessments for outlying data points. The EBMT provides assistance (e.g., completion guidelines per data collection form, training modules, help desk support) for form completion. Although there is no external audit system of the EBMT Registry, the present study the contractual agreement with the EBMT Registry will include the remote and/or on-site monitoring and source data verification of 10% of all patients enrolled in the study with the costs charged to the sponsor.

Primary data collection for this study implies ethics committee procedures to have Informed Consent Forms in place with the option to share the data with the sponsor.

With study-specific funding to the EBMT, processes to ensure higher data quality and completeness will be implemented. Additional site personnel training will be applied by the EBMT with dedicated clinical study unit personnel. These specialists may be recruited specifically to support the study and their costs will be charged to the sponsor.

Furthermore, to facilitate the completeness of the data in the present study a documentation fee will be provided to the participating centers, which will be reduced when the data provided is significantly incomplete or of poor quality. Data completeness will need to be maintained at the 80% level or higher to receive the full documentation fee.

For sponsored studies the EBMT is planning to have a third party audit every 2 to 3 years.

9.8.2 CIBMTR

The CIBMTR enacts a range of automatic and in-person procedures to ensure data quality and complete reporting from the associated transplant centers. Data submitted electronically through the FormsNet system (including data collected by study-specific / supplemental forms) is automatically checked for consistency of patient data across individual forms, validation of the

numeric information entered, and mandatory field entry for core questions. Centers are queried with follow-up until resolution of inconsistent data fields.

The CIBMTR monitors form completion, data verification, and IRB documentation according to its continuous process improvement (CPI) standards. To maintain CPI compliance, a center must submit at least 98% of pre-transplant essential data, 100% of supplemental study data, and >95% of all other data due each trimester to maintain "good standing" for CPI. Throughout the 15-year post-gene therapy timeframe, form submission will be monitored on a regular basis with follow-up with centers that are not submitting forms in a timely manner.

In addition, CIBMTR transplant centers are audited every 4 years to assure appropriate and quality procedures are in place. All data elements on all forms are subject to audit. However, the audit concentrates on "critical" data, i.e., data most likely to be included in a research study. Data elements considered "non-critical" are randomly audited to increase the validity of the audit error rates. An average of 10,000 fields are reviewed per audit. Any center's audit(s) resulting in a critical field error rate of >3% for 2 consecutive audits results in audit consequences.

9.9 Limitations of the Research Methods

9.9.1 Limitations of Registry Data Collection

The transplant registries used for this study have definite strengths for the collection of real-world data, particularly for those outcomes that are transplant-specific such as neutrophil recovery and secondary malignancy development. While registry data to be collected for this study is very broad, it may not be as granular as clinical trial data. This is an expected limitation of observational, real-world studies. Where feasible, additional data collection is being integrated in consultation with the registry personnel, balancing appropriate level of detail in the data collection to meet the study objectives with the burden of time placed on transplant personnel and their ultimate willingness to participate in the study.

For example, it is deemed by the registries that collection of the laboratory results most proximal to the patient's data reporting period (e.g., 6 months, 1 year) is sufficient to identify any long-term abnormalities and allows to limit the burden of data entry placed on the transplant center personnel. While longitudinal laboratory results will only be collected at pre-specified timepoints, it is unlikely that safety events will be missed due to this limitation because a broad range of hard endpoints (i.e., disease diagnoses) are included in this study and uploaded into the registry by transplant center personnel.

In a similar manner, registries will collect comprehensive data on number of severe VOC events among patients with SCD in each reporting interval and time from HSCT to most recent severe VOC event but will not capture the date of each possible severe VOC event over the 15-year study duration. This approach was deemed to be optimal, allowing the capture of information necessary to meet the study objectives without limiting the feasibility of the study by the undue burden of data collection on the participating transplant centers.

Of note, study analyses will be based on a combination of both standard, routinely collected registry data (secondary data) and de-novo data collected specifically for the study (primary data). Primary versus secondary data availability will vary by registry, due to different regional collection practices. All de novo study questions will be designed with the aid of registry personnel, in combination with transplant center personnel, to ensure question comprehensibility and data availability. As with the standard registry questions, de novo questions will be accessed

through the registry platform and subject to CIBMTR and EBMT quality control standards as described in the study data management plan.

9.9.2 Potential Confounding Factors

Though patients receiving an allogeneic transplant for SCD or TDT are generally expected to be of similar disease severity and undergo similarly rigorous conditioning regimens as patients receiving exa-cel, the final characteristics of the Allo-HSCT Cohorts may differ from the Exa-cel Cohorts. Confounding factors in the SCD and TDT literature affecting the major safety outcomes include increased age at transplant (neutrophil recovery / graft failure, mortality), allogeneic donor source (neutrophil recovery / graft failure, mortality), allogeneic stem cell source (neutrophil and platelet recovery) and conditioning regimen (malignancy development). Additional factors affecting the safety outcomes relevant to individuals with SCD or TDT may include impaired splenic function (neutrophil and platelet recovery), baseline iron overload (platelet recovery, malignancy development), and infused cell dose (neutrophil and platelet recovery). The potential confounding factors for each of the key safety outcomes are discussed in more detail below:

- **Neutrophil engraftment failure**: Both increased age (e.g., >15 years) at time of transplant[18] and mismatched allogeneic donor type have been identified as risk factors to graft failure in SCD and TDT populations.[19, 20] Relevant factors from the general transplant outcomes literature include splenic enlargement[21, 22] and infused cell dose.[23, 24]
- **Platelet recovery**: Risk factors for delayed platelet recovery are not well studied in SCD and TDT populations, but include cord blood transplant[25, 26] and, relevant from the more general HSCT literature, splenic enlargement[21, 22], pre-transplant iron overload[27, 28], pre-transplant transfusion dependence[24], and infused cell dose.[23, 24]
- **Post-allogeneic transplant malignancy**: The literature has reported primarily hematologic malignancy development among patients receiving transplants for SCD[29] and solid tumor development among patients receiving transplants for TDT.[30, 31] Risk factors for malignancy development among allo-HSCT treated patients with SCD include graft failure and/or receipt of low-intensity non-myeloablative conditioning regimens[29]; these factors are presumed to be applicable to patients receiving transplants for TDT. Treated patients with TDT may also be at risk of malignancy due to chronic iron exposure to the major organs / tissues.[32]
- **Post-transplant mortality**: Transplant-related factors associated with increased risk of mortality include older age (e.g., >15 years) at transplant and transplants from mismatched donor sources.[18-20, 25]

Subgroup comparison (stratification) will be the primary analytical method used to adjust for factors (confounders) known or suspected to be associated with post-transplant outcomes. Subgroup analyses pre-specified in the protocol include: (i) age group at transplant, (ii) patient genotype, and (iii) country of transplant (if sufficient patient counts to preserve anonymity), but may also include allogeneic stem cell source (cord blood, bone marrow, peripheral blood), level of donor matching in the Allo-HSCT comparator(human leukocyte antigen [HLA]-matched related or unrelated, HLA-mismatched, haploidentical) or conditioning regimen (e.g., fully myeloablative, reduced intensity, non-myeloablative) after assessment of the enrolled cohort differences. Additional ad hoc statistical analyses may be implemented, as needed – this may include modeling to adjust for differences in cohort characteristics in between-cohort analyses

and/or time to event analyses for select outcomes. Subgroup analyses, split by these potential confounding factors, may be performed on a post-hoc basis to control for unexpected differences between the final enrolled comparator and exa-cel treated cohorts, unexplained differences in outcomes or other findings that require exploration.

9.9.3 Sample Size Limitations

Small sample sizes are a known challenge inherent in working with rare disease populations.[33] Exa-cel therapy, indicated for individuals with the most severe phenotypes within known rare disease populations, is expected to only be available to relatively small numbers of individuals. Smaller sample sizes may limit identification of uncommon safety signals or prevent powerful analytic comparisons. In addition, given the smaller sample size, some subgroup analyses may not produce informative results. To maximize the data collection and inferential ability within this study, a broad range of hard endpoints (i.e., disease diagnoses) and early indicator (i.e., laboratory value) variables are included in this study; these variables, in combination with data on disease-related symptoms and therapies, will aid in characterizing the safety and durability of exa-cel effects. Moreover, data collection will occur at least annually, allowing repeated measures of patient outcomes over time.

9.9.4 Missing Data

Due to the observational nature of this study, some patients may have missing visits and/or missing data. Data may be missing from either the pre-treatment or post-treatment periods. The registries included in this study incorporate robust systems to minimize missing data. As described in Section 9.8, participating centers will be incentivized and monitoring procedures and source data verification will be put in place to maximize the data quality and completeness. All efforts will be made to ensure that the level of missing data for key variables of interest does not exceed 20% (considered acceptable to support regulatory decision-making based on the published literature).[34]

The study progress reports will include statistics on the percent missing data for the key variables of interest.

Although no imputation of missing data will be conducted in the course of statistical analyses, if data are missing for more than 20% of the patients, additional analyses may be performed to understand if there are any systematic differences between patients with and without missing data to assess the direction and magnitude of potential bias.

9.9.5 Loss to Follow-Up

Due to the targeted 15-year duration of follow-up, patients may be lost to follow-up over time. This may occur as adult and pediatric patients change their resident city, state, or country over time. Importantly, this loss to follow-up may be differential as patients experiencing the best post-transplant outcomes may reduce contact with their care providers. All efforts will be made to minimize losses to follow-up among the study participants, regardless of transplant type received or transplant outcome.

Measures to ensure long-term follow-up will include a combination of both transplant center and patient-specific interventions. In addition to standard patient-tracking routines, transplant centers participating in this sponsored study may receive additional education, patient tracking support, and/or tracking incentives based on annual patient follow-up. Patients, at the time of treatment

and/or initial consent / assent, will receive education on the importance of long-term follow-up contacts and, with additional consent / assent, may receive patient-friendly study updates.

The study progress reports and interim analysis reports will include statistics on the potential loss to follow-up for each study cohort. Analyses will be performed to understand if there are any systematic differences between patients lost to follow-up and remaining in the study to assess the direction and magnitude of potential bias.

9.9.6 Study Generalizability

This is a study conducted in a real-world setting using primary and secondary data collected from the EBMT and CIBMTR patient registries. Though the registries provide robust coverage across their target regions, the availability of exa-cel in the commercial setting will be limited to: (i) countries where regulatory and reimbursement approvals are achieved and (ii) select treatment centers with physicians experienced in HSCT and treatment of patients with β-hemoglobinopathies. As such, exa-cel may only be available to a limited number of indicated patients globally - this study will further include only a subset of those patients, which warrants a discussion of study generalizability to the broader population of patients who might be eligible for exa-cel. Two factors, the indicated diseases presentation and exa-cel mechanism of action, suggest that the findings from this study will be generalizable to the global indicated population:

- **Indicated diseases presentation**
    - *TDT Patient Population*: β-thalassemia is a rare, autosomal recessive disorder that is highly linked to ethnicity and is often associated with individuals originating from the Mediterranean, the Middle East, South Asia, and Southeast Asia. Transfusion dependence occurs in all ethnicities and regions and is the same irrespective of ethnicity or region.[35]
    - *SCD Patient Population*: SCD is a rare, autosomal recessive disorder that is highly linked to ethnicity. Globally, including in the US, SCD occurs at disproportionately high rates among individuals of African descent and, to a lesser extent, among individuals of Middle Eastern, Mediterranean, Indian, and Asian descent.[36, 37] Severe VOCs requiring a medical visit occur in all ethnicities and regions and are the same irrespective of ethnicity or region.[38]
- **Mechanism of action**: The nature of the exa-cel drug product, an autologous gene-edited cellular therapy, is such that it is "ethnically insensitive" (based on Regulatory Guidance ICH E5 [R1])[39]; with no differences in efficacy or safety related to difference in pharmacokinetics or pharmacodynamics anticipated based on the mechanism of action. Furthermore, there was no difference in safety or efficacy identified based on geographic location of subjects that were dosed with exa-cel in the clinical program.

Furthermore, as discussed previously in Section 9.2, international and regional guidelines suggest that the standard of care for patients with SCD and TDT is similar across regions.[1-4] In summary, results from this study are expected to be generalizable to patients treated with exa-cel in Europe and US, and more broadly, across all regions where exa-cel is expected to be available.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Subject Information and Informed Consent

Informed consent and/or informed assent will be collected for all study participants. The patient or patient's guardian (if the patient is a minor) will be provided with appropriate forms at the transplant centers prior to any data collection. Patients who are minors at the time of assent may be requested to re-confirm their individual consent / assent when they reach the age of majority, as specified by country.

10.1.1 EBMT

Following the General Data Protection Regulation (GDPR), and to ensure the maximum accordance with the law in all EU / European Economic Area nations, personal data of patients residing in EU member countries shall only be used for research through the EBMT when appropriate informed consent is ensured. This has been common practice for many years. The informed consent is collected by the individual centers or donor registries submitting data to the EBMT to make certain that the respective national laws are followed. The EBMT makes patient consent a prerequisite for submitting the data and provides all necessary information about usage of the data, to ensure appropriate consent is obtained in all cases. Post-authorization study informed consent form templates are provided to all countries. Copies have been / will be submitted to Competent Authorities and ethics committees where applicable for approval.

10.1.2 CIBMTR

Data are collected, stored and shared under terms of the *Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries* and its accompanying consent forms.[40] To be compliant with US federal regulations for human research subject protection, all US centers are required to have a Federal Wide Assurance with the Office for Human Research Protection and, as part of their Data Transmission Agreement with the CIBMTR, agree to obtain local IRB approval for the CIBMTR Research Database Protocol (http://www.ClinicalTrials.gov; Identifier: NCT01166009). The National Marrow Donor Program IRB serves as the IRB of record for all research conducted by the CIBMTR. The center is responsible for obtaining the necessary institutional review and recipient consent for participation in the CIBMTR Research Database and submitting the documents to the CIBMTR Protocol Coordinator.

If the recipient does not consent to participate according to the respective country's laws and regulations, the CIBMTR requests that only the Pre-TED and Pre-TED Disease Classification be submitted. This information helps ensure the epidemiological integrity of the Research Database is maintained and does not require provision of any protected health information that could identify the recipient, nor is this information used in any analysis.

The CIBMTR works within the NMDP / Be The Match maintained comprehensive Human Research Protection Program to ensure the rights and welfare of participants in its research are protected and to ensure compliance with all pertinent US federal regulations. The NMDP / Be The Match Human Research Protection Program is fully accredited by the Association for the Accreditation of Human Research Protection Programs.

10.2 Access to Records

The study sponsor will not have access to patient records.

10.3 Subject Privacy

10.3.1 EBMT

All personal data under the responsibility of the EBMT are processed according to the EU GDPR. The data are stored in an Amazon Web Services environment with infrastructures located in Europe (EU-west-1, EU-west1a, and EU-west-1b) which is protected by safeguards that ensure security, including compliance with ISO27001 certification. The data are only accessible by EBMT employees for the performance of their job following a stringent access control policy. The EBMT has Privacy Policies, a Register of Processing Activities, and data use and processing policies in place.

EBMT has developed a Joint Controllership agreement with centers with full EBMT membership which describes the responsibilities concerning data protection of the data reported to the EBMT.

10.3.2 CIBMTR

The CIBMTR protects the data and information received from centers and patients and is committed to the ethical conduct of research. CIBMTR obeys the US Health Insurance Portability and Accountability Act (HIPAA) and the EU GDPR.

The CIBMTR maintains comprehensive information security and data protection practices that align with the National Institute of Technology and Standards (NIST 800-53) Security and Privacy Control for Federal Systems framework as well as the policies and procedures of the CIBMTR and its parent institutions. These practices are continuously monitored and subject to annual assessment by a qualified, independent third-party auditor. Assessment findings and a statement of fact are reported to the CIBMTR Information Security and Data Protection Committee for acceptance and, upon request, are made available as part of a security assurance package to key stakeholders.

When releasing data, the CIBMTR is obligated to ensure that datasets do not contain protected health information. CIBMTR staff follow a standard procedure for creation of de-identified datasets that specifies removal of all patient, donor, and center identifiers, which could lead to the identification of a patient or center from data files. The CIBMTR does not release to the principal investigator or any other member of his / her research team identifiable patient or center variables unless these data are critical to the approved study / project or will be used for linking to another data file via an established honest broker relationship. In these cases, special procedures outlined in the CIBMTR Linking Data to External Databases or Data Sources Standard Operating Procedures are followed and documented with a Data Use Agreement and established prior to final approval of the request.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

The reporting procedures defined below by this non-interventional study protocol are applicable to study patients exposed to exa-cel accessed via commercial availability.

In addition to the reporting procedures defined in this protocol, the HCP is responsible for reporting safety information to regulatory authorities, ethics committees, and other local agencies, in accordance with local regulatory requirements, as applicable.

11.1 Definitions

- **Adverse Event**

  An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency. A subset of AEs may meet serious criteria.

  Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was screened in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

- **Serious Adverse Event**

  An SAE is any AE that meets any of the following criteria:

  - Results in death
  - Life-threatening
  - Requires hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability / incapacity (substantial disruption of the ability to conduct normal life functions)
  - Congenital anomaly or birth defect
  - Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., a new hematologic malignancy diagnosis).

11.2 Adverse Event Causality

Every effort should be made by the HCP to assess the relationship of the AE, if any, to exa-cel exposure. Causality should be classified using the categories presented in Table 3.

Table 3 Classifications for Adverse Event Causality

Classification	Definition
Related	There is a suspected association between the event and exa-cel, a plausible mechanism for the event to be related to exa-cel and causes other than the exa-cel have been ruled out.
Not Related	The event is believed related to an etiology other than the exa-cel.

exa-cel: exagamglogene autotemcel

11.3 SAE Reporting Procedure

All SAEs observed in patients exposed to exa-cel accessed via commercial availability, regardless of the presumed relationship to any Vertex medication exposure, must be reported to

the MAH using the Non-interventional (NI) Study Safety Information Collection Form (study number must be included on the form).

Any hematologic malignancy diagnosis is considered an important medical event that must be reported to the MAH following SAE reporting guidance.

This reporting is required from the time informed consent and assent, where applicable, is signed and while the patient is participating in the study, for all SAEs that occur at any time after exa-cel infusion. Complete and comprehensive case information must be documented and causality assessments performed.

Reportable SAEs should be reported by the HCP to the MAH **within 24 hours** of awareness. NI Study Safety Information Collection Forms should be submitted to:

Vertex Global Patient Safety

Email: globalpatientsafety@vrtx.com *(preferred)*

Or via fax: +1-617-341-6159

For questions, contact telephone: +1-617-341-6677

11.4 Pregnancy Reporting

If a female patient or female partner of a male patient becomes pregnant while being treated with exa-cel, the HCP must notify the MAH (Vertex Global Patient Safety) of the pregnancy using the Pregnancy Information Collection Form. The patient will be followed until the end of the pregnancy, and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate informed consent form will be provided to explain these follow-up activities.

12 HEMATOLOGIC MALIGNANCY REPORTING AND FOLLOW-UP EVALUATION

The procedures defined below apply to the treating HCP and MAH and are applicable to all patients in the study treated with exa-cel.

Should a hematologic malignancy be diagnosed in any of the patients included in the Exa-cel Cohorts in this study, the HCP is to contact the local representative of the MAH to report the event (Section 11) and determine appropriate samples for analysis.

The MAH will then work with the HCP to

1. collect all relevant available information from the treating physician (e.g., event, diagnosis, medical history, associated evaluations, and risk factors) using a structured Hematologic Malignancy Information Collection Form; and
2. determine any required samples to be provided by the HCP to MAH for analysis.

For each case of confirmed hematological malignancy, MAH will perform an investigation to evaluate if genome editing may have played a role. The investigation may include, but is not limited to: 1) evaluation of on-target editing in the malignant cells using appropriate controls, 2) determination if off-target editing occurred using unbiased sequencing-based methods, and 3) screening for pre-existing genomic drivers of hematologic malignancy present in the patient samples and determination of their potential contribution to malignancy. This investigation may

include testing of stored samples of patient's unedited $CD34^+$ cells and edited $CD34^+$ (drug product) retains, subject to patient consent in line with local regulations.

13 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim and final study results will be periodically discussed in periodic aggregate safety reports (e.g., Periodic Safety Update Report, Period Adverse Drug Experience Report) and will also be summarized in the Development Safety Update Report. Study results will be used to adjust the safety specifications and the pharmacovigilance plan of the risk management plan, as appropriate.

The MAH plans to publish the study results after the final study analysis is completed in collaboration with the registry partners, no later than 18 months after the closure of the current study (which shall be defined as the final lockdown of all data and the resolution of all queries). Final study results will also be posted to the HMA-EMA Catalogue no later than 12 months after the study close.

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15 ANNEXES

Annex 1 Justification for Leveraging Existing Registries

Annex 2 EBMT Feasibility Assessment

Annex 3 CIBMTR Feasibility Assessment

Annex 4 List of Stand-alone Documents

Number	Document Title
1	Mapping of Study Variables to EBMT and CIBMTR Existing and Study-specific Forms
2	EBMT Standard Forms
3	CIBMTR Standard Forms

CIBMTR: Center for International Blood and Marrow Transplant Research; EBMT: European Society for Blood and Marrow Transplantation

Annex 5. ENCePP Checklist for Study Protocols

Annex 6. Minimal Detectable Risk for Key Safety Outcomes