1 TITLE PAGE

VERTEX PHARMACEUTICALS (EUROPE) LIMITED

Non-interventional Study Protocol

Routine practice data collection to compare Exagamglogene autotemcel with patient-individualized treatment in severe sickle cell disease: A prospective non-interventional study mandated by G-BA

Vertex Study Number: HEOR-24-001-028

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2 SUMMARY

With its resolution from 21 December 2023, effective date 15 January 2025, the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA) has required Vertex to conduct a routine practice data collection (AbD) to generate comparative data for the treatment with Exagamglogene autotemcel (Exa-cel) compared to existing treatment alternatives in the German healthcare system. The patient population of interest comprises patients ≥12 to <21 years of age with severe sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) for whom hematopoietic stem cell transplantation (HSCT) is appropriate and a human leukocyte antigen (HLA)-matched related hematopoietic stem cell (HSC) donor is not available.

The aim of this study is to evaluate the effectiveness and safety of Exa-cel compared with patient-individualized treatment in patients with severe SCD. Patient-individualized treatment is defined as hydroxycarbamide (hydroxy urea, HU) and / or chronic red blood cell (RBC) transfusions. The two co-primary objectives are to compare the annualized VOC rate and the proportion of VOC-free patients between both treatment groups. Further objectives relate to comparison of mortality and safety (restricted to total rate of serious adverse events (SAE), operationalized as adverse events leading to hospitalization or prolonging an existing hospitalization, or result in death).

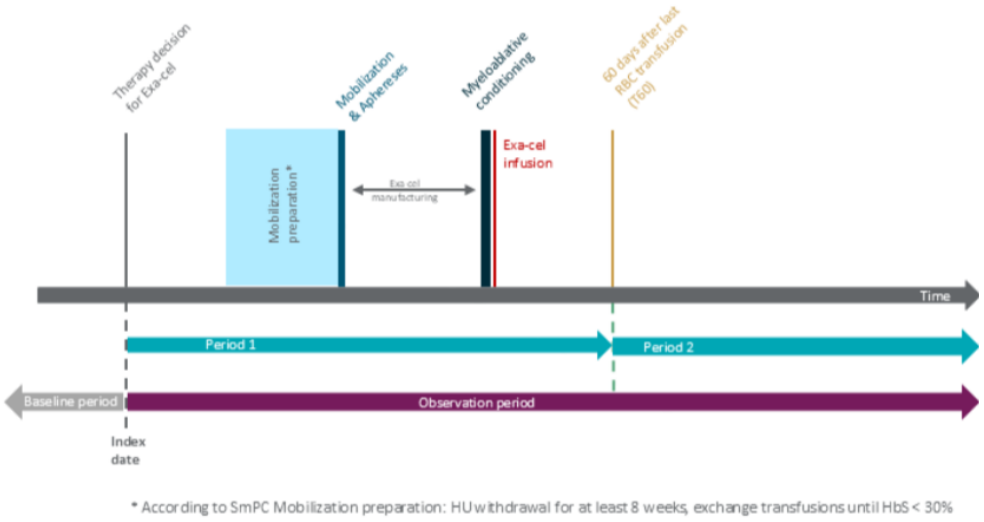
The study is a prospective, non-interventional, registry-based, comparative study. The SCD patient registry, mandated by the Society for Pediatric Oncology and Hematology (Register Sichelzellkrankheit der Gesellschaft für Pädiatrische Onkologie und Hämatologie, GPOH) and set up and administrated by Heidelberg University Hospital (UKHD), will be used as the data source. All patients will be identified in the GPOH SCD registry and must meet the requirements for eligibility according to the currently approved EU label for Exa-cel. Furthermore, individuals must reside and be treated for their SCD in Germany, be receiving patient-individualized treatment with HU and / or chronic RBC transfusions at start of observation, have provided written informed consent, and the number of VOCs must be available in their medical records for at least 2 years prior to start of observation.

3 PROTOCOL SYNOPSIS

Title	Routine practice data collection to compare Exagamglogene autotemcel with patient-individualized treatment in severe sickle cell disease: A prospective non-interventional registry-based study mandated by G-BA
Brief Title	Routine practice data collection of Exagamglogene autotemcel in severe sickle cell disease in Germany
Study Type	Non-interventional, prospective, comparative registry-based study
Study Rationale	The Federal Joint Committee (G-BA) has mandated Vertex to conduct a routine practice data collection (AbD) comparing Exagamglogene autotemcel (Exa-cel) with patient-individualized treatment for patients ≥12 to <21 years of age with severe sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) for whom hematopoietic stem cell transplantation (HSCT) is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available. The results of the AbD will be used to support a benefit assessment of Exa-cel according to §35a Social Code Book V.
Study Objectives	The aim of this non-interventional study is to evaluate the effectiveness and safety of Exa-cel compared with patient-individualized treatment in patients with severe SCD with recurrent VOCs. In SCD, the prevention of VOCs is the main treatment goal, ideally resulting in VOC freedom. Therefore, the co-primary objectives of this study are to compare the annualized VOC rate and the proportion of VOC-free patients between both treatment groups. Further objectives relate to comparison of mortality as well as safety (total rate of serious adverse events (SAEs)).
Data Sources	This study will use clinical data from routine patient care as available in the patients' medical files. Data will be documented into the GPOH SCD registry and into eCRFs specifically designed for this data collection. AbD-specific data fields will be restricted only to treatment centers who participate in the AbD and will only be documented for patients who have signed informed consent to be included in the AbD. The GPOH SCD registry is an independent multicenter, clinical and epidemiological registry including patients with SCD irrespective of disease severity in Germany.
Study Design	The study includes a patient identification period that will start with the first index date that can be documented in the AbD (after implementing all required changes to the registry) and continuing for 2 years thereafter. Therapy decision for Exa-cel during this time window will trigger each respective patient to be offered inclusion in the study. Their index date will be set as the date of therapy decision for Exa-cel (i.e. date when written treatment consent has been provided by the patient). As soon as an Exa-cel patient no longer requires red blood cell (RBC) transfusions for at least 60 days for post-transplant support (defined as time point T60 for the patient), a follow-up period of at least 3 years begins. For each patient, the period from the index date to T60 (or to the end of the study or to study discontinuation, whichever comes first), is defined as period 1. The period from T60 to the end of the study (or study discontinuation) is defined as period 2 (period 1, period 2, and T60, see figure below in this section).

Eligible patients within the GPOH SCD registry who are on patient-individualized treatment and have been determined sufficiently similar to any included Exa-cel patient by use of a matching algorithm during the patient identification period will be included in the study subject to informed consent. Their **index date**, T60 date, and observation periods 1 and 2 will be linked to the calendrical milestones of the respective Exa-cel patient to whom they were matched.

Figure: Overview of Exa-cel treatment from therapy decision to end of study and time periods relevant for the AbD at a patient level.



Modified Active Comparator New-User (MACNU) Design

To identify eligible Standard of Care (SoC) patients who are sufficiently similar to any Exa-cel patient and to assign meaningful index dates, a novel study design named Modified Active Comparator New-User (MACNU) Design is proposed. The MACNU design employs a systematic four-step process:

(1) identification of eligible SoC patients within the GPOH SCD registry,

(2) definition of exposure sets for each Exa-cel patient based on relevant clinical characteristics,

(3) calculation of time-conditional propensity scores, and

(4) matching Exa-cel patients with SoC patients to form a balanced study cohort.

The MACNU design enables the selection of SoC patients with disease severity characteristics similar to those of the Exa-cel patients, which is essential to ensure comparable treatment cohorts. Hereby, similarity is defined based on the number of VOCs in the 2 years preceding the index date, genotype and chronic RBC transfusions treatment.

Study Population

All study patients must meet the requirements for eligibility according to the currently approved EU label for Exa-cel and will be identified by screening patients in the GPOH SCD registry. Eligibility of SoC patients has to be confirmed for each inclusion into an exposure set (see section 11.4.2)

Patients are eligible to be included in the study if all of the following criteria apply:

1. Residing and treated for their SCD within Germany
2. Severe SCD with recurrent VOCs*
3. Eligible for HSCT and all aspects related to Exa-cel treatment (e.g., full myeloablation, stem cell mobilization, apheresis) according to the assessment of the treating physician**
4. An HLA-matched related HSC donor is not available (discretion of treating physician)
5. ≥12 and <21 years of age at index date
6. Complete records of VOCs leading to hospitalization available in the registry and/or patient's file for at least 2 years prior to index date

7. Receives patient-individualized treatment with hydroxycarbamide (HU) and / or chronic RBC transfusions at index date
8. Provided written, signed informed consent for their data to be included in the study

* As per the label of Exa-cel, severe SCD is defined by the recurrence of VOCs; "recurrent VOCs" for the purposes of this study are aligned to the patient selection criteria for Exa-cel proposed by the Kompetenzcentrum Onkologie (KCO, (1)), where "recurrence" is defined as the occurrence of at least 2 VOCs per year over the course of 2 years; Of note, patients who, due to severe previous VOCs and/or other SCD complications, are receiving chronic RBC transfusion therapy may have none or less than 2 VOCs/year as a consequence of this therapy; such patients are also eligible for the AbD, as per definition their disease severity is sufficiently high to meet the Exa-cel requirements (see section 11.3.1 for further details).

** In the context of this study, "eligibility for HSCT" is defined as per the label of Exa-cel, where a full myeloablation is required (see section 11.3.1 for further details).

Patients are excluded from the study if any of the following criteria apply:

1. Treatment with Exa-cel or any of the agents / procedures used along the Exa-cel treatment journey is contraindicated or not recommended; this includes prior HSCT, pregnant women, active human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B and C virus (HBV and HCV) infections, and severe alloimmunization/transfusion reactions that preclude RBC transfusions (discretion of treating physician)
2. Treatment (including preparation to receive treatment) with allogeneic HSCT, alternative gene therapy or experimental therapies

Note: Treatment centers are not obliged to but may apply for patient-individual cost-coverage prior to Exa-cel therapy decision. To be able to estimate uncertainties in positivity, patients for whom a cost-coverage application was submitted but denied, but who fulfill all inclusion criteria and none of the exclusion criteria, will be included in the study but handled as a separate group for which only patient characteristics will be reported. It will be differentiated whether the assumption of costs was rejected due to clinical or non-clinical (other) reasons. If there are non-clinical reasons, an inclusion of the person in the comparator arm may be considered. All of these patients not included in the comparator arm will be excluded from the Full Analysis Set and consequently not considered for any subsequent analysis.

Treatment

- Exagamglogene autotemcel

Comparator

- Hydroxycarbamide
- Chronic RBC transfusions

Endpoints

Primary:

Morbidity:

For the purposes of this study, VOCs are defined as hospitalization due to pain event, acute chest syndrome, splenic sequestration or priapism.

- Annualized VOC rate in period 2
- Proportion of responders where VOC freedom over 36 months starting from T60 (period 2) is considered a response

Secondary:

Morbidity:

- Annualized VOC rate in period 1

Mortality:

- Proportion of patients who died by period
- Annualized death rate by period

Safety:

- Proportion of patients with SAEs (adverse events leading to hospitalization or prolonging an existing hospitalization, or result in death) by period
- Annualized rate of SAEs by period

Study Size

The estimated sample size for a powered comparative analysis of the co-primary endpoints VOC freedom and annualized VOC rate is a minimal number of 81 eligible patients (27 patients to Exa-cel group and 54 patients in the comparator group) to provide 80% power testing against the null hypothesis of risk ratio 2.0 (a shifted null hypothesis as required by G-BA and the Institute for Quality and Efficiency in Health Care [IQWiG]) and rate ratio 0.5. This calculation is driven by VOC freedom endpoint and based on assumed response rates of 91.3% for Exa-cel derived from CLIMB-121/131 data and 25% for the comparator group as proposed by G-BA. To account for an assumed 18% rate of patients with a decision for Exa-cel treatment who do not receive Exa-cel, who withdraw informed consent, who die or are lost to follow-up after receiving Exa-cel, and an assumed 50% drop-out rate for patients in the comparator arm, inclusion of at least 33 Exa-cel patients and 108 SoC patients is targeted resulting in a total sample size of 141 patients to be enrolled.

Statistical Methods

All endpoints will be analyzed comparatively (Exa-cel group vs. SoC) as well as descriptively unless specified otherwise. All endpoints except the co-primary endpoint VOC freedom will be analyzed separately for period 1 and 2. VOC freedom will be analyzed only for period 2. Propensity score weighting will be used to adjust for the following confounders in all comparative analyses:

- Age
- Alloimmunization
- Cerebrovascular events
- Chronic pain
- Chronic transfusion therapy
- HbF level
- Hepatopathy
- Nephropathy
- Pulmonary hypertension
- Sex
- Siderosis (iron overload)
- Number of VOCs
- Other SCD complications

Confounders will be assessed during the baseline period.

Planned Analyses

Two interim analyses are requested by the G-BA and will be conducted 18 months and 36 months after AbD start (defined by the G-BA). It is expected that 18 months after official study start only very few patients will be enrolled and none of those reached T60 (all patients still in period 1). 36 months after AbD start it is expected that the identification window is already closed with all study patients enrolled and assigned to either the Exa-cel or the SoC arm. A futility analysis for VOC freedom is likely unfeasible because none of the enrolled patients will have sufficient follow-up after T60 at that time period.

Therefore, a futility analysis for number of enrolled patients 14 months after the start of the identification period will additionally be conducted.

The final analysis will be conducted after the end of study, which is reached when all patients with a defined T60 have completed (or prematurely discontinued) 36 months of follow-up starting at T60.

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Abbreviation	Definition
AbD	Routine practice data collection (*Anwendungsbegleitende Datenerhebung*)
ACS	Acute thorax syndrome
AE	Adverse event
ANC	Absolute neutrophil count
ATMP	Advanced therapy medicinal products
AUC	Area under the curve
BDSG	German Federal Data Protection Act (*Bundesdatenschutzgesetz*)
CD	Cluster of differentiation
CI	Confidence interval
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats/CRISPR-associated 9
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End of study
Exa-cel	Exagamglogene autotemcel
FAS	Full Analysis Set
G-BA	Federal Joint Committee (*Gemeinsamer Bundesausschuss*)
GDPR	General Data Protection Regulation
GPOH	Society for Pediatric Oncology and Hematology *(Gesellschaft für Pädiatrische Onkologie und Hämatologie)*
GvHD	Graft versus host disease
Hb	Hemoglobin
HbA	Hemoglobin A
HbC	Hemoglobin C
HbF	Fetal hemoglobin
HbS	Sickle cell hemoglobin
HbSC	Hemoglobin SC
HbSS	Hemoglobin SS
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSC(T)	Hematopoietic stem cell (transplantation)
HSPC	Hematopoietic stem and progenitor cell
HU	Hydroxycarbamide (Hydroxyurea)
ICE	Intercurrent event
ICF	Informed consent form
IDAT	Identifying data
IQWiG	Institute for Quality and Efficiency in Health Care *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)*
KCO	Medical services of the German payers *(Kompetenzcentrum Onkologie der Medizinischen Dienste)*

Abbreviation	Definition
LFU	Lost to follow-up
MACNU Design	Modified Active Comparator New-User (MACNU) Design
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MDAT	Medical data
MUD	Matched unrelated donor
NI	Non-interventional
PIC	Patient informed consent
PICO	Population, Intervention, Comparator, Outcome
PNUD	Prevalent New-User Design
PRO	Patient reported outcome
PS	Propensity score
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sickle cell disease
SD	Standard deviation
SDV	Source data verification
SoC	Standard of Care
TCD	Transcranial Doppler
UKHD	Heidelberg University Hospital
VOC	Vaso-occlusive crisis
WHODRUG	World Health Organization drug dictionary

8 RESPONSIBLE PARTIES

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9 INTRODUCTION

9.1 Background

Sickle cell disease (SCD) encompasses a range of inherited red blood cell (RBC) disorders that arise from a point mutation in the *HBB* gene, which codes for the β-globin chain of the adult hemoglobin (Hb) (2). The most severe and prevalent form of SCD is an autosomal recessive disease due to homozygous mutations in which a valine replaces a glutamic acid at position 6 in the β-globin protein – this is referred to as sickle cell Hb (HbS). HbS polymerizes in the deoxygenated state producing abnormal, sickle shaped RBCs with limited flexibility and lifespan. Other, phenotypically similar variants of SCD occur when a person inherits one abnormal copy of the *HBB* gene leading to HbS formation and another abnormal hemoglobin gene, such as a thalassemia mutation associated with a total lack or severe reduction of HBB expression (3).

In SCD, the abnormal HbS causes RBCs to become rigid and crescent or 'sickle' shaped. These irregularly shaped, rigid erythrocytes can form aggregates that block and damage blood vessels (vaso-occlusions), which can cause severe pain (known as sickle cell or vaso-occlusive crisis [VOC]); the manifestations of SCD are multisystemic and vary depending on the localization of vaso-occlusions: Patients suffer from a wide range of symptoms like severe chronic hemolytic anemia, an increased risk of infections, inflammation, ischemic and / or hemorrhagic strokes, retinopathy, renal, hepatic and other organ failure and early mortality (4).

In SCD, the presence of fetal hemoglobin (HbF) during the first months of life provides a protective effect, delaying the onset of symptoms until several months after birth when adult hemoglobin (bearing the HbS defect) becomes predominant (5). Instead of β-globin, HbF contains γ-globin, which is coded by a different gene, thus HbF is not affected by the HbS-causing mutations. Persons with SCD who coinherit the condition of hereditary persistence of HbF and have increased levels of HbF that persist throughout life have few or no symptoms of the disease (6-8).

SCD is common throughout large areas of sub-Saharan Africa, the Middle East, and India (9). Estimates suggest that in 2021 almost 8 million individuals globally were living with the disease and over 500,000 babies were born with SCD, with more than three quarters residing in countries of sub-Saharan Africa (10). In Germany, the prevalence of SCD in 2019 was estimated to be approximately 3,160 patients (11). First results from the nationwide newborn screening established in Germany in 2021 show an incidence of 80-160 newborns affected by SCD per year (12, 13). About 90% of children born with SCD in the US or EU survive into adulthood, but their lifespan is shortened by 2 to 3 decades compared to the general population, with a median age of death of approximately 40 to 50 years (14-18).

The current mainstay of treatment for SCD is hydroxycarbamide, which reduces the complications of SCD including VOCs, acute chest syndrome (ACS), and stroke, while also decreasing hospitalization rates and prolonging survival (4). However, hydroxycarbamide is not effective in all patients, is not always well tolerated, nor curative, has carcinogenic and teratogenic risks and patients can continue to experience breakthrough VOCs. The transfusion of RBC concentrates is an important pillar in the treatment of patients with SCD. Transfusions are necessary for the treatment of certain acute complications but can also be part of a chronic therapy concept upon prior, critical appraisal of the indication. Transfusions are associated with potentially serious side effects, particularly due to the risk of alloimmunization, iron overload and the transmission of infections, and therefore are only

used when clearly indicated, e.g. for the acute treatment of stroke or when transcranial Doppler readings indicated an increased cerebrovascular risk (19).

The only curative therapy currently available for patients with SCD is allogeneic hematopoietic stem cell transplantation (HSCT). The gold standard for allogeneic HSCT is using stem cells from a human leukocyte antigen (HLA)-matched related (usually sibling) donor. However, in Germany only a minority of SCD patients (less than 20%) have a matched related donor available (20). Graft failure or graft versus host disease (GvHD) and infections are major risks associated with allogeneic HSCT, with risk increasing when alternative donors are used, such as HLA-matched unrelated donors (MUDs). Importantly, MUDs are even more sparsely available for patients with SCD. Alternative approaches, e.g. utilizing T-cell depleted HSCs from mismatched related donors, most commonly haploidentical donors, are still only considered an option within clinical trials and limited to centers with a sufficient experience due to higher risk of acute and chronic GvHD and graft failure or transplant related mortality; thus, haploidentical HSCT is not considered an appropriate comparator within this study by the Federal Joint Committee (*Gemeinsamer Bundesausschuss,* G-BA).

Exagamglogene autotemcel (Exa-cel, Casgevy®) is indicated for the treatment of severe SCD in patients 12 years of age and older with recurrent VOCs for whom HSCT is appropriate, and an HLA-matched related HSC donor is not available.

Exa-cel is a cellular product consisting of enriched autologous $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) 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 HbF production. Gene editing with Exa-cel is intended to induce changes in the deoxyribonucleic acid (DNA) sequence of the erythroid enhancer region of the *BCL11A* gene in the autologous $CD34^+$ HSPC such that upon erythroid differentiation in the patient, the expression of γ-globin is increased, leading to an increase in HbF expression levels in adult erythroid cells. The increase in HbF is expected to ameliorate the clinical manifestations of SCD.

Data from the pivotal clinical trial for Exa-cel (CLIMB-121, NCT03745287) showed that a rapid and durable increase in HbF and total Hb levels that was brought about by Exa-cel eliminated severe VOCs for 12 or more consecutive months in the vast majority of patients; likewise, hospitalizations due to severe VOCs were markedly reduced and most patients were free from such events after Exa-cel infusion. Exa-cel treatment was associated with improvements in markers of hemolysis. The overall safety profile of Exa-cel in the pivotal trial was generally consistent with myeloablative busulfan-based conditioning and autologous transplantation (21-23).

Exa-cel received a conditional marketing authorization in the EU for the treatment of SCD and beta thalassemia on 9 February 2024. The market entry in Germany took place on 15 January 2025. For medicinal products with a conditional marketing authorization or orphan designation, the German payer G-BA may require the pharmaceutical company to conduct a routine practice data collection (*Anwendungsbegleitende Datenerhebung,* AbD) for the purpose of a future benefit assessment. Procedures to investigate the necessity and feasibility of such an AbD for Exa-cel in SCD were initiated by G-BA in June 2023. In February 2024, G-BA requested Vertex to conduct a prospective, comparative study comparing Exa-cel with existing therapy alternatives for patients with SCD, with the decision becoming effective with market entry (24, 25).

9.2 Study Rationale

The G-BA has mandated Vertex to conduct an AbD comparing Exa-cel with patient-individualized treatment with severe SCD with recurrent VOCs for whom HSCT is appropriate and a HLA-matched related HSC donor is not available. (24, 25). The collected data will be analyzed and submitted to G-BA for consideration in a new benefit assessment of Exa-cel according to §35a Social Code Book V in Germany (24, 25).

10 STUDY OBJECTIVES AND ENDPOINTS

The aim of this prospective, non-interventional, registry-based study is to evaluate the effectiveness and safety of Exa-cel compared to patient-individualized treatment in patients with severe SCD.

The PICO (Population, Intervention, Comparator, Outcome) scheme of this study is shown in Table 1.

Table 1: PICO scheme of the present study

Population	Patients aged ≥12 to <21 years with severe SCD with recurrent VOCs* for whom HSCT is appropriate** and a HLA-matched related HSC donor is not available
Intervention	Exa-cel
Comparator	• Hydroxycarbamide • Chronic RBC transfusions
Outcome	Objectives and endpoints of this study are presented in detail in Table 2.

* As per label of Exa-cel, severe SCD is defined by the recurrence of VOCs; "recurrent VOCs" for the purposes of this study are aligned to the patient selection criteria for Exa-cel proposed by the Kompetenzcentrum Onkologie (KCO, (1)), where "recurrence" is defined as the occurrence of at least 2 VOCs per year over the course of 2 years. The KCO criteria further define VOCs as any of the following, regardless of hospitalization:

- **acute pain event** requiring a visit to a medical facility and the administration of pain medication *(opioids or intravenous nonsteroidal anti-inflammatory drugs)* or **RBC transfusions**,
- **acute chest syndrome**, confirmed by the appearance of a new **pulmonary infiltrate** accompanied by **pneumonia-like symptoms, pain, or fever**,
- **priapism** lasting longer than **two hours** and requiring a visit to a medical facility,
- **splenic sequestration**, defined by an **enlarged spleen**, **left upper quadrant pain**, and an **acute drop in hemoglobin concentration (Hb) of ≥ 2 g/dL**.

Of note, patients who, due to previous severe VOCs and/or other SCD complications, are receiving chronic RBC transfusion therapy may have no or less than 2 VOCs/year as a consequence of this therapy; such patients are also eligible for the AbD, as per definition their disease severity is sufficiently high to meet the Exa-cel requirements.

** In the context of this study, "eligibility for HSCT" is defined as per the label of Exa-cel, where a full myeloablation is required. In this context the criteria proposed by the KCO should be observed, especially considering the patient's general condition, absence of organ damage and/or comorbidities which in the opinion of the investigator would prohibit the administration of a full myeloablative conditioning regimen.

Severe SCD, as a chronic disease, is characterized by recurrent VOCs, that lead to pain, progressive tissue injury, organ dysfunction, impaired quality of life and premature death. The prevention of VOCs (freedom from VOCs) and the reduction of VOCs are therefore the main treatment goals of Exa-cel.

Accordingly, the two co-primary objectives in this study are as follows:

- To compare the annualized VOC rate between Exa-cel and patient-individualized treatment referred to as Standard of Care (SoC).
- To compare the proportion of VOC-free patients over 36 months between Exa-cel and SoC.

In this study, the assessment of VOCs for the study objectives are defined as hospitalization for VOC for any of the following events: pain crises, acute chest syndrome (ACS), priapism or splenic sequestration.

For the comparison of the proportion of VOC-free patients over 36 months, it is appropriate that the 36-month period starts from T60. This is because the treatment with Exa-cel can only exert its effect on VOCs after the infusion of Exa-cel has taken place and its effect is only clearly measurable after a washout period of 60 days after the last RBC transfusion for post-transplant management has been completed; the 60-day washout period is based on well-known and studied viability of transfused erythrocytes (26).

For the same reason, it is also appropriate for the comparison of annualized VOC rate, that the effectiveness of Exa-cel is measured for period 2, starting from T60, **Figure 1**.

To provide the complete picture from treatment decision, annualized VOC rate will also be analyzed from treatment decision to T60 (period 1), **Figure 1**.

Definitions for all relevant time periods for the study are contained in section 11.2.

An overview of the objectives and endpoints of this study is shown in Table 2.

Table 2: Objectives and endpoints

Objective	**Endpoint with respective analysis period(s)**[a]
Primary	
Morbidity	
To compare the annualized rate of VOCs	Annualized VOC rate in period 2
To compare the proportion of VOC-free patients over 36 months	Proportion of responders where VOC freedom over 36 months in period 2 is considered a response
Secondary	
Morbidity	
To compare the annualized rate of VOCs	Annualized VOC rate in period 1
Mortality	
To compare the occurrence of death	• Proportion of patients who died by period • Annualized death rate by period
Safety	
To compare the occurrence of SAEs (adverse events leading to hospitalization or prolonging an existing hospitalization, or result in death)	• Proportion of patients with SAEs by period • Annualized rate of SAEs by period
a: For definitions of analysis periods, see section 11.2	

11 RESEARCH METHODS

11.1 Data Sources and Data Collection

The data source for this study is clinical data from routine patient care as documented in the patients' medical files. Data will be entered into the GPOH SCD registry, capturing data from a mixture of variables already existing in the registry, with additional variables added to the registry to fulfill AbD requirements (see section 11.5). AbD-specific data fields will be restricted only to treatment centers that participate in the AbD and will only be documented for patients who have signed informed consent to participate in the registry and an additional consent to be included in the AbD.

The GPOH SCD registry is an independent, multicenter, clinical and epidemiological registry including patients with SCD irrespective of disease severity in Germany and Austria who have consented to transfer data to the registry. Currently, 50 centers in Germany are actively participating and about one third of all SCD patients living in Germany are included in the GPOH SCD registry. The majority of patients are pediatric since adults receiving current therapies are mainly treated in the outpatient setting instead of specialized clinics.

The main aim of the GPOH SCD registry is the documentation of the clinical course of SCD, genetic variants, modifying factors and complications. Baseline characteristics of patients are included in the registry, with treatment and complications also recorded. Information on the course of the disease and the treatment of patients is requested from the participating centers once a year. For patients participating in the AbD, more frequent (preferably quarterly) documentation of their routine clinical data (as available) is targeted. The data are documented online via the Remote Data Entry System MARVIN, which is operated by the company XClinical. The registry protocol in German language can be accessed on the GPOH website; a detailed list of assessed parameters can be found starting on page 52 (27).

For the present study, patients in the GPOH SCD registry and meeting the inclusion and not meeting the exclusion criteria may be offered inclusion in this study depending on the selection via the MACNU algorithm (see section 11.4.2). Retrospectively and prospectively collected data from included patients will be used.

Treatment centers need to fulfill certain criteria regarding center structure and transplant expertise as a prerequisite to be eligible to prescribe Exa-cel. These criteria are specified in the Advanced Therapy Medicinal Products (ATMP) quality assurance guideline by G-BA (28) and in the checklist for individual cost-coverage requests with the medical services of the German payers (KCO checklist) (1). Similar criteria will be applied for all participating centers treating SoC patients because the evaluation of a patient's eligibility according to the selection criteria (see section 11.3) as well as the decision for or against a prescription of Exa-cel require transplant expertise.

With small amendments, the GPOH SCD registry is regarded by G-BA as a suitable primary data source.

11.2 Study Design

This is a prospective, non-interventional, comparative study conducted as an AbD mandated by the G-BA. The study uses (retrospective and prospective) data recorded in the GPOH SCD registry. Use of retrospective data is limited to baseline characteristics including confounders. Data will be collected only for those patients who have granted their informed consent and waived data privacy privileges for the purposes of the AbD.

As this is a non-interventional study, no stipulations regarding patient treatment, visit frequency or monitoring will be mandated by this protocol. However, for appropriate longitudinal documentation of the patients' progression physicians are encouraged to contact the study patients and document data at least quarterly. Physicians will treat and monitor study patients in accordance with their medical judgment and local standard of care and in agreement with respective label information. All eligible patients are to receive patient-individual treatment for their SCD as prescribed by their treating physician at inclusion and the therapy decision for Exa-cel is made independently of the decision to include a patient in the study. SCD treatment at time of inclusion can only consist of HU, and /or chronic RBC transfusions (see Table 1).

The observation period for each patient will start with therapy decision for Exa-cel (i.e., index date), Figure 1. For SoC patients, the observation period starts at index date of the matched Exa-cel patient (see section 11.4.2). From the index date onwards, data from both Exa-cel and SoC patients will be collected until end of study.

The treatment journey for Exa-cel includes several consecutive phases: mobilization preparation (withdrawal of HU for at least 8 weeks and exchange transfusions to reduce HbS levels < 30%), mobilization and apheresis (it is expected that the majority of patients will require multiple mobilization and apheresis cycles, each separated by at least 2 weeks), Exa-cel manufacturing, myeloablative conditioning, Exa-cel infusion and waiting for engraftment of the infused edited HSCs. After Exa-cel infusion, all patients require RBC transfusions for post-transplant management with variable (individual) duration.

In order to be able to assign treatment effects to Exa-cel and not to the RBC transfusions, a washout period of 60 days after last RBC transfusion is defined (time point referred to as T60, based on well-known and described viability of transfused erythrocytes (26)). T60 was utilized within the pivotal Exa-cel study CLIMB-121 for the primary endpoint 'Proportion of patients without VOCs for 12 consecutive months'[*]. Thus, T60 is the time point for separating the observation period for analysis of outcomes (period 1 and period 2, see Figure 1 below). Period 1 encompasses the time from treatment decision until T60; period 2 starts at T60 and represents the follow-up period of at least 36 months required to assess the co-primary endpoint of VOC freedom over 36 months. Like the index date, T60 for SoC patients is determined based on the matched Exa-cel patient.

Figure 1 provides a schematic overview of the course of Exa-cel treatment from therapy decision to end of study and time periods relevant for the AbD at a patient level.

[*] The treatment with Exa-cel can only exert its effect on VOCs after the infusion of Exa-cel has taken place and its effect is only clearly measurable after a washout period of 60 days after the last RBC transfusion for post-transplant management has been completed.

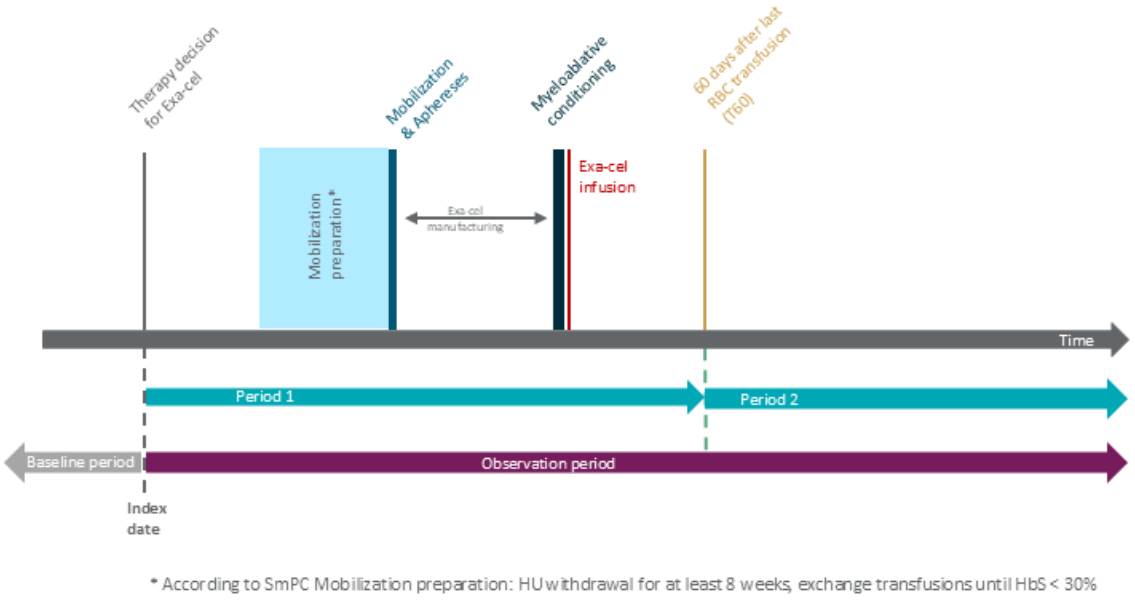

Figure 1: Overview of Exa-cel treatment from therapy decision to end of study and time periods relevant for the AbD at a patient level.

Definitions for time periods and study dates at a patient level and at the study level are provided in Table 3.

Table 3. Definitions of time periods and study dates

Time period / study date	Definition
Study period	The overall study period is from AbD start (exact date will be determined by G-BA) to end of study (EoS).
Patient identification period	The patient identification period will start with the first index date that can be documented in the AbD (after implementing all required changes to the registry) and will continue for 2 years thereafter.
Index date	For Exa-cel patients, the index date is defined as the date of therapy decision for Exa-cel (treatment consent). For SoC patients, the index date is defined as the index date of the Exa-cel patient they were matched to via propensity score.

Time period / study date	Definition
T60	For Exa-cel patients, the time point "60 days after the last RBC transfusion for post-transplant management" is referred to as T60. T60 is not defined for an Exa-cel patient who does not reach that time point during the study (e.g. due to not being infused with Exa-cel). For a SoC patient, the T60 date is defined as the T60 date of the Exa-cel patient they were matched to via propensity score. If the matched Exa-cel patient does not have a T60 date, the SoC patient will also not be assigned a T60 date.
Baseline period	The two-year period prior to the index date is defined as the baseline period for each patient. Use of retrospectively collected data is planned for this period. During this period all confounders will be assessed (see section 12.3 for confounder details).
Observation period	The observation period is defined as the period from the index date to the end of the study or death, withdrawal of consent or loss of follow-up, whichever comes first. For the purpose of analyses, the observation period is divided into two periods, period 1 and period 2, separated by T60.
Period 1	The period from the index date up to and not including T60 or up to the end of the study or death, withdrawal of consent or loss of follow-up, whichever comes first, is defined as period 1.
Period 2	The period from T60 (inclusive) to the end of the study or study discontinuation is defined as period 2.
End of study (EoS)	EoS is reached when all patients with a defined T60 date have either completed 36 months of follow-up starting at T60 or for whom observation was ended prematurely due to death, withdrawal of consent or loss of follow-up.

Patients will be discontinued from the study at time of death, informed consent withdrawal, loss to follow-up, or change to a center not documenting in the GPOH SCD registry.

During the observation period, intercurrent events such as treatment decision for Exa-cel or HSCT for SoC patients may occur. This will not change data collection, which will continue as part of routine clinical practice in the GPOH SCD registry and in the AbD. Information on how intercurrent events will be considered in effect estimation is included in section 12.2 of this protocol and in the statistical analysis plan (SAP).

11.3 Study Population

All patients must meet the requirements for eligibility according to the currently approved EU label for Exa-cel:

Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom hematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA) matched related HSC donor is not available.

All individuals in the GPOH SCD registry fulfilling the inclusion / exclusion criteria will be considered for potential inclusion into the AbD per the Modified Active Comparator New-User (MACNU) design. Eligibility of SoC patients has to be confirmed for each inclusion into an exposure set (see section 11.4.2).

11.3.1 Inclusion Criteria

Patients are eligible to be included in the study if all of the following criteria apply:

1. Residing and treated for their SCD within Germany
2. Severe SCD with recurrent VOCs*
3. Eligible for HSCT and all aspects related to Exa-cel treatment (e.g., full myeloablation, stem cell mobilization, apheresis) according to the assessment of the treating physician**
4. An HLA-matched related HSC donor is not available (discretion of treating physician)
5. ≥12 and <21 years of age at index date
6. Complete records of VOCs leading to hospitalization available in the registry and/or patient's file for at least 2 years prior to index date
7. Receives patient-individualized treatment with HU and / or chronic RBC transfusions at index date
8. Provided written, signed informed consent for their data to be included in the study

* As per label of Exa-cel, severe SCD is defined by the recurrence of VOCs; “recurrent VOCs” for the purposes of this study are aligned to the patient selection criteria for Exa-cel proposed by the Kompetenzcentrum Onkologie (KCO, (1)), where “recurrence” is defined as the occurrence of at least 2 VOCs per year over the course of 2 years. The KCO criteria further define VOCs as any of the following, regardless of hospitalization:

- **acute pain event** requiring a visit to a medical facility and the administration of pain medication *(opioids or intravenous nonsteroidal anti-inflammatory drugs)* or **RBC transfusions**,
- **acute chest syndrome**, confirmed by the appearance of a new **pulmonary infiltrate** accompanied by **pneumonia-like symptoms, pain, or fever**,
- **priapism** lasting longer than **two hours** and requiring a visit to a medical facility,
- **splenic sequestration**, defined by an **enlarged spleen**, **left upper quadrant pain**, and an **acute drop in hemoglobin concentration (Hb) of ≥ 2 g/dL**.

Of note, patients who, due to severe previous VOCs and/or other SCD complications, are receiving chronic RBC transfusion therapy may have no or less than 2 VOCs/year as a consequence of this therapy; such patients are also eligible for the AbD, as per definition their disease severity is sufficiently high to meet the Exa-cel requirements.

** In the context of this study, “eligibility for HSCT” is defined as per the label of Exa-cel, where a full myeloablation is required. In this context the criteria proposed by the KCO should be observed, especially considering the patient’s general condition, absence of organ damage and/or comorbidities which in the opinion of the investigator would prohibit the administration of a full myeloablative conditioning regimen.

Note: Treatment centers are not obliged to but may apply for patient-individual cost-coverage prior to Exa-cel therapy decision. To be able to estimate uncertainties in positivity, patients for whom a cost-coverage application was submitted but denied, who fulfill all inclusion criteria and none of the exclusion criteria, will be included in the study but handled as a separate group for which only patient characteristics will be reported. It will be differentiated whether the assumption of costs was rejected due to clinical or non-clinical (other) reasons. If there are non-clinical reasons, an inclusion of the person in the comparator arm may be considered. All of these patients not included in the comparator arm will be excluded from the Full Analysis Set and consequently not considered for any subsequent analysis.

SCD patients with therapy decision for Exa-cel who do not receive patient-individualized treatment (SoC) (HU and / or chronic RBC transfusions) will not be included in the study, in line with inclusion criterion 7.

SoC patients included in the study may have a treatment decision for a HSCT after index date. How this change in treatment is handled in the analysis is described in section 12.2 of this protocol and in the SAP.

11.3.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Treatment with Exa-cel or any of the agents / procedures used along the Exa-cel treatment journey is contraindicated or not recommended; this includes prior HSCT, pregnant women, active human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B and C virus (HBV and HCV) infections and severe alloimmunization/transfusion reactions that preclude RBC transfusions (discretion of treating physician)
2. Treatment (including preparation to receive treatment) with allogeneic HSCT, with alternative gene therapy or experimental therapies

11.4 Patient Identification

11.4.1 Patient Identification Period

A minimum follow-up time of 36 months starting at T60 is planned for each individual included in the study. In order to fulfill this requirement and comply with the mandated date for final analysis, individuals have to be identified within a *patient identification period*. The patient identification period will start with the first index date that can be documented in the AbD (after implementing all required changes to the registry) and will continue for 2 years thereafter.

Patients for whom an Exa-cel therapy decision is made during the patient identification period will be assigned to the Exa-cel group if they provide their informed consent for use of their data for the purposes of this study. For these patients, the time of the therapy decision for Exa-cel represents the start of the observation period for this study, i.e. the index date.

For each Exa-cel patient, sufficiently similar (in terms of genotype, disease severity and use of chronic transfusions) and potentially eligible patients from the registry receiving patient-individualized treatment will be identified. If these patients are considered by their treating physician to fulfill all inclusion criteria and do not fulfill any of the exclusion criteria, they will be included in the comparator group (SoC) if they provide informed consent for use of their data for the purposes of this study. These patients will remain to be observed in the

comparator group unless a therapy decision for Exa-cel is made for them during the patient identification period, at which point they become an Exa-cel patient. Their index date is linked to the index date of the respective Exa-cel patient they have been matched to (for details see explanation of MACNU design in section 11.4.2).

In case SoC patients have a therapy decision for Exa-cel after the patient identification period, they will remain in the comparator group. Details on how a treatment switch to Exa-cel after the patient identification period or a decision for allogeneic HSCT after inclusion into the SoC group will be handled in the analysis of endpoints are described in section 12.2 of this protocol and the SAP.

All patients for whom Exa-cel therapy was already decided before AbD start will not be included in the study to ensure a focus on prospective data collection after index date.

11.4.2 Modified Active Comparator New-User Design

The inclusion and exclusion criteria of this study (see section 11.3) are based on the EU label of Exa-cel, which defines an SCD population with no clear specificity regarding the following aspects:

- Severity of SCD
- Recurrence of VOCs
- Eligibility of patients for HSCT

The EU label additionally requires patients to be sufficiently fit to undergo an HSCT and able to undergo full myeloablation. According to the criteria proposed by the KCO , patients fulfilling the in- and exclusion criteria of the pivotal study CLIMB-121 are particularly recommended to receive Exa-cel. While being eligible for Exa-cel treatment per EU label wording, the majority of patients on SoC are not expected to be considered for potential treatment with Exa-cel in practice. Therefore, an appropriate patient selection procedure is needed for the study design to form a comparator group that is generally comparable to the Exa-cel group.

All eligible patients for this study are, per inclusion criteria, already on continuous SCD SoC treatment (HU and/or chronic RBC transfusions). For patients who are assigned to the Exa-cel group, the index date (and thus start of observation) is defined as the date of therapy decision for Exa-cel. Patients assigned to the comparator group will continue their SoC treatment. To compare patients of both treatment groups without added bias, a uniform start of observation is defined for all patients. Therefore, one further step after patient selection and inclusion will be taken to identify a meaningful index date for all SoC patients to enable concurrent observation period for the Exa-cel group and the comparator group.

To fulfill the aims outlined above, patient selection and index date assignment for this study will be assigned according to a newly proposed study design named *Modified Active Comparator New-User (MACNU) Design*. The MACNU design is a modification of the Prevalent New-User Design (PNUD) suggested by Suissa et al. (2017) (29). PNUD compares prevalent users of a SoC treatment to new users switching from the established treatment to a new intervention. The PNUD assumes that exposure to patient-individualized treatment, or SoC, (either as number of prescriptions or as time on treatment) represents the severity of the disease and necessitates access to retrospective data on treatment, confounding factors and endpoints of interest. As SCD is an inherited disorder, patients with severe SCD who have recurrent VOCs started SoC therapy early during childhood. Retrospective data of all these

patients from start of their SoC therapy will not be available. Furthermore, the decision for a curative HSCT is not based on pre-treatment experience, but rather on donor availability.

The MACNU design allows for selection of SoC patients with similar disease severity characteristics to the Exa-cel patients, which is essential to ensure comparable treatment cohorts. Hereby, similarity is based on the number of VOCs in the 2 years prior to the index date, genotype and chronic treatment with RBC transfusions.

- The number of VOCs (with hospitalization) in the patient's recent past is a main factor determining the severity of SCD. It is not necessarily only associated with the patient's age but is also very closely related to the success or failure of previous treatments, compliance with treatment and supportive measures. The number of past VOCs leading to hospitalization is also a well-known risk factor for the occurrence of future VOCs.

- While patient eligibility for Exa-cel as well as Exa-cel mode of action and outcomes are genotype-agnostic (30), it is known that the natural course of manifestation of SCD is impacted by genotype. Patients with HbSS and HbSβ^0 genotypes have near identical, severe course of disease with recurrent VOCs and chronic organ damage(31-33). Patients with the HbSβ^+ genotype, on the other hand, may produce on one allele residual levels of beta-globin not affected by the sickle cell mutation and therefore have variable levels of adult Hb (HbA). In a recent publication (34) by the Sickle Cell Disease Study Group of the GPOH, patients with HbSβ^+ genotypes were grouped according to their HbA levels (type 1 and 2 with HbA levels ranging from 1% - 14% and type 3 with HbA levels ≥14%). The clinical outcomes of HbSβ^+ types 1 and 2 were very similar to those of the HbSß^0 genotypes, while patients with HbSβ^+ type 3 genotype experience fewer VOC on average. Around 25% of SCD patients have the HbSC genotype, another compound heterozygous genotype where equal portions of HbS and HbC are produced; this genotype is associated on a population level with a milder course of disease, however HbSC patients can also have severe presentations (35). It is therefore possible that HbSC patients may be included in the AbD. Other genotypes represented in the registry are very rare and are associated with highly diverse phenotypes. To account for this, the following genotype strata are implemented:
    - HbSS, HbS$\beta^{0,}$ HbSβ^+ types 1 and 2 (34)
    - HbSC
    - HbSβ^+ type 3 (34) and other

- Chronic RBC transfusions are another main factor associated with the severity of SCD. They represent a major escalation of SCD therapy, which is carefully chosen by the treating physician, usually triggered by recurrence of VOCs under maximal HU therapy, by life-threatening events like ACS, or when the patient is at high risk for cerebrovascular complications. Patients on chronic RBC transfusions are therefore often those with a poor health state, risk of deterioration, or those with no other treatment option. Finally, if a patient is already on chronic RBC transfusions, this will likely affect the therapy decision for curative therapy options.

Taken together, these 3 variables best reflect disease severity.

The flow chart in Figure 2 illustrates the MACNU design.

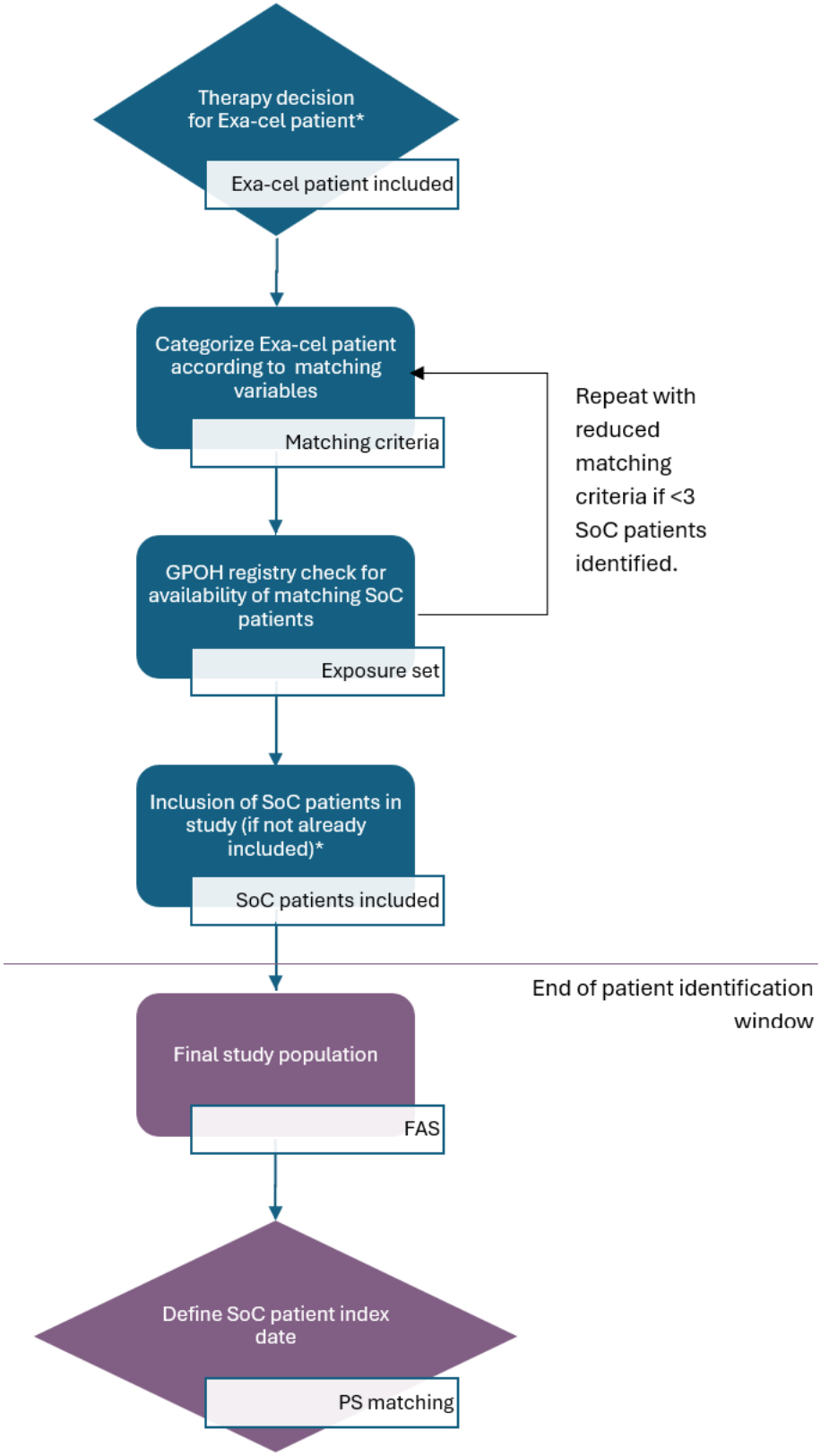

Figure 2 Flow chart of the MACNU design

*Therapy decision has to fall within the patient identification period.

The patient identification process for this AbD and the determination of index dates for each patient included per the MACNU design are explained step-by-step below.

Exa-cel patient included

The steps of the MACNU design are initiated with the first chronological Exa-cel patient included into the study and steps for inclusion of SoC patients are repeated with every new therapy decision for an Exa-cel patient.

Matching criteria

An Exa-cel patient is categorized according to the following 3 variables:

- Treatment with chronic RBC transfusions (yes / no) at therapy decision for the Exa-cel patient
- Number of VOCs leading to hospitalization during the baseline period defined as the year before therapy decision for the Exa-cel patient, categorized as 0, 1-2, ≥3
- Genotype group: HbSS, HbSβ0, HbSβ+ types 1 and 2 or HbSC or HbSβ+ type 3 (34) and other

Exposure set

Once the decision has been made to treat a patient with Exa-cel and patient is categorized according to the matching criteria, the GPOH SCD registry will be checked for availability of eligible SoC patients who have comparable patient characteristics (as per matching criteria above) with regard to the three stratification factors at the time of the index date of the Exa-cel patient.

Once a SoC patient has been identified within the GPOH SCD registry, the documenting center will be asked to confirm that all inclusion and exclusion criteria for the AbD are met (including frequency of VOCs (regardless of hospitalization) and the treating physician's assessment of eligibility for full myeloablation e.g. following the guidance provided in the KCO checklist); if that is the case, patients will be asked to sign an Informed consent form (ICF) for the AbD (if not already included) and thereafter be included in the study.

If at least 3 SoC patients are not identified and consented to match the Exa-cel patient, the matching criteria will be reduced:

- Criterion "genotype" will be eliminated (resulting in 6 strata), and the GPOH SCD registry will be searched for patients again.

If even after criterion "genotype" was eliminated, still less than three SoC patients are identified, the repetition will be stopped and the 0-2 SoC patients will be accepted.

The enrolled SoC patients are assigned to that Exa-cel patient to form an exposure set.

Accordingly, an exposure set is a set of SoC patients with comparable patient characteristics at the time a decision is made for a given patient to receive Exa-cel therapy.

Note: The term „exposure set" is defined in the PNUD based on their exposure to SoC (either with the duration on treatment or with the number of prescriptions); although in this design it is no longer defined on exposure to SoC, the term is still kept.

For each patient included in the study with a treatment decision for Exa-cel during the patient identification period, an exposure set is defined at the time of treatment decision. A SoC patient may be included in multiple exposure sets.

Formation of the study population at the end of the patient identification period:

The study cohort will consist of:

- all patients who have had a therapy decision for Exa-cel within the identification period and who have provided their ICF for use of their data in the study
- all SoC patients who have been identified for at least one exposure set and who have provided their ICF for use of their data in the study

Each patient who signed ICF is included in the study and remains in the study cohort, even if:

- a patient was included as a SoC patient for an exposure set, but the corresponding Exa-cel patient discontinued and never received Exa-cel
- a patient was included as a SoC patient, but had a therapy decision for Exa-cel during the identification period, in which case the new Exa-cel patient will trigger the steps of the MACNU design and will no longer be part of the exposure sets previously assigned to

Use of time-conditional propensity scores to determine index dates for all SoC patients at the end of patient identification period:

SoC patients included in the study might be included in more than one exposure set, with time-conditional characteristics (stratification factors). It is therefore necessary to select only one exposure set for each SoC patient that defines their index date.

A stepwise approach to select the index date for each SoC patient will be used:

1. Calculate time-conditional propensity score (PS) using a conditional logistic regression model with the stratification factors (with number of VOCs as continuous variable) included on stacked exposure sets
2. Match each Exa-cel patient with up to one SoC patient from the respective exposure set (as available) based on time-conditional PS in chronological order (first new user of Exa-cel therapy in calendar time is matched first to an SoC patient based on nearest neighbor matching)
3. Matching without replacement induces that once a SoC patient is matched, the patient is no longer available for further subsequent matching
4. When all Exa-cel patients have been considered consecutively for matching within their exposure sets, matching of the remaining SoC patients continues by repeating the above (step 2) until all SoC patients have been matched. The identified index date for a SoC patient is thus the aligned date with the therapy decision date (index date) of the matched Exa-cel patient.

Note that this matching procedure is only implemented to assign index dates to the included SoC patients; matches will not be used to adjust for confounding in effect estimation for endpoints.

Figure 3 shows exemplary treatment patterns for patients identified in line with the MACNU design. For an overview of definitions for time periods and study dates, see Table 3.

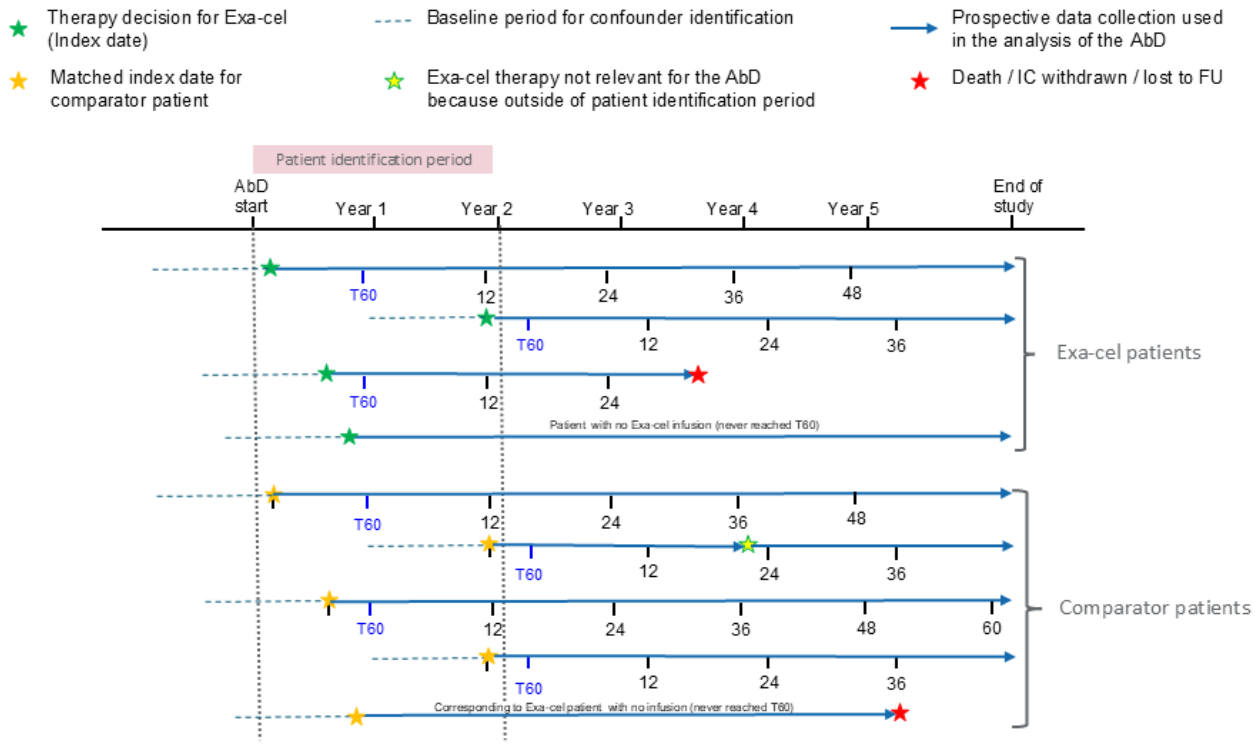

Figure 3: Exemplary treatment patterns, formation of exposure sets and allocation to Exa-cel and comparator group

The four top blue arrows represent four exemplary patients with a therapy decision for Exa-cel during the patient identification period. Time of treatment decision corresponds to their index dates, presented as green stars. The patients are observed from index date to end of study (EoS) or study discontinuation due to death, withdrawal of informed consent, change to a center not documenting in the GPOH SCD registry or loss to follow-up (red star). These four patients belong to the Exa-cel group.

The lower five blue arrows represent five further exemplary patients with no treatment decision for Exa-cel within the patient identification period. These patients are matched to the upper Exa-cel patients and have the same matched index dates (yellow stars) as their matched Exa-cel patients. The patients are observed from matched index date to EoS or censoring due to death, withdrawal of informed consent, change to a non-participating center, or loss to follow-up (red star). These five patients belong to the SoC comparator group.

The numbers below the timelines indicate the number of months after T60 (time point '60 days after last RBC transfusion for post-transplant management'). EoS is dependent on the last patient identified during the identification period to be observed for 36 months after T60.

Alternative approach for the MACNU design described above

Since the MACNU design is to identify eligible SoC patients who are sufficiently similar to any Exa-cel patient and to assign meaningful index dates, an alternative approach for the MACNU design is only meaningful during the identification window. Therefore, a futility analysis during the identification period (as outlined in the SAP) will be conducted to examine whether, at this time, a sufficient number of patients have been included for the planned sample size goal (outlined in section 12.5) at the end of the patient identification period.

If the number of Exa-cel patients is lower than expected, continued conduct of the study will be discussed with G-BA.

Considering the number of enrolled SoC patients at this time, a futility criterion is defined to decide whether the MACNU design can continue as planned. The futility criterion defines the probability that continuing enrollment as up to this point the planned sample size is expected

to be achievable at the end of the identification (see section 13 for details). If not achievable, the MACNU design will be modified from this point onwards: Once a new Exa-cel patient is identified, the exposure set for this Exa-cel patient will only contain SoC patients who are not yet included in another exposure set, i.e. have not yet been included in the study. This means that, starting at this point, all new SoC patients will only be included in one exposure set, and previously included SoC patients will not be considered for future exposure sets. This alternative approach ensures each new exposure set contains at least three newly enrolled SoC patients (potentially by reducing the matching criteria) and exposure sets from that time point onward do not overlap any more. This will increase the number of SoC patients enrolled and aims to ensure that a sufficient number of SoC patients will be included in the study. If this modified approach still deems insufficient to reach the planned sample size, continued conduct of the study will be discussed with G-BA.

11.5 Variables

For each individual, patient demographic and clinical characteristics as well as a broad range of safety and effectiveness outcomes will be collected according to Table 4.

The baseline value of a variable is the closest measurement before or at index date during the two-year baseline period.

Table 4: Variables and their operationalization

Variable	Operationalization
Demographics and Baseline characteristics*	
Inclusion criteria • Residing and treated for their SCD within Germany • Severe SCD with recurrent VOCs[a] • Eligible for HSCT and all aspects related to Exa-cel treatment (e.g., full myeloablation, stem cell mobilization, apheresis) according to the assessment of the treating physician[b] • An HLA-matched related HSC donor is not available (discretion of treating physician) • ≥12 and <21 years of age at index date • Complete records of VOCs leading to hospitalization available in the registry and/or patient's file for at least 2 years prior to index date • Receives patient-individualized treatment with HU and / or chronic RBC transfusions at index date	Yes / no for each [a] As per label of Exa-cel, severe SCD is defined by the recurrence of VOCs; "recurrent VOCs" for the purposes of this study are aligned to the patient selection criteria for Exa-cel proposed by the Kompetenzcentrum Onkologie (KCO, (1)), where "recurrence" is defined as the occurrence of at least 2 VOCs per year over the course of 2 years. The KCO criteria further define VOCs as any of the following, regardless of hospitalization: •acute pain event requiring a visit to a medical facility and the administration of pain medication (opioids or intravenous nonsteroidal anti-inflammatory drugs) or RBC transfusions, •acute chest syndrome, confirmed by the appearance of a new pulmonary infiltrate accompanied by pneumonia-like symptoms, pain, or fever, •priapism lasting longer than two hours and requiring a visit to a medical facility, •splenic sequestration, defined by an enlarged spleen, left upper quadrant pain, and an acute drop in hemoglobin concentration (Hb) of ≥ 2 g/dL.

Variable	Operationalization
• Provided written, signed informed consent for their data to be included in the study Exclusion criteria • Treatment with Exa-cel or any of the agents / procedures used along the Exa-cel treatment journey is contraindicated or not recommended; this includes prior HSCT, pregnant women, active human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B and C virus (HBV and HCV) infections and severe alloimmunization/transfusion reactions that preclude RBC transfusions (discretion of treating physician) • Treatment (including preparation to receive treatment) with allogeneic HSCT, alternative gene therapy or experimental therapies	Of note, patients who, due to severe previous VOCs and/or other SCD complications, are receiving chronic RBC transfusion therapy may have none or less than 2 VOCs/year as a consequence of this therapy; such patients are also eligible for the AbD, as per definition their disease severity is sufficiently high to meet the Exa-cel requirements. [b] In the context of this study, "eligibility for HSCT" is defined as per the label of Exa-cel, where a full myeloablation is required. In this context the criteria proposed by the KCO should be observed, especially considering the patient's general condition, absence of organ damage and/or comorbidities which in the opinion of the investigator would prohibit the administration of a full myeloablative conditioning regimen. If not eligible for HSCT, specify reason
Sex	Male / female
Age (years) at index date	Age at index date
Body height	cm
Body weight	kg
Genotype	Diagnosis / subtype: HbSS, HbSC, HbSß0 Thal, HbSß+ Thal type 1, 2 or 3, other
Age (years) at diagnosis	Age at diagnosis
Prior and concomitant diseases (including chronic SCD complications) • Nephropathy • Chronic pain • Hepatopathy • Pulmonary hypertension • Cerebrovascular event (prior stroke, neurological deficit) • Alloimmunization • Siderosis (iron overload) • Endocrine dysfunction • Cardiomyopathy • Osteoporosis	Yes / no If endocrine dysfunction or „Other underlying diseases", specify and code according to Medical Dictionary for Regulatory Activities (MedDRA) If yes, date of first diagnosis and ongoing yes/no

Variable	Operationalization
• Proliferative retinopathy • Ulcus cruris • Gallstones • Aseptic osteonecrosis (incl. status post-surgical correction) • Asplenia • „Other underlying diseases“	
Smoking regularly	Yes / no
Alpha-thalassemia	Yes / no Among patients with “yes”, specify genotype
Modifiers of fetal hemoglobin (HbF) synthesis	Yes / no Among patients with “yes”, specify genotype
Total hemoglobin (Hb)	g/dL
Sickle cell hemoglobin (HbS) level	% of total Hb
Fetal Hb (HbF) level	% of total Hb
Number of VOCs	Start and end date of VOCs over 24 months prior to index date VOC defined as hospitalization with overnight stay for any of the following: • Priapism: yes / no • Splenic sequestration(s): yes / no • Acute chest syndrome(s) (ACS): yes / no • Pain crises: yes / no
Other SCD complications	Any complication at baseline yes / no and by type (see below). Other SCD complications are defined as either one of the following occurring: low Hb, pulmonary complications (excluding pulmonary hypertension), splenectomy/asplenia, ulcus cruris, aseptic osteonecrosis
Chronic transfusion therapy	Yes / no Among patients with “yes”: Number of chronic transfusions in past 12 months prior to index date, total volume per year (ml), Type (exchange transfusions, erythrocyte apheresis, on top transfusion)
HU therapy	Yes / no Among patients with “yes”: dose (mg/kg*d), start date Among patients with “no”: stop date if applicable, reason (neutropenia, anemia, thrombopenia, nausea, cutaneous side effects, other side effects, desire to

Variable	Operationalization
	have children, pregnancy, lack of efficacy, inadequate increase of HbF, start of chronic transfusions, patient's decision, other)
Acute transfusions within 12 months prior to index date	• Number • Total volume of acute transfusions per year (ml) • Type (exchange transfusion, erythrocyte apheresis, on top transfusion)
Splenectomy	Yes / no
Prior and concomitant medication • Infection prophylaxis • Pain medication • Iron chelation / phlebotomy • Other	Yes /no for each Among patients with "yes": start and stop date, verbatim coded per WHODRUG
Variables for morbidity endpoints	
Number of VOCs	Start and end date of all VOCs defined as hospitalization with overnight stay for any of the following: • Priapism: yes / no • Splenic sequestration(s): yes / no • Acute thorax syndrome(s) (ACS): yes / no • Pain crises: yes / no
Variables for safety endpoints including mortality	
Serious adverse events (SAE):	• Term (coded via MedDRA PT) • Start date, stop date, ongoing • Seriousness (death, hospitalization) • CTCAE grade • Relatedness / causality assessment (underlying condition, medicinal product coded with WHODRUG, other) • Medication changed due to event (yes / no) • Outcome (resolved yes / no)
Death	• Date of death dd/mm/yyyy • Relatedness / causality assessment (underlying condition, medicinal product coded with WHODRUG, other) • Cause of death: Sepsis, splenic sequestration, acute chest syndrome, cerebral infarction, Girdle syndrome, aplastic crisis, pulmonary hypertension, cardiac insufficiency, perioperative complication, sudden death without apparent cause, other cause related to SCD, probable cause unrelated to SCD

Variable	Operationalization
Variables for Exa-cel therapy	
Exa-cel therapy 1. Mobilization (incl. preparation) 2. Apheresis 3. Conditioning 4. Infusion 5. Post-infusion	1. Number of mobilization cycles, start date of HU withdrawal, start date exchange transfusion, plerixafor dose or if other agent used name and dose of the other mobilization agent, date of first day of mobilization 2. Number of cycles, start date of each apheresis cycle 3. Conditioning agent, date start of conditioning, dose, posology (qd, q6, other), total AUC 4. Date of infusion, total Exa-cel dose infused 5. Date patient weaned off from post-transplant RBC transfusions, date neutrophil engraftment achieved (3 consecutive measurements of absolute neutrophil count (ANC) ≥500 cells/µL on 3 different days after Exa-cel infusion, without use of the unmodified rescue CD34+ cells), date thrombocyte engraftment achieved (3 consecutive measurements of platelet counts ≥50 × 10^9/L obtained on 3 different days after Exa-cel infusion without administration of platelet transfusions for 7 days), date hospital discharge
Discontinuation from Exa-cel therapy journey before infusion	Date and reason for discontinuation
Variables for treatment exposure	
HU therapy (including changes to existing HU therapy or de novo prescriptions)	• Start date, stop date, ongoing • Dose (mg/kg*d) • Reason for start (bridge therapy yes / no, ACS yes / no, pain crisis yes / no, increased Transcranial Doppler (TCD) velocity yes / no, prior cerebrovascular event yes / no, chronic pain yes / no, symptomatic anemia yes / no, priapism yes / no, other) • Reason for discontinuation (planned during Exa-cel treatment regimen, neutropenia, anemia, thrombopenia, nausea, cutaneous side effects, other side effects, desire to have children, pregnancy, lack of efficacy, inadequate increase of HbF, start of chronic transfusions, patient's decision, other)

Variable	Operationalization
Acute RBC transfusions	• Number • Total volume (ml), as estimated from the average volume of red cell units • Start date, stop date
Chronic RBC transfusions	• Number • Total volume (ml), as estimated from the average volume of red cell units • Start date, End date
Therapy decision for Exa-cel outside of patient identification period	Yes / no Among patients with "yes": reason, date
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Yes / no Among patients with "yes": reason, date
Eligibility for HSCT according to the assessment of the treating physician	Yes / no Among patients with "no": reason, date
Variables for study discontinuation	
Reason for study discontinuation	• Date of last contact: mm/dd/yyyy • Reason for study discontinuation: change to a non-participating center, consent to inclusion in the AbD withdrawn, LFU: lost contact or moved away unknown, deceased • Date of death: mm/dd/yyyy • Cause of death: Sepsis, splenic sequestration, acute chest syndrome, cerebral infarction, Girdle syndrome, aplastic crisis, pulmonary hypertension, cardiac insufficiency, perioperative complication, sudden death without apparent cause, other cause related to SCD, probable cause unrelated to SCD Description: free text entry

* Baseline characteristics are taken in the two-year period before or at therapy decision unless otherwise specified

11.6 Confounder Operationalization

Table 5: Operationalization of confounders relevant for adjusted analysis

Confounder variable	Operationalization	Collection time or window
Age (years) at index date	Age	Index date
Alloimmunization	Yes / no	Value closest to index date within baseline period
Cerebrovascular event (prior stroke, neurological deficit)	Yes / no	Value closest to index date within baseline period
Chronic pain	Yes / no	Value closest to index date within baseline period
Chronic transfusion therapy	Yes / no	Value closest to index date within baseline period
HbF level	% of total Hb	Value closest to index date within baseline period
Hepatopathy	Yes / no	Value closest to index date within baseline period
Nephropathy	Yes / no	Value closest to index date within baseline period
Other SCD complications	Any complication at baseline yes / no and by type (see below). Other SCD complications are defined as either one of the following occurring: low Hb, pulmonary complications (excluding pulmonary hypertension), splenectomy/ asplenia, ulcus cruris, aseptic osteonecrosis	Any other SCD complications during baseline period
Pulmonary hypertension	Yes / no	Value closest to index date within baseline period
Sex	Male / female	Any
Siderosis (iron overload)	Yes / no	Value closest to index date within baseline period
Number of VOCs	Number of VOCs over 2 years prior to index date VOC defined as hospitalization with overnight stay for any of the following: • Priapism: yes / no • Splenic sequestration(s): yes / no • Acute chest syndrome(s) (ACS): yes / no • Pain crises: yes / no	Number of VOCs within entire baseline period

For confounder age, the derived value at index date will be used as confounding variable.

Sex is assumed to be constant, and any collection time point will be considered acceptable.

VOCs and other SCD complications are identified by start and stop date to be within baseline period or not. The total number of VOCs collected during the baseline period will be used as confounding variable. If the patient experienced any SCD complications during the baseline period, the confounding variable will be “Yes”.

11.7 Data Management

Data management for the AbD is conducted by the GPOH SCD registry. Therefore, the same electronic data capture (EDC) system will be used for the AbD, and for patients in the AbD additional fields will be populated in the EDC system; in brief, data are documented by the centers participating in the AbD into the MARVIN-RDE system and stored in the MARVIN-RDE database operated by XClinical company servers.

The study uses data (retrospective- and prospective) recorded in the GPOH SCD registry. Use of retrospective data is limited to baseline characteristics including confounders and only for those patients who have granted their informed consent and waived data privacy privileges for the purposes of the AbD.

For patients participating in the AbD, (preferably) quarterly documentation of their routine clinical data (as available) is targeted. To facilitate data entry, documentation aids may be made available upon request by the documenting center to the GPOH SCD registry.

11.8 Quality Control

As the AbD will be implemented based on the GPOH SCD registry, the same principles for standardization of the data entry are applied in the AbD. This is achieved through the use of a coding manual and training of the staff responsible for data entry. Data are checked for plausibility using automated queries. For patients included in the AbD, additional automatic and manual plausibility checks will be implemented. Discrepancies are clarified with the documenting center and implausible data are corrected. These measures increase the likelihood of high data quality.

11.8.1 Study Monitoring

On-site monitoring for source data verification (SDV) is performed by a UKHD representative (personnel different from the site staff who perform entry) on the basis of all available patient records. The frequency of on-site monitoring visits is determined based on the number of enrolled patients and the quality of the site’s data documentation: for each study site, a site visit is planned after the inclusion of five patients or one year after inclusion of the first patient, before data cuts for each interim analysis and before the data cut for the final analysis.

Patient informed consent (PIC) will be verified for each patient. SDV for 100% of patients per center for eligibility of patients for the AbD, the primary endpoint (VOCs leading to hospitalization) and for at least 10% of randomly selected AbD patients per center for all other endpoints, including dates, over the period since the start of data collection for this study will be performed. On average, 2.5 on-site visits per site are expected to be conducted per center. SDV will be possible for each patient with PIC.

However, it is important to note that after patients reach the age of 21 years, a change of treating site/physician is likely in the course of the study, especially in the SoC group, which may bring some uncertainties regarding the possibilities and limitations of performing SDV as part of this study; this is particularly relevant if the patient re-locates or starts treatment at a center which is not participating in the GPOH SCD registry or the AbD. If necessary, changes to the possible extent of SDV will be depicted in an amendment to the study project plan.

11.8.2 Audits and Inspections

For quality assurance reasons the sponsor or a third party on behalf of the sponsor may conduct quality assurance audits at any time during or following the study. Regulatory agencies may conduct inspections. The physician must agree to allow auditors and inspectors direct access to all study-related documents including source documents and must agree to allocate his/her time and the time of his/her study staff to the auditors/inspectors in order to discuss findings, issues and potential remedies. All persons involved are bound to maintain strict confidentiality concerning the identification of the patients.

11.8.3 Control of Data Entered in the eCRF

During the electronic data entry in the eCRF, data are automatically checked for plausibility by programmed edit checks. Incomplete data fields in the eCRF are clearly labelled as incomplete (red symbols). Other discrepancies may be clarified by addressing manual queries to the site within the eCRF. eCRF entries are screened for potential unreported adverse events according to the manual ‘Inhouse Review for unreported (S)AEs’.

There will be a regular reconciliation between the adverse events documented in the study database and in the safety database. Due to the non-interventional character of the study, missing values and/or implausibility may persist and will not be corrected.

12 STATISTICAL METHODS

This section presents key information on the planned analyses for this study. The full details of the analyses are provided in the SAP.

12.1 General Considerations

All objectives will compare patients in the Exa-cel group to patients in the patient-individualized treatment (SoC) group. All endpoints, both co-primary and secondary, will be summarized descriptively for both treatment groups and analyzed comparatively unless specified otherwise.

Continuous variables will be summarized using the following descriptive summary statistics where appropriate: the number of observations and patients with missing values, mean, standard deviation (SD), 95% confidence interval (CI) for the mean, median, minimum value (min), maximum value (max), and 25^{th} and 75^{th} percentile values.

Categorical variables will be summarized using counts, percentages, and 95% CIs for the proportion as appropriate.

For all endpoints, **comparative analyses** will include adjustment for confounding factors (see section 12.3) using PS methods. The analysis strategy to compare Exa-cel patients against SoC patients will comprise a two-step approach:

1) One-time calculation of PS based on baseline characteristics for each analysis set and endpoint category to be used as weights in the comparative analyses
2) Comparative, PS-adjusted analysis for all endpoints

Baseline value of a variable (including confounders but excluding number of VOCs) is defined as the closest measurement before or at index date during the baseline period.

Baseline value for confounder "Number of VOCs" is the number of VOCs leading to hospitalization (as documented in the GPOH SCD registry) during the two-year baseline period.

Annualized rate of VOCs for each period will only be calculated in patients with at least 9 months (assumed minimum duration of period 1) of observation for the respective period.

The following analysis sets are defined:

The **Full Analysis Set (FAS)** comprises all Exa-cel patients and all SoC patients included in the study except those for whom reimbursement of Exa-cel therapy was not secured. The FAS will be used for all analyses of period 1.

Of note, SoC patients matched to Exa-cel patients excluded from FAS due to reimbursement not secured will remain in the FAS.

The **Full Analysis Set period 2 (FAS Period 2)** is defined as a subset of FAS patients that did not discontinue the study before their T60 date. FAS Period 2 will be used for the analyses in period 2 except the co-primary endpoint of VOC freedom.

The **Full Analysis Set 36 (FAS36)** is defined as a subset of FAS Period 2 patients with at least 36 months of follow-up starting from T60. FAS36 will be used for analysis of VOC freedom.

Hereby, T60 is defined as described in Table 3. Periods 1 and 2 are defined in section 11.2 on Study Design. For analysis in period 2, patients will be included only if they did not discontinue the study before their T60 date.

Analysis periods

Endpoints will be analyzed for the following analysis periods:

Table 6: Analysis strategy for endpoints

Endpoint	Period 1	Period 2
Annualized rate of VOCs	Yes	Yes (primary)
VOC freedom over 36 months		Yes (primary)
Death	Yes	Yes
SAEs	Yes	Yes

Serious adverse events (SAEs) during period 1 will additionally be analyzed split into the following sub-periods patients receiving Exa-cel:

- Index date to first mobilization (time from index date to start of mobilization)
- Mobilization & apheresis (start of first mobilization until last day of apheresis of last apheresis cycle)
- Between apheresis and conditioning (day after last day of apheresis of last apheresis cycle until day before start of conditioning)
- Conditioning to infusion (start of conditioning until day before Exa-cel infusion)
- Infusion to T60 (Exa-cel infusion to 60 days after last RBC transfusion for post-transplant management)

For patients in the SoC group with a therapy decision for Exa-cel (or any alternative gene therapy or experimental therapy or allogeneic HSCT), SAEs occurring starting from the timepoint of therapy decision will be analyzed descriptively for periods 1 and 2 and additionally split into the above sub-periods.

12.2 Analysis Strategy

In this study, the assessment of VOCs for the study objectives are defined as VOC leading to hospitalization for any of the following events: pain crises, acute chest syndrome (ACS), priapism or splenic sequestration.

Primary objectives

For the co-primary endpoints of VOC freedom and the annualized VOC rate, the following intercurrent events (ICEs) will be considered:

- Therapy decision for Exa-cel outside of patient identification period (SoC group only)
- Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT

- HSCT or any aspects related to Exa-cel treatment (e.g., full myeloablation, stem cell mobilization, apheresis) according to the assessment of the treating physician are no longer appropriate

A change within SoC therapy, including changes to dose and frequency of HU or chronic transfusions, is considered part of the SoC treatment regimen and will not be considered intercurrent events.

Table 7 summarizes the analysis strategy for the primary endpoint **VOC freedom (in period 2)** within the estimand framework.

Table 7: Analysis strategy for VOC freedom, Period 2

VOC freedom, Period 2	**Primary Estimand**
Treatment	Exa-cel vs. patient-individualized treatment (SoC)
Population	FAS36
Endpoint	Proportion of patients VOC-free over 36 months
Analysis period	Period 2 (T60 until 36 months after T60)
Population-level summary	Risk ratio
Handling of ICE	
Therapy decision for Exa-cel outside of patient identification period[a]	Treatment policy
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Hypothetical[b]
HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate[a]	Treatment policy
Analysis (Estimator)	
Confounder[c] adjustment method	Calculation of weights based on PS
Analysis model	Log binomial regression model including weights
a: Potential ICE for SoC group only b: Hypothetical strategy: Data up to the ICE will be used for analysis assuming the calculated endpoint for the patient represents the scenario for the whole study period had the ICE not occurred. c: Missing values in confounders will be imputed using Multiple Imputation.	

For the primary endpoint VOC freedom, the analysis of period 2, i.e. starting at T60, is of primary interest. ICEs “therapy decision for Exa-cel outside of patient identification period” and “HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate” are handled via Treatment Policy approach: Once an ICE occurs, no censoring happens, and patients continue to be observed until 36 months after T60. ICE “therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT” will be handled using Hypothetical strategy: Only data up to the ICE will be used for analysis. A patient having such an ICE is no longer considered representative of the population compared in the AbD from that point forward. Treatment groups will be compared via risk ratio, estimated from a weighted log binomial regression model.

Table 8 summarizes the analysis strategy for the primary endpoint **annualized VOC rate in period 2** within the estimand framework.

Table 8: Analysis strategy for annualized VOC rate, Period 2

Annualized VOC rate, Period 2	**Primary Estimand**
Treatment	Exa-cel vs. patient-individualized treatment (SoC)
Population	FAS, period 2
Endpoint	Annualized VOC rate
Analysis period	Period 2 (T60 until EoS)
Population-level summary	Rate ratio
Handling of ICE	
Therapy decision for Exa-cel outside of patient identification period[a]	Hypothetical[b]
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Hypothetical[b]
HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate[a]	Treatment policy
Analysis (Estimator)	
Confounder[c] adjustment method	Calculation of weights based on PS
Analysis model	Negative binomial regression model including weights with log (follow-up time in years) as offset
a: Potential ICE for SoC group only b: Hypothetical strategy: Data up to the ICE will be used for analysis assuming the calculated endpoint for the patient represents the scenario for the whole study period had the ICE not occurred. c: Missing values in confounders will be imputed using Multiple Imputation	

In this analysis of the annualized VOC rate on period 2, starting at T60, the ICE "HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICEs "therapy decision for Exa-cel outside of patient identification period" and "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT", the Hypothetical approach is used: Only data up to the ICE will be used for analysis. It is assumed that the calculated endpoint for the patient represents the scenario for the whole study period, had the ICE not occurred. The Hypothetical approach for "therapy decision for Exa-cel outside of patient identification period" is used, as it is expected that transplantation with Exa-cel has a significant impact on VOC rate. In addition, it is expected that a relevant portion of matched SoC patients will start with Exa-cel even after the patient identification period. Including such data in the comparison makes it impossible to estimate the treatment effect of Exa-cel over SoC. A patient having a "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT" is not considered representative of the population compared in the AbD from that point forward.

For the composite endpoints annualized VOC rate for period 1&2, descriptive analyses will be performed for each VOC component (pain crises, ACS, priapism, splenic sequestration) as secondary endpoints (SAP section 9.8.2 Secondary Endpoints).

Secondary Objectives

Table 9 summarizes the analysis strategy for the secondary endpoint **annualized VOC rate for period 1** within the estimand framework.

Table 9: Analysis strategy for annualized VOC rate, Period 1

Annualized VOC rate, Period 1	**Primary Estimand**
Treatment	Exa-cel vs. patient-individualized treatment (SoC)
Population	FAS
Endpoint	Annualized VOC rate
Analysis period	Period 1
Population-level summary	Rate ratio
Handling of ICE	
Therapy decision for Exa-cel outside of patient identification period[a]	Hypothetical[b]
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Hypothetical[b]
HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate	Treatment policy
Analysis (Estimator)	
Confounder[c] adjustment method	Calculation of weights based on PS
Analysis model	Negative binomial regression model including weights with log (follow-up time in years) as offset
a: Potential ICE for SoC group only b: Hypothetical strategy: Data up to the ICE will be used for analysis assuming the calculated endpoint for the patient represents the scenario for the whole study period had the ICE not occurred. c: Missing values in confounders will be imputed using Multiple Imputation.	

Annualized VOC rate during period 1 will be analyzed analogous to period 2. The ICE "HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICEs "therapy decision for Exa-cel outside of patient identification period" and "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT", the Hypothetical approach is used: Only data up to the ICE will be used for analysis. It is assumed that the calculated endpoint for the patient represents the scenario for the whole study period, had the ICE not occurred. Treatment groups will be compared via rate ratio, estimated from a weighted negative binomial regression model with log (follow-up time in years) as offset in the model.

Endpoints where a proportion of patients having an event is compared between treatment groups (e.g. proportion of patients with SAEs) will use the risk ratio derived from a weighted log binomial regression model. Endpoints where the annualized rate of an event occurring is compared between treatment groups (e.g. annualized rate of death, annualized SAE rate) will use the rate ratio derived from a weighted negative binomial regression model with log (follow-up time in years) as offset. For further details on the analysis and handling of ICEs, see SAP.

12.3 Propensity Score Methods for Confounder Adjustment

Comparative analyses between Exa-cel and SoC treatment groups for all endpoints will be performed using PS weights to adjust for potential confounding.

As different analysis sets are used depending on the endpoint, all steps in the PS procedure to obtain an adjusted effect estimate will be conducted on relevant analysis sets independently of each other.

Confounding factors

To be able to account for relevant differences in baseline characteristics, a systematic identification of confounders in the indication SCD was carried out. The procedure was based on a publication by Pufulete et al. from 2022 (36) and comprised a literature search as well as the involvement of clinical experts. Further details on the methodological approach can be found in the report attached as a reference (37).

The following 13 confounders (including ranking for each endpoint category) that are relevant in the context of statistical evaluation of endpoints in a non-interventional study were identified and will be considered for PS weighting:

Table 10: Confounders relevant for adjusted analysis

Ranking for each endpoint category			Confounder	Operationalization used in adjustment
VOCs	Mortality	SAEs		
1	1	1	Siderosis (Iron overload)	Categorical (yes / no)
2	11	7	Chronic pain	Categorical (yes / no)
3	8	11	Number of VOCs	Continuous (number of VOCs recorded in baseline period)
4	2	6	Cerebrovascular event (prior stroke, neurological deficit)	Categorical (yes / no)
5	3	4	Pulmonary hypertension	Categorical (yes / no)
6	4	2	Nephropathy	Categorical (yes / no)
7	5	3	Hepatopathy	Categorical (yes / no)
8	6	5	Age (years) at index date	Continuous (in years)
9	10	9	Chronic transfusion therapy	Categorical (yes / no)

Ranking for each endpoint category			Confounder	Operationalization used in adjustment
VOCs	Mortality	SAEs		
10	7	12	HbF level	Continuous (% of total Hb at baseline)
11	9	10	Other SCD complications	Categorical (yes / no)
12	12	8	Alloimmunization	Categorical (yes / no)
13	13	13	Sex	Categorical (male / female)

The operationalization of these confounders is described in section 11.6.

Multiple Imputation will be performed to impute missing confounder values before PS estimation. Details of the steps for PS estimation and PS adjustment can be found in the SAP.

Effect estimation

For the co-primary endpoint **VOC freedom**, the objective is to compare Exa-cel vs. SoC regarding the proportion of patients who are VOC-free over 36 months, starting at T60 (period 2). To achieve this, on each imputed and weighted dataset of the FAS36 patients in period 2, the risk ratio with 95% confidence interval (CI) will be estimated via log binomial regression model with treatment group as the independent variable and including the PS weights.

The effect estimates are then pooled across all imputed datasets via Rubin's rule. The resulting risk ratio estimate is then tested against the shifted null hypothesis H_0: risk ratio=2.0. Superiority of Exa-cel is shown if the lower bound of the 95% CI is >2.0.

For the co-primary endpoint **annualized VOC rate**, the objective is to compare Exa-cel vs. SoC regarding the annualized VOC rate for period 2. On each imputed and weighted dataset of FAS Period 2 patients, the rate ratio with 95% CI will be estimated via negative binomial regression with treatment as the independent variable and including the PS weights and using log(follow-up in years) as offset in the model.

The effect estimates are then pooled across all imputed datasets. The rate ratio is tested against the shifted null hypothesis H_0: rate ratio=0.5. Superiority of Exa-cel is shown if the upper bound of the 95% CI is <0.5.

For the **secondary endpoints**, the risk ratio or the rate ratio will be estimated via weighted log binomial or negative binomial regression respectively. No testing against a shifted null hypothesis will be performed. For details, see the SAP.

If any model for effect estimation does not converge, stepwise removal of confounders will be performed as described in SAP.

To interpret the results in the context of confounder adjustment in this non-interventional study, the resulting imputed analysis populations are compared against the initial analysis sets descriptively based on baseline characteristics. Implications regarding generalizability of results onto the whole patient population and limitations regarding the adjustment process will be discussed.

12.4 Subgroup Analysis and Sensitivity Analysis

12.4.1 Subgroup Analysis

Subgroup analyses will be conducted for all endpoints by adding the subgroup as another independent variable and treatment × subgroup interaction term to the logistic regression and the negative binomial regression, respectively. Additionally, for each endpoint and each subgroup, an interaction p-value will be presented derived from the same model (SAP section 9.10).

Subgroup analyses will be performed for the following baseline characteristics:

- Sex (female vs. male)
- Number of VOCs during baseline period (0 vs. 1-2 vs. ≥3)

A subgroup analysis for a specific endpoint and subgroup combination will only be performed if both of the following rules apply:

1. Each subgroup level includes at least 10 patients across both treatment groups *and*
2. For binary endpoints, at least 10 events occur in at least one subgroup level combined across both treatment groups in the time period.

12.5 Sample Size Consideration

Because of the intended potential functional cure of the Exa-cel therapy, the primary goal is to prevent patients suffering from severe VOCs leading to hospitalization. This will be analyzed via two primary endpoints: the proportion of responders where freedom from severe VOC leading to hospitalization over 36 months in period 2 is considered a response as well as the annualized rate of severe VOCs leading to hospitalization in period 2.

Sample size required for the AbD is based on the sample size required for the analysis of each endpoint separately.

12.5.1 Sample Size Considerations VOC Freedom

The proportion of responders in Period 2 for Exa-cel vs SoC is compared by a risk ratio analyzed via log binomial regression in FAS36 (see Table 7).

Based on CLIMB-121/131 data, we will assume an Exa-cel response rate of 91.3%.

For SoC group no direct estimate is available and we will assume a response rate of 16.0% to 25.0% following discussions with G-BA.

For drop-out rate, we will assume 18% in the Exa-cel group based on CLIMB-121/131 data. For SoC group a considerably higher drop-out rate to complete the 36 months of follow-up is expected (higher number of patients expected to withdraw consent as in the Exa-cel group and increasing number of patients in the SoC group receiving therapy decision for Exa-cel). Therefore, a drop-out rate of 50% will be assumed for the comparator arm.

Table 11 shows the required assumptions and sample size for VOC freedom over 36 months for FAS36.

Table 11 Sample size assumptions and calculation for freedom of severe VOCs leading to hospitalization over 3 years following T60 (FAS36)

Parameter	Assumption		
Estimate	Risk Ratio		
Analysis method	Log binomial regression model		
Power	80%		
Alpha	0.05 (two-sided)		
Shifted null hypothesis	2.0		
Allocation ratio	1:2		
Exa-cel response rate	91.3%		
SoC response rate	25.0%	20.0%	16.0%
Evaluable patients*	81 (27 on Exa-cel, 54 on SoC)	51 (17 on Exa-cel, 34 on SoC)	38 (13 on Exa-cel, 25 on SoC)
Drop-out rate	18% for Exa-cel 50% for SoC		
Total sample size	141 (33 on Exa-cel, 108 on SoC)	89 (21 on Exa-cel, 68 on SoC)	66 (16 on Exa-cel, 50 on SoC)

*Derived via R function nBinomial from gsDesign package.

Therefore, 141 (33 Exa-cel and 108 SoC) patients will have to be enrolled in the AbD to have at least 80% power to show superiority of Exa-cel vs SoC risk ratio against a shifted null hypothesis of 2.0 for freedom of VOCs leading to hospitalization over at least 3 years measured from T60 onwards in FAS36 assuming an SoC response rate of 25.0%.

12.5.2 Sample Size Considerations Annualized VOC Rate

The annualized rate of severe VOCs leading to hospitalization in Period 2 for Exa-cel vs SoC is compared by a rate ratio analyzed via negative binomial regression in FAS Period 2 (see Table 8).

Based on CLIMB-121/131 data we can assume an Exa-cel annualized rate during period 2 of 0.1. For drop-out rate, we will assume 18% for FAS Period 2 following CLIMB-121/131 discontinuations.

For the dispersion factor, as an estimate derived from information from CLIMB-121 study, analysis of US MarketScan database and Mahesri et al. 2024 (38), a factor of 0.34 will be assumed.

Further assumptions are presented in Table 12.

Table 12 Assumptions for sample size for annualized rate of severe VOCs leading to hospitalization in Period 2 (FAS Period 2)

Parameter	Assumption			
Estimate	Rate Ratio			
Analysis method	Negative binomial regression model			
Power	80%			
Alpha	0.05 (two-sided)			
Shifted null hypothesis	0.5			
Allocation ratio	1:2			
Exa-cel annualized rate	0.1			
SoC annualized rate	3.0	2.5	2.0	1.5
Fixed exposure time	3 years			
Overdispersion factor	0.34			
Evaluable patients	14 (5 on Exa-cel, 9 on SoC)	15 (5 on Exa-cel, 10 on SoC)	18 (6 on Exa-cel, 12 on SoC)	24 (8 on Exa-cel, 16 on SoC)
Drop-out rate	18%			
Sample size*	18 (6 on Exa-cel, 12 on SoC)	21 (7 on Exa-cel, 14 on SoC)	24 (8 on Exa-cel, 16 on SoC)	30 (10 on Exa-cel, 20 on SoC)

*Derived via R function getSampleSizeCounts from rpact package.

12.5.3 Sample Size Conclusions

At least 141 (33 Exa-cel and 108 SoC) patients have to be enrolled in the AbD to have at least 80% power to show superiority of Exa-cel vs SoC in terms of freedom of VOCs leading to hospitalization over at least 3 years measured from T60 onwards in FAS36. This sample size will also suffice to have more than 80% power to show superiority for Exa-cel over SoC in terms of annualized rate of severe VOCs in period 2 for FAS Period 2.

This sample size is expected to also suffice to adjust for all confounders. If not, confounders will be removed from analysis as needed and discussed as described in more detail in SAP.

13 PLANNED REPORTS

The following status reports, interim reports and final report are planned according to the requirements in the resolution by G-BA (Table 13). All dates refer to the study start date, which will be defined by G-BA. Note: The patient identification period will start with the first index date that can be documented in the AbD (after implementing all required changes to the registry) and will continue for 2 years thereafter.

Table 13: Planned reports to G-BA

Report	Date	Content
Status report 1	6 months after study start defined by the G-BA	As no patient is anticipated to be enrolled after 6 months (study still in set-up phase), only information about study set-up will be included; presented in the status report template (39)
Interim report 1 and status report 2	18 months after study start	At this time it is expected that the identification window is open for some months only with very few patients already enrolled (all patients in period 1); interim analysis results include disposition, baseline characteristics and descriptive safety analysis; presented in module 4 of the dossier template (40) Information on patient inclusion; presented in the status report template (39)
Futility analysis regarding required MACNU design adaptation*	14 months after start of identification period	Review of SoC response rate to reassess assumptions for sample size derivation Review of number of Exa-cel and SoC patients included (see below) Review of necessity to switch to alternative MACNU approach (as per section 11.4.2)
Interim report 2 and status report 3	36 months after study start Data cut: 32 months after study start	It is expected that at this time the identification period has already been closed; interim analysis results including disposition, baseline characteristics and descriptive analyses for annualized VOC rate during period 1 as well as descriptive safety analysis by period presented in module 4 of the dossier template (40) Futility analysis for study success Information on patient inclusion; presented in the status report template (39)

Report	Date	Content
Status report 4	54 months after study start Data cut: 50 months after study start	Information on patient inclusion; presented in the status report template (39)
Final report	Expected 6 months after EoS	Final analysis presented in module 4 of the dossier template (40)

*Interim analysis not requested by G-BA

Futility analysis regarding required MACNU design adaptation

A futility analysis will be conducted 14 months after start of the identification period to assess whether the study will meet the required sample size for final analysis using the MACNU design for study inclusion.

The futility analysis will examine the SoC response rate, the total number of patients included in the study and the number of patients in each of the SoC and Exa-cel groups in the FAS at that time.

If the observed SoC response rate is higher than the assumed SoC response rate of 25.0%, the sample size will be recalculated with an updated SoC response rate.

If the number of Exa-cel patients is according to expectations, but the recruitment of SoC group is behind expectations, the alternative approach for the MACNU design (see section 11.4.2) will be applied. Recruitment of SoC patients will be considered behind expectations of currently planned sample size, if less than

$$\frac{14}{24} * Total\ number\ of\ SoC\ patients\ to\ be\ recruited = 63$$

patients are in the SoC group at time of futility analysis. Recruitment into Exa-cel group is considered behind expectations of currently planned sample size, if less than

$$\frac{14}{24} * Total\ number\ of\ Exacel\ patients\ to\ be\ recruited = 20$$

patients are in the Exa-cel group at time of futility analysis.

If the number of Exa-cel patients is lower than expected, continued conduct of or alterations to the study will be discussed with G-BA.

Futility analysis for study success (interim report 2)

At the second interim report, the final number of included patients is compared against the current sample size assessment. Continued conduct of or alterations to the study based on this futility assessment will be discussed with G-BA.

Content of reports

Interim analyses will include a disposition table, descriptive summary of baseline characteristics in the total patient population and by treatment group, descriptive safety analyses, as applicable, at IA1 and descriptive analyses of endpoints during period 1 at IA2. For details, see the SAP.

For the final report, all analyses will be presented according to the specifications of the SAP.

14 LIMITATIONS OF RESEARCH METHODS

This is a non-interventional study based on the observation of routine practice with secondary use of data. Assessments are not mandatory but are based solely on routine medical care and the procedures followed at the treatment centers. Data collection will be conducted in a standardized manner (uniform electronic case report form [eCRF]) to avoid differences between centers or data entry personnel as well as missing and incorrect entries. There could be a difference in visit routine and therefore reporting frequency between Exa-cel and SoC, with more routine visits for patients treated with Exa-cel than SoC patients, potentially leading to reporting bias.

Missing data are an important potential limitation. This can be caused by patients no longer visiting the center (lost to follow-up), no longer giving the necessary informed consent (e.g. when patients turn 18 and need to be re-consented), or by data being entered into the database incompletely or with a delay.

Center staff are advised to make any reasonable effort to follow-up on missing data and obtain relevant medical records (e.g. via the primary treating physician, if possible) and to track the reason for missing visits (e.g. relocation) as carefully as possible.

All staff entering data into the study database should be able to demonstrate training for the MARVIN software and in particular be trained in the study protocol and data entry that differs from standard registry entry.

Regular monitoring of the data should ensure the completeness and accuracy of the data. See section 11.8.1 for more details.

Every effort will be made to minimize missing or erroneous data, but complete elimination may not be achieved. Suitable statistical methods will be applied to account for incomplete or missing data, as described in the SAP.

According to AbD methodology, at least 100 patients need to be enrolled in the study to ensure adequate confounder control. As all AbD patients need to be, in general, eligible for Exa-cel to assure positivity, the sample size needs to be set in relation to the overall eligible patient population. The Exa-cel eligible patient population in Germany, as acknowledged by the G-BA, is 130 to 330 patients (midpoint 230). The age group of ≥12 to <21 years is represented by 286 patients in the registry (age at registration, data as of 10/2025). The median follow-up time is 3 years. The feasibility of recruitment for the AbD will depend on the willingness of patients to consent.

The G-BA resolution addresses the challenges involved in a comparative study without randomization. The selection criteria for patient inclusion into this study ensure that all patients are eligible for Exa-cel and at least one of the comparator treatments (positivity). However, eligibility for Exa-cel treatment depends on a number of examinations that are not part of routine care unless a patient is considered to receive HSCT. Therefore, patients in the comparator arm are likely not going to have all assessments done as requested by KCO checklist for Exa-cel and therefore in these patients merely the expert physician judgment determines eligibility as the best possible approximation. All eligible patients fulfilling the selection criteria and who have a therapy decision for Exa-cel or were selected for at least one exposure set similar to an Exa-cel patient during the identification period (see study design) are planned to be included in the study. For patients eventually observed in the study, the bias due to confounders will be dealt with using suitable statistical methods, as outlined in section 12.3 of this protocol and detailed in the SAP.

15 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

15.1 Changes / Amendments to Protocol

Protocol modifications may become necessary during the course of the study, especially when requested by G-BA. Modifications will require approval from Vertex and relevant study stakeholders.

15.2 Ethical Considerations

The study will be conducted in accordance with the ethical, legal and regulatory requirements, including the declaration of Helsinki in the currently valid form.

15.3 Patient Information and Informed Consent

All patients need to have provided written informed consent for participation in the GPOH SCD registry. Before being included in the study, each patient and / or the parents / legal representatives of the patient will be informed by the treating physician about the nature, aims, expected benefits, possible risks and duration of the study and will be asked to sign an additional informed consent for participation in the study. In the case of underage patients, the parents / legal representatives of the patient are informed and can sign the declaration of consent. The presumed will of the patient must be taken into account. If an underage patient is capable of recognizing the nature, significance and scope of the consent and can express their will accordingly, they will also be informed in an appropriate form and can give their consent. For this purpose, the patient information document is available in child-friendly and age-appropriate wording for different age groups. If a patient reaches 18 years of age while in the study, they will be asked by the treating center for their continued consent to be included in the study. If the patient does not give consent, inclusion in the study is terminated.

The patient and / or the parents / legal representatives of the patient must be given sufficient time and opportunity to decide on their inclusion and clarify any unanswered questions before giving consent. The declaration of consent must be personally dated and signed by the patient and / or both parents / legal representatives and the treating physician.

15.4 Patient Privacy

The patient data collected as part of the study is documented by the treating center directly in the database. The data are given a pseudonym (numerical code) and the personal identifying data (IDAT) are kept physically separated from the medical data (MDAT) in accordance with §40 German Federal Data Protection Act (*Bundesdatenschutzgesetz*, BDSG). Only the administrator, the study management and the documenting center have access to the personal identifying data. Compliance with the relevant regulations is regularly audited. The data are processed in accordance with the regulations of the General Data Protection Regulation (GDPR).

Data on individual patients will no longer be collected if consent has been withdrawn. If a patient withdraws consent to be included in the study, the data collected so far will be deleted.

Vertex will not have access to patient-identifying information.

15.5 Reporting of Safety Information to the Sponsor

The reporting procedures defined below by this non-interventional study protocol are applicable to study patients after therapy decision to receive Exa-cel via commercial availability.

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

15.5.1 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 (these SAE shall also be captured in the study database)
  - Life-threatening
  - Requires hospitalization or prolongation of existing hospitalization (these SAE shall also be captured in the study database)
  - 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 one of the outcomes listed above (e.g., a new hematologic malignancy diagnosis).

  Of note: VOCs leading to hospitalization are considered disease-related events and will therefore not be additionally captured as SAEs in the study database, however these still need to be reported to the sponsor as an SAE (see section 15.7 below).

15.6 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 14.

Table 14: 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.

15.7 SAE Reporting Procedure

All SAEs observed in patients after therapy decision to receive Exa-cel via commercial availability, regardless of the presumed relationship to Exa-cel regimen exposure, must be reported to the Marketing Authorization Holder (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.

SAE reporting is required from the time informed consent and assent, where applicable, is signed and while the patient is included in the study, for all SAEs that occur at any time after initiation of mobilization stage of the Exa-cel regimen. Complete and comprehensive case information must be documented and causality assessments performed.

Reportable AEs meeting seriousness criteria should be reported by the investigator in an expedited manner (e.g. **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

15.8 Pregnancy Reporting

If a female patient or female partner of a male patient becomes pregnant after therapy decision to be 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.

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17 SIGNATURE PAGE

17.1 Sponsor Signature Page

Protocol #: VX##-###-###	**Version #:**	**Version Date:**
Study Title:		

This Protocol has been reviewed and approved by:

<Vertex Sponsor>

_____ _____

Printed Name Title

_____ _____

Signature Date

18 PROTOCOL APPROVAL AND SIGN-OFF

I confirm that I have read the contents of this document and its attachments. I approve the document in its current form.

Vertex Pharmaceuticals Europe LTD

Print name here	Signature	Date

19 REVISION HISTORY

Version	Date	Changes made and reasons for change
1.0	13-Jun-2025	N/A, first version
2.0	16-Oct-2025	Title page: Insertion of the Vertex Study Number (administrative) Omission of the GPOH SCD registry, which declined to participate due to its inability to meet the G-BA requirements; adjustment of data sources Update of comparator treatment definition and intercurrent events following G-BA request Update of HU therapy recording within Exa-cel group following G-BA request Insertion of PRO collection (Morbidity/Pain and Health-related quality of life) according to G-BA review Amendment of selection criteria (inclusion criterion #3 to include all aspects related to Exa-cel treatment; inclusion criterion #8 to specify clinical and PRO data; exclusion criterion #1 to include any of the agents / procedures used during the Exa-cel treatment journey; exclusion criteria #2 to exclude treatment with alternative gene therapy or experimental therapies) according to G-BA review Revision of sample estimation following G-BA recommendation Expansion of the list of specific AEs with scientific justification according to G-BA review Study design: Clarification of retrospective data collection only for baseline characteristics according to G-BA review Addition to the possibilities for securing reimbursement for Exa-cel therapy; clarification that patients will be excluded from the FAS if reimbursement is not secured according to G-BA review Revision of the MACNU design and the alternative approach for the MACNU design, adaptation to the modified study design without a registry, according to G-BA review Update the list of variables according to the new study design without registry, inclusion of PROs, inclusion of specific AEs, and according to G-BA review Adjustments and clarifications of various aspects of statistical methods according to the new study design without registry and according to G-BA review Inclusion of a schedule of data collection according to G-BA review Addition of sections on data management, quality control including monitoring, retention of documents, audits and inspections, and control of data entered in the eCRF according to the new study design without registry Update of the list of confounding factors according to G-BA review Update of study futility criterion following G-BA review
3.0	21-May-2026	Title page: Insertion of the Vertex Study Number (administrative) Data Source: Re-inclusion of GPOH SCD registry as key data source following adjusted G-BA requirements; utilizing GPOH SCD registry infrastructure Identification period start: clarified start of identification period as the first index date that can be documented after implementing all required changes to the GPOH SCD registry Population & age restriction: Updated population to include patients ≥12 to <21 years of age following G-BA proposal to reflect GPOH SCD registry set-up Inclusion criteria: clarification of definition of “severe SCD” and recurrent VOC in accordance with the KCO eligibility criteria; Chronic RBC transfusion patients eligible with <2 VOCs/year Exclusion criteria: Updated exclusion criteria 1 to include patients with severe alloimmunization/transfusion reactions that preclude RBC transfusions (discretion of treating physician)

Version	Date	Changes made and reasons for change
3.0 (continued)		Key endpoints: Secondary endpoints limited to mortality + SAE rates. PROs, chronic organ damage assessments, specific AE tracking removed SAE operationalization change: SAEs narrowed to "adverse events leading to hospitalization or prolonging existing hospitalization, or result in death" Baseline period extension: Introduced 2-year baseline period to reflect KCO criteria time period MACNU design modifications: Age removed as matching criterion following population update; genotype added as primary stratification factor following feedback from GPOH SCD registry Sample size & feasibility: Recalculated sample size considering population change; added feasibility considerations Data collection & monitoring: Updated source data verification Reimbursement & inclusion criteria: Added new provision of handling of patients with denied cost-coverage Comparator definition: Adjusted to reflect only HU and/or chronic RBC transfusions; allogeneic HSCT (incl. MUD) now exclusion criterion Interim analysis strategy: Adjusted timing and scope of interim and futility analyses Confounder adjustment: Added endpoint-specific confounder prioritization; added more details on operationalization of confounders

VERTEX PHARMACEUTICALS (EUROPE) LIMITED

Statistical Analysis Plan (Methods)

Non-interventional Study

Routine practice data collection to compare Exagamglogene autotemcel with patient-individualized treatment in severe sickle cell disease: A prospective non-interventional study mandated by G-BA

Version: 3.0 final

Version Date of SAP: 21 May 2026

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street London,
W2 6BD, UK

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AbD	Routine practice data collection (*Anwendungsbegleitende Datenerhebung*)
ACS	Acute thorax syndrome
AE	Adverse event
ANC	Absolute neutrophil count
ATE	Average treatment effect
ATO	Average Treatment Effect on the Overlap Set
AUC	Area under the curve
CD	Cluster of differentiation
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EoS	End of study
Exa-cel	Exagamglogene autotemcel
FAS	Full Analysis Set
FS	Fine stratification
G-BA	Federal Joint Committee (*Gemeinsamer Bundesausschuss*)
GPOH	Society for Pediatric Oncology and Hematology *(Gesellschaft für Pädiatrische Onkologie und Hämatologie)*
Hb	Hemoglobin
HbF	Fetal hemoglobin
HbS	Sickle cell hemoglobin
HbSC	Hemoglobin SC
HbSS	Hemoglobin SS
HLA	Human leukocyte antigen
HSC(T)	Hematopoietic stem cell (transplantation)
HU	Hydroxycarbamide (Hydroxyurea)
IA	Interim analysis
ICE	Intercurrent event
IPTW	Inverse probability of treatment weighting
IQWiG	Institute for Quality and Efficiency in Health Care *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)*
KCO	Medical services of the German payers *(Kompetenzcentrum Onkologie der Medizinischen Dienste)*
LFU	Lost to follow-up
MACNU Design	Modified Active Comparator New-User Design
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MICE	Multiple imputation by chained equations
OW	Overlap weighting
PICO	Population, Intervention, Comparator, Outcome
PRO	Patient reported endpoint
PS	Propensity score

Abbreviation	Definition
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sickle cell disease
SD	Standard deviation
SMD	Standardized mean difference
SoC	Standard of care
TCD	Transcranial doppler
VOC	Vaso-occlusive crisis
WHODRUG	World Health Organization drug dictionary

5 MODIFICATIONS TO STATISTICAL ANALYSIS

Table 1: History of modifications to statistical analysis

SAP Version	Version Date	List of changes compared to previous version, including justification
1.0	13 June 2025	Not applicable
2.0	16 October 2025	Version number and version date have been updated. Implemented mandated changes from G-BA resolution of 18 September 2025: • Update of comparator arm and intercurrent events following G-BA request. • Updates resulting from change of study from registry-based to site-faced, specifically variable operation. • Clarified that VOCs leading to hospitalization are recorded as disease-related events and not additionally as SAEs. • Detailed the multiple imputation procedure. • Added criteria for assessing balance and overlap. • Provided additional details on regression models, including specification of the offset term. • Added analyses for additional secondary endpoints individual components of the VOC endpoints, AE of special interest and PROs. • Update of analysis sets to clarify reimbursement and Period 2 analyses. • Added explanation of how propensity scores will be incorporated into subgroup analyses. • Added explanation of how missing values in endpoints will be handled. • Added explanation regarding the handling of shifted null hypotheses. • Adjusted dates for interim analysis and study futility criterion. • Updated list of confounders and confounder ranking.
3.0	21 May 2026	Alignment with updates in protocol v3 including definition of analysis sets, population in terms of age, list of endpoints, SAE definition, baseline definition Disposition summary added Minimum observation time for calculation of annualized rate added.

6 INTRODUCTION

This statistical analysis plan (SAP) addresses the primary and secondary objectives of the routine practice data collection (*Anwendungsbegleitende Datenerhebung*, AbD) for Exagamglogene autotemcel (Exa-cel, Casgevy®) mandated by the German payer authority Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA) and documents all planned statistical analyses. It is based on the study protocol, dated 21 May 2026, Version 3.0.

This AbD is a non-interventional, prospective, comparative study in patients ≥12 to <21 years old with severe sickle cell disease (SCD). Real-world data generated in this study is to be used for the benefit assessment of Exa-cel according to §35a Social Code Book V in Germany.

7 STUDY OBJECTIVES AND ENDPOINTS

The aim of this study is to evaluate the effectiveness and safety of Exa-cel compared with patient-individualized treatment in patients with severe SCD with recurrent vaso-occlusive crises (VOCs). Information on **P**opulation, **I**ntervention, **C**omparator and **O**utcome (PICO) is outlined in Table 2.

Table 2: PICO scheme of the present study

Population	Patients aged ≥12 to <21 years with severe SCD with recurrent VOCs* for whom hematopoietic stem cell transplantation (HSCT) is appropriate** and a human leukocyte antigen (HLA)-matched related HSC donor is not available.
Intervention	Exa-cel
Comparator	• Hydroxycarbamide • Chronic red blood cell (RBC) transfusions
Outcome	Objectives and endpoints of this study are presented in detail in Table 3.

* As per label of Exa-cel, severe SCD is defined by the recurrence of VOCs; "recurrent VOCs" for the purposes of this study are aligned to the patient selection criteria for Exa-cel proposed by the Kompetenzcentrum Onkologie (KCO), where "recurrence" is defined as the occurrence of at least 2 VOCs per year over the course of 2 years. The KCO criteria further define VOCs as any of the following, regardless of hospitalization:

- **acute pain event** requiring a visit to a medical facility and the administration of pain medication *(opioids or intravenous nonsteroidal anti-inflammatory drugs)* or **RBC transfusions**,
- **acute chest syndrome**, confirmed by the appearance of a new **pulmonary infiltrate** accompanied by **pneumonia-like symptoms, pain, or fever**,
- **priapism** lasting longer than **two hours** and requiring a visit to a medical facility,
- **splenic sequestration**, defined by an **enlarged spleen**, **left upper quadrant pain**, and an **acute drop in hemoglobin concentration (Hb) of ≥ 2 g/dL**.

Of note, patients who, due to previous severe VOCs and/or other SCD complications, are receiving chronic RBC transfusion therapy may have no or less than 2 VOCs/year as a consequence of this therapy; such patients are also eligible for the AbD, as per definition their disease severity is sufficiently high to meet the Exa-cel requirements.

** In the context of this study, "eligibility for HSCT" is defined as per the label of Exa-cel, where a full myeloablation is required. In this context the criteria proposed by the KCO should be observed, especially considering the patient's general condition, absence of organ damage and/or comorbidities which in the opinion of the investigator would prohibit the administration of a full myeloablative conditioning regimen.

Severe SCD, as a chronic disease, is characterized by recurrent VOCs, that lead to pain, progressive tissue injury, organ dysfunction, impaired quality of life and premature death. The prevention of VOCs (freedom from VOCs) and the reduction of VOCs are therefore the main treatment goals of Exa-cel.

Accordingly, the two co-primary objectives in this study are as follows:

- To compare the annualized VOC rate between Exa-cel and patient-individualized treatment referred to as Standard of Care (SoC), and
- To compare the proportion of VOC-free patients over 36 months, between Exa-cel and SoC.

In this study, the assessment of VOCs for the study objectives are defined as hospitalization for VOC for any of the following events: pain crises, acute chest syndrome (ACS), priapism or splenic sequestration.

For the comparison of the proportion of VOC-free patients over 36 months and annualized VOC rate, it is appropriate that the 36-month period starts from 60 days after last RBC transfusion for post-transplant management (T60). To provide the complete picture from treatment decision, annualized VOC rate will also be analyzed from treatment decision to T60 (Period 1).

The following table provides an overview of the specific objectives and endpoints in this study.

Table 3: Objectives and endpoints

Objective	Endpoint with respective analysis period(s)[a]
Primary	
Morbidity	
To compare the annualized rate of VOCs	Annualized VOC rate in Period 2[a]
To compare the proportion of VOC-free patients over 36 months	Proportion of responders where VOC freedom over 36 months in Period 2 is considered a response
Secondary	
Morbidity	
To compare the annualized rate of VOCs	Annualized VOC rate in Period 1
Mortality	
To compare the occurrence of death	• Proportion of patients who died by period • Annualized death rate by period
Safety	
To compare the occurrence of SAEs (adverse events leading to hospitalization or prolonging an existing hospitalization, or result in death)	• Proportion of patients with SAEs by period • Annualized rate of SAEs by period
a: For definitions of analysis periods, see section 9.2	

8 OVERALL STUDY DESIGN AND POPULATION

This is a prospective, non-interventional, comparative study conducted as an AbD mandated by the G-BA. The study uses (retrospective and prospective) data recorded in the GPOH SCD registry. Use of retrospective data is limited to baseline characteristics including confounders. Data will be collected only for those patients who have granted their informed consent and waived data privacy privileges for the purposes of the AbD.

As this is a non-interventional study, no stipulations regarding patient treatment, visit frequencies or monitoring will be provided by the protocol. All eligible patients are to receive patient-individual treatment for their SCD as prescribed by their treating physician at inclusion and the therapy decision for Exa-cel is made independently of the decision to include a patient in the study. SCD treatment at time of inclusion can only consist of HU, and /or chronic RBC transfusions.

The observation period for each patient will start with therapy decision for Exa-cel (i.e., index date). For SoC patients, the observation period starts at index date of the matched Exa-cel patient. From the index date onwards, data from both Exa-cel and SoC patients will be collected until end of study.

Patients must meet the requirements for eligibility according to the currently approved EU label for Exa-cel and must reside and be treated for their SCD within Germany. Patients for whom an Exa-cel therapy decision (treatment consent) is made during the patient identification period will be assigned to the Exa-cel group if they provide their informed consent for use of their data for the purposes of this study. Index date for Exa-cel patients will be set at the time of therapy decision. For each Exa-cel patient, sufficiently similar (in terms of age, disease severity and use of chronic transfusions) and potentially eligible patients receiving patient-individualized treatment will be identified. If these patients are considered by their treating physician to fulfill all inclusion criteria and do not fulfill any of the exclusion criteria, they will be included in the comparator group (SoC) if they provide informed consent for use of their data for the purposes of this study. These patients will remain in the comparator group provided that no therapy decision for Exa-cel is made for them during the patient identification period. Their index date is linked to the index date of the respective Exa-cel patient they have been matched to using the *Modified Active Comparator New-User Design* (MACNU) outlined in protocol section 11.4.2. The MACNU design allows for selection of SoC patients with similar disease severity characteristics to the Exa-cel patients and furthermore allows the identification of meaningful index dates for all patients in the comparator group.

The treatment journey for Exa-cel includes several consecutive phases: mobilization preparation (withdrawal of HU for at least 8 weeks and exchange transfusions to reduce HbS levels <30%), mobilization and apheresis (it is expected that the majority of patients will require multiple mobilization and apheresis cycles, each separated by at least 2 weeks), Exa-cel manufacturing, myeloablative conditioning, Exa-cel infusion and waiting for engraftment of the infused edited HSCs. After Exa-cel infusion, all patients require RBC transfusions for post-transplant management with variable (individual) duration.

In order to be able to assign treatment effects to Exa-cel and not to the RBC transfusions, a washout period of 60 days after last RBC transfusion is defined. T60 is the time point for

separating the observation period for analysis of outcomes (Period 1 and Period 2). Period 1 encompasses the time from treatment decision until T60; Period 2 starts at T60 and represents the follow-up period of at least 36 months required to assess the co-primary endpoint of VOC freedom over 36 months. Like the index date, T60 for SoC patients is determined based on the matched Exa-cel patient.

9 STATISTICAL ANALYSIS

9.1 General Considerations

All objectives will compare patients in the Exa-cel group to SoC patients both descriptively and using comparative analysis unless specified otherwise. For all endpoints, **comparative analyses** will include adjustment for confounding factors using propensity score (PS) methods, explained in detail in section 9.9.

Continuous variables will be summarized using the following descriptive summary statistics where appropriate: the number of observations and patients with missing values, mean, standard deviation (SD), 95% confidence interval (CI), median, minimum value (min), maximum value (max), and 25^{th} and 75^{th} percentile values.

Categorical variables will be summarized using counts, percentages, and 95% CIs as appropriate.

Baseline value of a variable (including confounders but excluding number of VOCs) is defined as the closest measurement before or at index date during the baseline period.

Baseline value for confounder "Number of VOCs" is the number of VOCs leading to hospitalization (as documented in the GPOH SCD registry) during the two-year baseline period.

Incomplete or missing values will be dealt with in the following way:

For start and stop dates, e.g., of study treatment or concomitant medication initiation and discontinuation or clinical events, partially missing data will be imputed. For missing values in the day, the missing date will be set to the first of the month for start dates and to the last of the month for stop dates. Missing month values in dates will not be imputed, and date will be considered missing. Instead, efforts will be made to minimize missing values during collection.

Missing values in confounding variables used in PS estimation will be imputed; see section 9.9.1 for details.

For missing values in endpoints, the number of patients with missing values will be reported for each endpoint. Methods to account for missing values in analyses are described in section 9.8.

Annualized rate of VOCs for each period will only be calculated in patients with at least 9 months (assumed minimum duration of Period 1) of observation for the respective period.

9.2 Time Periods and Time Points Relevant to Analysis

Table 4 provides an overview of definitions for time periods and study dates relevant to analysis. All endpoints will be analyzed separately for both Period 1 and Period 2. Exceptions and other relevant sub-time periods are described in section 9.8 for each endpoint where they apply.

Table 4: Definitions for time periods and study dates

Time period / study date	Definition
Study period	The overall study period is from AbD start (exact date will be determined by G-BA) to end of study (EoS).
Patient identification period	The patient identification period will start with the first index date that can be documented in the AbD (after implementing all required changes to the registry) and will continue for 2 years thereafter.
Index date	For Exa-cel patients, the index date is defined as the date of therapy decision for Exa-cel (treatment consent). For SoC patients, the index date is defined as the index date of the Exa-cel patient they were matched to via propensity score.
T60	For Exa-cel patients, the time point "60 days after the last RBC transfusion for post-transplant management" is referred to as T60. T60 is not defined for an Exa-cel patient who does not reach that time point during the study (e.g. due to not being infused with Exa-cel). For a SoC patient, the T60 date is defined as the T60 date of the Exa-cel patient they were matched to via propensity score. If the matched Exa-cel patient does not have a T60 date, the SoC patient will also not be assigned a T60 date.
Baseline period	The two-year period prior to the index date is defined as baseline period for each patient. Use of retrospective data collection is planned for this period. During this period all confounders will be assessed (see section 9.9.1)
Observation period	The observation period is defined as the period from the index date to the end of the study or death, withdrawal of consent or loss of follow-up, whichever comes first. For the purpose of analyses, the observation period is divided into two periods, Period 1 and Period 2, separated by T60.
Period 1	The period from the index date up to and not including T60 or to the end of the study or death, withdrawal of consent or loss of follow-up, whichever comes first, is defined as Period 1.
Period 2	The period from T60 (inclusive) to the end of the study or study discontinuation is defined as Period 2.

Time period / study date	Definition
End of study (EoS)	EoS is reached when all patients with a defined T60 date have either completed 36 months of follow-up starting at T60 or for whom observation was ended prematurely due to death, withdrawal of consent or loss of follow-up.

Patients will be discontinued from the study at time of death, informed consent withdrawal, loss to follow-up, or change to a center not documenting in the GPOH SCD registry.

During the observation period, intercurrent events such as treatment decision for Exa-cel or HSCT for SoC patients may occur. This will not change data collection, which will continue as part of routine clinical practice in the GPOH SCD registry and in the AbD. Information on how intercurrent events will be considered in effect estimation is available in section 9.8.

9.3 Analysis Sets

The following analysis sets are defined:

The **Full Analysis Set (FAS)** comprises all Exa-cel patients and all SoC patients included in the study except those for whom reimbursement of Exa-cel therapy was not secured. The FAS will be used for all analyses of Period 1.

Note: Treatment centers are not obliged to but may apply for patient-individual cost-coverage prior to Exa-cel therapy decision. To be able to estimate uncertainties in positivity, patients for whom a cost-coverage application was submitted but denied, who fulfill all inclusion criteria and none of the exclusion criteria, will be included in the study but handled as a separate group for which only patient characteristics will be reported. It will be differentiated whether the assumption of costs was rejected due to clinical or non-clinical (other) reasons. If there are non-clinical reasons, an inclusion of the person in the comparator arm may be considered. All of these patients not included in the comparator arm will be excluded from the FAS and consequently not considered for any subsequent analysis.

Of note, SoC patients matched to Exa-cel patients excluded from FAS due to reimbursement not secured will remain in the FAS.

The **Full Analysis Set Period 2 (FAS Period 2)** is defined as a subset of FAS patients that did not discontinue the study before their T60 date. FAS Period 2 will be used for the analyses in Period 2 except the co-primary endpoint of VOC freedom.

The **Full Analysis Set 36 (FAS36)** is defined as the subset of FAS Period 2 patients with at least 36 months of follow-up starting from T60. FAS36 will be used for analysis of VOC freedom.

Hereby, T60, Period 1 and Period 2 are defined as described in Table 4. For analysis in Period 2, patients will be included only if they did not discontinue the study before their T60 date.

9.4 Disposition

Disposition will be summarized based on FAS, using descriptive statistics, including number and percentage of patients of

- FAS
- FAS, Period 2
- FAS36
- Completed study
- Discontinued study
    - Change to a non-participating center
    - Consent to inclusion in the AbD withdrawn
    - LFU: lost contact or moved away unknown
    - Deceased
- Discontinued Exa-cel therapy
    - Reason for discontinuation

Percentages will be based on FAS. Percentages for reason for discontinuation will be based on the number of patients discontinued.

Exa-cel patients excluded from FAS due to reimbursement not secured will be presented separately together with the reason, if applicable.

9.5 Baseline Characteristics

Baseline characteristics will be summarized based on the FAS, using descriptive statistics.

Baseline characteristics for Exa-cel patients excluded from FAS due to reimbursement not secured will be summarized separately.

Baseline characteristics comprise basic demographic characteristics, disease and past treatment characteristics and all confounders that were identified systematically using a literature review and expert input.

Baseline characteristics will include the following:

Table 5: Demographics and baseline characteristics

Variable	Operationalization
Sex*	Male / female
Age (years) at index date*	Age at index date
Body height	cm
Body weight	kg

Variable	Operationalization
Genotype	Diagnosis / subtype: HbSS, HbSC, HbSß0 Thal, HbSß+ Thal type 1, 2 or 3, other
Age (years) at diagnosis	Age at diagnosis
Prior and concomitant diseases (including chronic SCD complications) • Nephropathy* • Chronic pain* • Hepatopathy* • Pulmonary hypertension* • Cerebrovascular event (prior stroke, neurological deficit)* • Alloimmunization* • Siderosis (iron overload)* • Endocrine dysfunction • Cardiomyopathy • Osteoporosis • Proliferative retinopathy • Ulcus cruris • Gallstones • Aseptic osteonecrosis (incl. status post-surgical correction) • Asplenia • „Other underlying diseases“	Yes / no If endocrine dysfunction or „Other underlying diseases“, specify and code according to Medical Dictionary for Regulatory Activities (MedDRA) If yes, date of first diagnosis and ongoing yes/no
Smoking regularly	Yes / no
Alpha-thalassemia	Yes / no Among patients with “yes”, specify genotype
Modifiers of fetal hemoglobin (HbF) synthesis	Yes / no Among patients with “yes”, specify genotype
Total hemoglobin (Hb)	g/dL
Sickle cell hemoglobin (HbS) level	% of total Hb
HbF level*	% of total Hb

Variable	Operationalization
Number of VOCs*	Start and end date of all VOCs over 24 months prior to index date VOC defined as hospitalization with overnight stay for any of the following: • Priapism: yes / no • Splenic sequestration(s): yes / no • Acute chest syndrome(s) (ACS): yes / no • Pain crises: yes / no
Other SCD complications*	Any complication at baseline yes / no and by type (see below). Other SCD complications are defined as either one of the following occurring: low Hb, pulmonary complications (excluding pulmonary hypertension), splenectomy/asplenia, ulcus cruris, aseptic osteonecrosis.
Chronic transfusion therapy*	Yes / no Among patients with "yes": number of chronic transfusions in past 12 months prior to index date, total volume per year (ml), type (exchange transfusions, erythrocyte apheresis, on top transfusion)
HU therapy	Yes / no Among patients with "yes": dose (mg/kg*d), start date Among patients with "no": stop date if applicable, reason (neutropenia, anemia, thrombopenia, nausea, cutaneous side effects, other side effects, desire to have children, pregnancy, lack of efficacy, inadequate increase of HbF, start of chronic transfusions, patient's decision, other)
Acute transfusions within 12 months prior to index date	• Number • Total volume of acute transfusions per year (ml) • Type (exchange transfusion, erythrocyte apheresis, on top transfusion)
Splenectomy	Yes / no

Variable	Operationalization
Prior and concomitant medication • Infection prophylaxis • Pain medication • Iron chelation / phlebotomy • Other	Yes /no for each Among patients with "yes": start and stop date, verbatim coded per WHODRUG

* Confounder variables, see also section 9.9.1

Baseline characteristics will be summarized by treatment group with the descriptive summary statistics listed in section 9.1.

9.6 Concomitant Medications

Concomitant medication use will be collected during the study (see Table 5) and analyzed descriptively by category and preferred term.

9.7 Treatment Exposure

Treatment exposure to any study medication - SoC and Exa-cel - will be described on the FAS for Period 1 and FAS Period 2 for Period 2. Treatments that patients in both groups can receive (e.g. RBC transfusions or hydroxycarbamide) will be summarized descriptively for both groups separately for Period 1 and Period 2. Treatment exposure specific to Exa-cel will be summarized for patients in the Exa-cel group and for the subset of patients in the SoC group with treatment decision for Exa-cel after the patient identification period.

Table 6: Treatment exposure

Variable	Operationalization
HU therapy (including changes to existing HU therapy or de novo prescriptions)	• Start date, stop date, ongoing • Dose (mg/kg*d) • Reason for start (bridge therapy yes / no, ACS yes / no, pain crisis yes / no, increased Transcranial Doppler (TCD) velocity yes / no, prior cerebrovascular event yes / no, chronic pain yes / no, symptomatic anemia yes / no, priapism yes / no, other) • Reason for discontinuation (planned during Exa-cel treatment regimen, neutropenia, anemia, thrombopenia, nausea, cutaneous side effects, other side effects, desire to have children, pregnancy, lack of efficacy, inadequate increase of HbF, start of chronic transfusions, patient's decision, other)

Variable	**Operationalization**
Acute RBC transfusions	• Number • Total volume (ml), as estimated from the average volume of red cell units • Start date, stop date
Chronic RBC transfusions	• Number • Total volume (ml), as estimated from the average volume of red cell units • Start date, End date
Exa-cel therapy 1. Mobilization 2. Apheresis 3. Conditioning 4. Infusion 5. Post-infusion	The number of patients going through each step will be reported. 1. Number of mobilization cycles, start date of hydroxycarbamide withdrawal, start date exchange transfusion, plerixafor dose or if other agent used, name and dose of the other mobilization agent, date of first date of mobilization 2. Number of cycles, start date of each apheresis cycle 3. Conditioning agent, date start of conditioning, dose, posology (qd, q6, other), total AUC 4. Date of infusion, total Exa-cel dose infused 5. Date patient weaned off from post-transplant RBC transfusions, date neutrophil engraftment achieved (3 consecutive measurements of absolute neutrophil count (ANC) ≥500 cells/µL on 3 different days after Exa-cel infusion without the use of unmodified rescue CD34+ cells), date thrombocyte engraftment achieved (3 consecutive measurements of platelet counts ≥50 × 10^9/L obtained on 3 different days after Exa-cel infusion without administration of platelet transfusions for 7 days), date hospital discharge
Discontinuation from Exa-cel therapy journey before infusion	Date and reason for discontinuation
Therapy decision for Exa-cel outside of patient identification period	Yes / no Among patients with “yes”: reason, date

Variable	Operationalization
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Yes / no Among patients with "yes" reason, date
Eligibility for HSCT according to the assessment of the treating physician	Yes / no Among patients with "no": reason, date

9.8 Analysis Strategy

The analysis strategy to compare Exa-cel patients against SoC patients will comprise a two-step approach:

1) One-time calculation of PS based on baseline characteristics for each analysis set and endpoint category (VOCs, mortality and SAEs, see Table 12) to be used as weights in the comparative analyses
2) Comparative, PS-adjusted analysis for all endpoints

Section 9.9 provides details on PS and weight calculation.

Analysis periods

Endpoints will be analyzed for the following analysis periods:

Table 7: Analysis strategy for endpoints

Endpoint	Period 1	Period 2
Annualized rate of VOCs	Yes	Yes (primary)
VOC freedom over 36 months		Yes (primary)
Death	Yes	Yes
SAEs	Yes	Yes

9.8.1 Primary Endpoints

In this study, the assessment of VOCs for the study objectives are defined as VOC leading to hospitalization for any of the following events: pain crises, acute chest syndrome (ACS), priapism or splenic sequestration.

For the co-primary endpoints of VOC freedom and the annualized VOC rate, the following intercurrent events (ICEs) will be considered:

- Therapy decision for Exa-cel outside of patient identification period (SoC group only)
- Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT

- HSCT or any aspects related to Exa-cel treatment (e.g., full myeloablation, stem cell mobilization, apheresis) according to the assessment of the treating physician are no longer appropriate

A change within SoC therapy, including changes to dose or frequency of HU or chronic transfusions, is considered part of the SoC treatment regimen and will not be considered intercurrent events.

Table 8 summarizes the analysis strategy for the primary endpoint **VOC freedom over 36 months in Period 2** within the estimand framework.

Table 8: Analysis strategy for VOC freedom over 36 months, Period 2

VOC freedom, Period 2	**Primary Estimand**
Treatment	Exa-cel vs. patient-individualized treatment (SoC)
Population	FAS36
Endpoint	Proportion of patients VOC-free over 36 months
Analysis period	Period 2 (T60 until 36 months after T60)
Population-level summary	Risk ratio
Handling of ICE	
Therapy decision for Exa-cel outside of patient identification period[a]	Treatment policy
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT[a]	Hypothetical[b]
HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate[a]	Treatment policy
Analysis (Estimator)	
Confounder[c] adjustment method	Calculation of weights based on PS
Analysis model	Log binomial regression model including weights
a: Potential ICE for SoC group only b: Hypothetical strategy: Data up to the ICE will be used for analysis assuming the calculated endpoint for the patient represents the scenario for the whole study period had the ICE not occurred. c: Missing values in confounders will be imputed using multiple imputation.	

For the primary endpoint VOC freedom over 36 months, i.e. starting at T60, is of primary interest, i.e. during Period 2. ICEs “therapy decision for Exa-cel outside of patient identification period” and “HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate” are handled via Treatment Policy approach: once an ICE occurs, no censoring happens, and patients continue to be observed until 36 months after T60. As analysis on FAS36 ensures the full 36 months of follow-up, no imputation of missing endpoint values is necessary. ICE “therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT” will be handled

using Hypothetical strategy: Only data up to the ICE will be used for analysis. A patient having such an ICE is no longer considered representative of the population compared in the AbD from that point forward. Treatment groups will be compared via risk ratio, estimated from a weighted log binomial regression model.

Table 9 summarizes the analysis strategy for the primary endpoint **annualized VOC rate for Period 2** within the estimand framework.

Table 9: Analysis strategy for annualized VOC rate, Period 2

Annualized VOC rate, Period 2	**Primary Estimand**
Treatment	Exa-cel vs. patient-individualized treatment (SoC)
Population	FAS, Period 2
Endpoint	Annualized VOC rate
Analysis period	Period 2 (T60 until EoS)
Population-level summary	Rate ratio
Handling of ICE	
Therapy decision for Exa-cel outside of patient identification period[a]	Hypothetical[b]
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Hypothetical[b]
HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate[a]	Treatment policy
Analysis (Estimator)	
Confounder[c] adjustment method	Calculation of weights based on PS
Analysis model	Negative binomial regression model including weights with log (follow-up time in years) as offset
a: Potential ICE for SoC group only b: Hypothetical strategy: Data up to the ICE will be used for analysis assuming the calculated endpoint for the patient represents the scenario for the whole study period had the ICE not occurred. c: Missing values in confounders will be imputed using multiple imputation.	

In this analysis of the annualized VOC rate for Period 2, starting at T60, the ICE "HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICEs "therapy decision for Exa-cel outside of patient identification period" and "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT", the Hypothetical approach is used: Only data up to the ICE will be used for analysis. It is assumed that the calculated endpoint for the patient represents the scenario for the whole study period, had the ICE not occurred. Missing values for this endpoint will be imputed via multiple imputation by chained equations (MICE) analogously to missing values in confounders (see section 9.9.1). It is expected that transplantation with Exa-cel has a significant impact on VOC rate. In addition,

it is expected that a relevant portion of matched SoC patients will start with Exa-cel even after the patient identification period. Including such data in the comparison makes it impossible to estimate the treatment effect of Exa-cel over SoC. A patient having a "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT" is not considered representative of the population compared in the AbD from that point forward.

9.8.2 Secondary Endpoints

All secondary endpoints will be evaluated on the FAS for analyses of Period 1 and on the FAS Period 2 for analyses of Period 2.

9.8.2.1 Secondary VOC Endpoints

Table 10 summarizes the analysis strategy for the secondary endpoint **annualized VOC rate for Period 1** within the estimand framework.

Table 10: Analysis strategy for annualized VOC rate, Period 1

Annualized VOC rate, Period 1	**Primary Estimand**
Treatment	Exa-cel vs. patient-individualized treatment (SoC)
Population	FAS
Endpoint	Annualized VOC rate
Analysis period	Period 1
Population-level summary	Rate ratio
Handling of ICE	
Therapy decision for Exa-cel outside of patient identification period[a]	Hypothetical[b]
Therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT	Hypothetical[b]
HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate	Treatment policy
Analysis (Estimator)	
Confounder[c] adjustment method	Calculation of weights based on PS
Analysis model	Negative binomial regression model including weights with log (follow-up time in years) as offset
a: Potential ICE for SoC group only b: Hypothetical strategy: Data up to the ICE will be used for analysis assuming the calculated endpoint for the patient represents the scenario for the whole study period had the ICE not occurred. c: Missing values in confounders will be imputed using multiple imputation.	

Annualized VOC rate during Period 1 will be analyzed analogous to Period 2. The ICE "HSCT or any aspects related to Exa-cel treatment according to the assessment of the treating physician are no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICEs "therapy decision for Exa-cel outside of patient identification period" and "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT", the Hypothetical approach is used: Only data up to the ICE will be used for analysis. It is assumed that the calculated endpoint for the patient represents the scenario for the whole study period, had the ICE not occurred. Treatment groups will be compared via rate ratio, estimated from a weighted negative binomial regression model with log (follow-up time in years) as offset in the model.

For annualized VOC rate for Period 1&2 separately, descriptive analyses will be performed for each VOC component (pain crises, ACS, priapism, splenic sequestration). Analyses will be conducted in the FAS Period 2 (for annualized VOC rate for Period 2), and in FAS (for annualized VOC rate for Period 1). For each component, the number of patients, number of events and annualized rate of that component during the relevant observation period will be summarized descriptively. The ICEs "therapy decision for Exa-cel outside of patient identification period" and "therapy decision for any alternative gene therapy or experimental therapy or allogeneic HSCT" will be handled using the Hypothetical approach, where only events up to the ICE will be included. For this descriptive analysis, no imputation of missing endpoint values will be performed.

9.8.2.2 Secondary Safety Endpoints

Regarding the estimand strategy of death and SAE secondary endpoints, endpoints where a proportion of patients having an event is compared between treatment groups will use the risk ratio derived from a weighted log binomial regression model. Endpoints where the annualized rate of an event occurring is compared between treatment groups will use the rate ratio derived from a weighted negative binomial regression model. Missing values in secondary morbidity endpoints will not be imputed but missing values in confounders will be imputed using multiple imputation by chained equations (MICE) (see section 9.9.1).

For descriptive safety analysis, occurrence of SAEs will be evaluated in three groups, analyzed for Period 1 and 2 separately:

1. Exa-cel group
2. SoC group:
3. SoC group with therapy decision for Exa-cel

SAEs during Period 1 will additionally be analyzed according to the split into the following sub-periods (patients receiving Exa-cel):

- Index date to first mobilization (time from index date to start of mobilization)
- Mobilization & apheresis (start of first mobilization until last day of apheresis of last apheresis cycle)

- Between apheresis and conditioning (day after last day of apheresis of last apheresis cycle until day before start of conditioning)
- Conditioning to infusion (start of conditioning until day before Exa-cel infusion)
- Infusion to T60 (Exa-cel infusion to 60 days after last RBC transfusion for post-transplant management)

For patients in the SoC group with a therapy decision for Exa-cel (or any alternative gene therapy or experimental therapy or allogeneic HSCT), SAEs occurring starting from the timepoint of therapy decision will be analyzed descriptively for Periods 1 and 2 separately and additionally split into the above sub-periods during Period 1.

This means that for patients assigned to the SoC group with therapy decision for Exa-cel, reported SAEs for descriptive analysis will be split between those occurring during SoC treatment and those starting at therapy decision for Exa-cel.

9.8.2.3 Operationalization and Analysis Time Periods

Table 11: Overview of operationalizations and analysis time periods of secondary endpoints

Endpoint	Operationalization	Analysis Time Periods
Morbidity		
Annualized VOC rate in Period 1	VOCs are defined as hospitalization with overnight stay for priapism, splenic sequestration(s), acute thorax syndrome or pain crises.	Period 1
Mortality		
Proportion of patients who die	Derived via date of death	Period 1, Period 2
Annualized death rate		
Safety		
Proportion of patients with SAEs	SAEs[a] are any AEs that meet any of the following criteria: • Results in death • Requires hospitalization or prolongation of existing hospitalization[b]	Period 1, Period 2 Period 1 split into additional sub-periods as described above[c]
Annualized rate of SAEs		

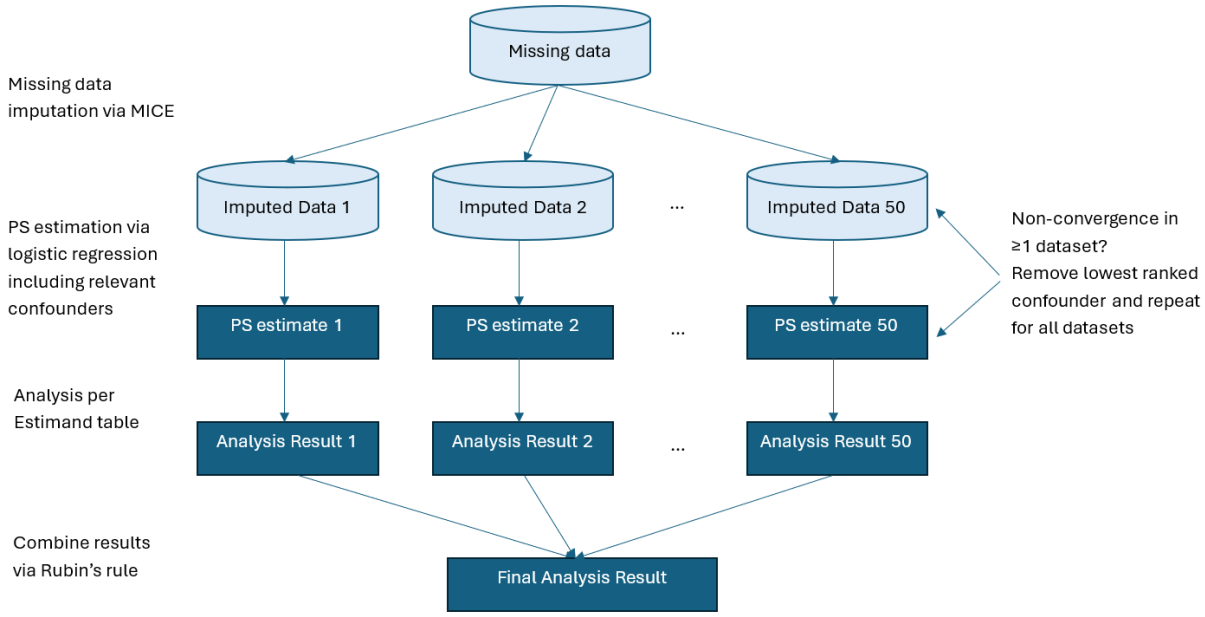
a: For SAEs, descriptive analyses regarding criteria, CTCAE grade, type (MedDRA PT), relatedness to Exa-cel treatment and outcome will additionally be performed.
b: VOCs leading to hospitalization are considered disease-related events and not additionally captured as SAEs.
c: Descriptive only for patients in the Exa-cel group.

9.9 Propensity Score Methods

Comparative analyses between Exa-cel and SoC treatment groups for all endpoints will be performed using PS weights to adjust for potential confounding.

Missing values in confounders will be imputed, and analysis will be performed in each imputed dataset. Then, all available estimates will be combined using Rubin's rules (see Figure 1).

Figure 1 Confounder adjustment and analysis per endpoint category and analysis set



As different analysis sets are used depending on endpoint, all steps in the PS procedure to obtain an adjusted effect estimate will be conducted on relevant analysis sets (FAS, FAS Period 2 and FAS36) independently of each other. The general terms "analysis population" will be used for all analysis sets to describe the methodology going forward to avoid redundancy. The following subsections describe the steps in Figure 1 in more detail.

9.9.1 Confounders

The following confounders relevant for this AbD were identified systematically using a literature review and expert input. The expected level of impact on endpoints in each endpoint category (VOCs, mortality and SAEs) were then ranked separately. Table 12 displays the list of relevant confounders and their rankings.

Table 12: Confounders relevant for adjusted analysis

Ranking for each endpoint category			Confounder[a]	Operationalization used in adjustment
VOCs	**Mortality**	**SAEs**		
1	1	1	Siderosis (iron overload)	Categorical (yes / no)
2	11	7	Chronic pain	Categorical (yes / no)
3	8	11	Number of VOCs	Continuous (number of VOCs recorded in entire baseline period)
4	2	6	Cerebrovascular event (prior stroke, neurological deficit)	Categorical (yes / no)
5	3	4	Pulmonary hypertension	Categorical (yes / no)
6	4	2	Nephropathy	Categorical (yes / no)
7	5	3	Hepatopathy	Categorical (yes / no)
8	6	5	Age (years) at index date	Continuous (in years)
9	10	9	Chronic transfusion therapy	Categorical (yes / no)
10	7	12	HbF level	Continuous (% of total Hb at baseline)
11	9	10	Other SCD complications	Categorical (yes / no)
12	12	8	Alloimmunization	Categorical (yes / no)
13	13	13	Sex	Categorical (male / female)

a: In the presence of sparse data or convergence issues, clinically related covariates may be grouped at the time of analysis to improve model stability and interpretability.

Details regarding definition of these confounders are listed in section 9.4 on baseline characteristics. All confounders are measured at baseline. Details on the methodological approach of confounder identification and ranking can be found in the report attached as a reference (1).

To adjust for these confounding factors, they will be included in PS estimation.

Missing values in confounders will be summarized descriptively per variable and per patient. Multiple imputation by chained equations (MICE) under the assumption of missing at random (MAR) will be performed to impute missing values in confounders. For categorical variables, logistic regression will be used as the conditional imputation method; for continuous variables, predictive mean matching will be applied. A total of m=50 imputed datasets will be created. If convergence cannot be achieved in at least 1 of the 50 data sets, the lowest ranked confounder of the endpoint category is removed and the analysis repeated.

9.9.2 Propensity Score Estimation

The PS, defined as the probability of being assigned to the Exa-cel treatment group given the confounding variables, will be estimated via logistic regression with treatment group (Exa-cel vs. SoC) as the dependent variable.

Confounding variables will be included in the model as independent variables. Binary confounding variables with “yes” and “no” options will have “no” as a reference category. The PS will be estimated on each imputed dataset separately. If convergence cannot be achieved in at least 1 of the 50 data sets, the lowest ranked confounder of the endpoint category is removed and the analysis repeated. This process is repeated until convergence is achieved. Consequently, for different endpoint categories different PS may be used. The number and type of excluded confounders per endpoint category will be reported. A shifted null hypothesis (or a further shift of an already shifted null hypothesis) when removing confounders, as suggested in the IQWiG-paper on confounders (2), will not be implemented. It is acknowledged that G-BA may define and apply a shifted null hypothesis (or a further shift) for their benefit assessment in that case.

9.9.3 Assessment of (Im)balance and Overlap

For each imputed dataset, the patient population will be characterized in terms of confounders and other baseline characteristics, and an aggregate description of the analysis population across imputed datasets before weighting will be presented.

The (im)balance of all confounders between treatment groups before and after weighting will be assessed by calculating standardized mean differences (SMDs) for each confounder in each imputed dataset and by summarizing all SMDs across imputed datasets via descriptive statistics. The SMD compares the difference in means (or prevalences, in case of binary variables) between groups, standardized through the pooled standard deviation of both groups. A confounder with a median SMD across all imputed datasets with absolute value above the threshold 0.25 before weighting will be considered imbalanced between treatment groups. After weighting an exact balance in terms of mean difference and thereby SMD is achieved using Overlap Weighting (OW) method (5,6). Therefore, the threshold is used for discussion only and is not used to alter planned analyses.

The overlap in PS distributions between groups will be quantified as the areal overlap percentage of the PS densities. Descriptive summary statistics for the overlap percentage across imputed datasets will be calculated and discussed. OW down-weights units with extreme PS, providing exact balance even in situations with low overlap before weighting. Therefore, no consequences on the analysis will be drawn based on the overlap percentage.

9.9.4 Propensity Score Weighting

After PS estimation, PS weights are used to estimate the Average Treatment Effect while adjusting for confounders.

Overlap weighting (OW) is a PS weighting method that looks to mimic the attributes of a randomized clinical trial: a clinically relevant population, covariate balance and precision. Using OW to adjust for confounding, each patient is assigned a weight that is proportional to the probability of that patient belonging to the opposite treatment group. Specifically, an Exa-cel patient is weighted by the probability of not receiving treatment (1 – PS) and a patient in the SoC arm is weighted by the probability of receiving treatment PS.

OW has desirable statistical properties. OW leads to exact balance on the mean of every measured covariate when the PS is estimated by a logistic regression and is proven to optimize precision of the estimated association between treatment and outcomes among a large class of PS weighting methods, including inverse probability of treatment weights (IPTW) (3, 4).

The mathematical distinction between IPTW and OW also coincides with a difference in interpretation (4). Namely, the primary estimand when using IPTW to estimate linear effects (e.g., risk differences) is the Average Treatment Effect (ATE), which is the average effect in a population where the confounding variables have the same marginal distribution as the observed data. The estimand when using OW is the Average Treatment Effect on the Overlap Set (ATO), which is a weighted average effect that upweights subjects who have treatment probability (true PS) closer to 0.5, making the ATO arguably more clinically relevant.

OW is superior to IPTW in ensuring covariate balance as well as mitigating the issue of extreme weights, thereby reducing the need for trimming. The advantages of OW are particularly significant when there is a large initial imbalance in covariates between treatment groups. Overlap weights are smaller for extreme PS values so that outliers who are nearly always treated (PS near 1) or never treated (PS near 0) do not dominate results and worsen precision, as occurs with IPTW (5).

OW was also found to be superior to fine stratification (FS) in terms of balancing covariates bias and precision (6).

9.9.5 Effect Estimation and Interpretation

For the co-primary endpoint **VOC freedom**, the objective is to compare Exa-cel vs. SoC regarding the proportion of patients who are VOC-free over 36 months, starting at T60 (Period 2). To achieve this, on each imputed and weighted dataset of the FAS36 patients in Period 2, the risk ratio with 95% confidence interval (CI) will be estimated via log binomial regression with treatment group as the independent variable and including the PS weights.

The effect estimates are then pooled across all 50 imputed datasets via Rubin's rule. The resulting risk ratio estimate is then tested against the shifted null hypothesis H_0: risk ratio=2.0. Superiority of Exa-cel is shown if the lower bound of the 95% CI is >2.0.

For the co-primary endpoint **annualized VOC rate**, the objective is to compare Exa-cel vs. SoC regarding the annualized VOC rate for Period 2. On each imputed and weighted dataset of FAS Period 2 patients, the rate ratio with 95% CI will be estimated via negative binomial regression with treatment as the independent variable and including the PS weights, with log (follow-up time in years) specified as an offset.

The effect estimates are then pooled across all 50 imputed datasets. The rate ratio is tested against the shifted null hypothesis H_0: rate ratio=0.5. Superiority of Exa-cel is shown if the upper bound of the 95% CI is <0.5.

For the **secondary endpoints**, the risk ratio or the rate ratio will be estimated via weighted log binomial model or negative binomial regression respectively, as described in section 9.8.2. No testing against a shifted null hypothesis will be performed. It is acknowledged that G-BA may define and apply a shifted null hypothesis for their benefit assessment.

If any model for effect estimation does not converge, stepwise removal of confounders will be performed as described in section 9.9.1.

Potential bias due to removal of confounders will be considered, and the implications for the interpretation of results will be discussed in the study report.

To interpret the results in the context of confounder adjustment in this non-interventional study, the resulting imputed analysis populations are compared against the initial analysis sets descriptively based on baseline characteristics. Implications regarding generalizability of results onto the whole patient population and limitations regarding the adjustment process will be discussed.

9.10 Subgroup Analyses

Subgroup analyses will be conducted for all endpoints by adding the subgroup and treatment x subgroup interaction term as additional independent variables to the log binomial regression and the negative binomial regression, respectively. For each endpoint and each subgroup, an interaction p-value will be presented derived from the same model.

For the subgroup analyses, the same PS weights as those derived in the primary analysis will be applied. Results of a methodological comparison in Wang et al. indicated that across the five strategies examined, no single method consistently outperformed the others in terms of achieving covariate balance, reducing bias, or improving precision (7) Chatelet et al. also recommends the calculation of PS weights across subsets in small groups (8). This approach was previously accepted by G-BA in other AbDs (9, 10).

Subgroup analyses will be performed for the following baseline characteristics:

- Sex (female vs. male)
- Number of VOCs during baseline period (0 vs. 1-2 vs. ≥3)

A subgroup analysis for a specific endpoint and subgroup combination will only be performed if both of the following rules apply:

1. Each subgroup level includes at least 10 patients across both treatment groups *and*
2. For binary endpoints, at least 10 events occur in at least one subgroup level combined across both treatment groups in the time period.

9.11 Sensitivity Analyses

No sensitivity analyses will be performed.

10 PLANNED ANALYSES

The following status reports, interim reports and final report are planned according to the requirements in the resolution by G-BA (Table 13). All dates refer to the study start date which will be defined by G-BA.

Table 13: Planned reports to G-BA

Report	Date	Content
Status report 1	6 months after study start defined by the G-BA	As no patient is anticipated to be enrolled after 6 months (study still in set-up phase), only information about study set-up will be included; presented in the status report template
Interim report 1 and status report 2	18 months after study start	At this time, it is expected that the identification window is open for some months only with very few patients already enrolled (all patients in Period 1); interim analysis results include disposition, baseline characteristics and descriptive safety analysis; presented in module 4 of the dossier template Information on patient inclusion; presented in the status report template
Futility analysis regarding required MACNU design adaptation*	14 months after start of identification period	Review of SoC response rate to reassess assumptions for sample size derivation Review of number of Exa-cel and SoC patients included (see below) Review of necessity to switch to alternative MACNU approach
Interim report 2 and status report 3	36 months after study start Data cut: 32 months after study start	It is expected that at this time the identification period has already been closed; Interim analysis results including disposition, baseline characteristics and descriptive analyses for annualized VOC rate during Period 1 as well as descriptive safety analysis by period presented in module 4 of the dossier template Futility analysis for study success Information on patient inclusion; presented in the status report template

Report	Date	Content
Status report 4	54 months after study start Data cut: 50 months after study start	Information on patient inclusion; presented in the status report template (11)
Final report	Expected 6 months after EoS	Final analysis presented in module 4 of the dossier template(12)

*Interim analysis not requested by G-BA

Status reports 2 through 4 will include information on number of patients included in the study.

Interim analyses will include a disposition table, descriptive summary of baseline characteristics in the total patient population and by treatment group.

As the patient identification period has not ended at IA1, group assignment and index dates for enrolled patients on SoC will not have been finalized. Therefore, the initial, preliminary index date will be used as baseline and start of observation at IA1 for SoC patients. In addition, descriptive analysis of safety endpoints by group will be performed at IA1.

14 months after start of identification period a futility analysis regarding required MACNU design adaptation will be performed reviewing the observed SoC response rate and number of Exa-cel and SoC patients included so far (see below) to review the necessity to witch to an alternative MACNU approach.

At IA2, descriptive analysis by group for annualized VOC rate for Period 1 will be performed. Period 1 in this interim analysis ends at the earlier of T60 (if defined), date of discontinuation or date of data cut for IA2. In addition, descriptive analysis of safety endpoints by group and period will be performed at IA2 and a futility analysis on study success (see below) will be performed.

Interim endpoint analyses will not be used to infer any treatment effects of Exa-cel vs. SoC. For the final report, all analyses will be presented according to the specifications of this SAP.

Futility analysis regarding required MACNU design adaptation

A futility analysis will be conducted 14 months after start of the identification period to assess whether the study will meet the required sample size for final analysis using the MACNU design for study inclusion.

The futility analysis will examine the SoC response rate, the total number of patients included in the study and the number of patients in each of the SoC and Exa-cel groups in the FAS at that time.

If the observed SoC response rate is higher than the assumed SoC response rate of 25.0%, the sample size will be re-calculated with an updated SoC response rate.

If the number of Exa-cel patients is according to expectations, but the recruitment of SoC group is behind expectations, the alternative approach for the MACNU design (see protocol

section 11.4.2) will be applied. Recruitment of SoC patients will be considered behind expectations of currently planned sample size, if less than

$$\frac{14}{24} * Total\ number\ of\ SoC\ patients\ to\ be\ recruited = 63$$

patients are in the SoC group at time of futility analysis. Recruitment into Exa-cel group is considered behind expectations of currently planned sample size, if less than

$$\frac{14}{24} * Total\ number\ of\ Exacel\ patients\ to\ be\ recruited = 20$$

patients are in the Exa-cel group at time of futility analysis.

If the number of Exa-cel patients is lower than expected, continued conduct of or alterations to the study will be discussed with G-BA.

Futility analysis for study success (interim report 2)

At the second interim report, the final number of included patients is compared against the current sample size assessment. Continued conduct of or alterations to the study based on this futility assessment will be discussed with G-BA.

Content of reports

Interim analyses will include a disposition table, descriptive summary of baseline characteristics in the total patient population and by treatment group, descriptive safety analyses, as applicable, at IA1 and descriptive analyses of endpoints during Period 1 at IA2.

For the final report, all analyses will be presented according to the specifications of this SAP.

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12 LIST OF APPENDICES

12.1 Appendix A: Algorithms for data calculations

Standardized Mean Differences

The SMD between Exa-cel and SoC groups in an analysis set for a continuous variable x will be calculated as:

$$SMD(x) = \frac{\overline{x}_{Exa-cel} - \overline{x}_{SoC}}{\sqrt{\frac{s^2_{Exa-cel} + s^2_{SoC}}{2}}}$$

With the differences in sample means as the numerator and the square of the mean of the sample variances as the denominator.

The SMD between Exa-cel and SoC groups in an analysis set for a binary variable x will be calculated as:

$$SMD(x) = \frac{\hat{p}_{Exa-cel} - \hat{p}_{SoC}}{\sqrt{\frac{\hat{p}_{Exa-cel}(1 - \hat{p}_{Exa-cel}) + \hat{p}_{SoC}(1 - \hat{p}_{SoC})}{2}}}$$

For a binary variable, p denotes the proportion (i.e. taking values between 0 and 1) of patients in each group falling into the non-reference category of that variable.

VERTEX PHARMACEUTICALS INCORPORATED

Supplement for Study Protocol / Statistical Analysis Plan v3.0 for a Routine Practice Data Collection („Anwendungsbegleitende Datenerhebung“) of Exagamglogene autotemcel (Exa-cel) in sickle cell disease (SCD)

Table of Contents

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AbD	Routine practice data collection (*Anwendungsbegleitende Datenerhebung*)
CHMP	Committee for Medicinal Products for Human Use
eCRF	Electronic case report form
EMA	European Medicines Agency
Exa-cel	Exagamglogene autotemcel
FAS	Full Analysis Set
G-BA	Federal Joint Committee (*Gemeinsamer Bundesausschuss*)
GPOH	Society of Pediatric Oncology and Hematology (*Gesellschaft für Pädiatrische Onkologie und Hämatologie*)
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
HU	Hydroxycarbamide (Hydroxyurea)
ICH	International Council for Harmonisation
IQWiG	Institute for Quality and Efficiency in Health Care *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)*
ITT	Intention-to-treat
KCO	Medical services of the German payers (*Kompetenzcentrum Onkologie der Medizinischen Dienste*)
PRO	Patient-reported outcome
RBC	Red blood cell
SAP	Statistical analysis plan
SCD	Sickle cell disease
SoC	Standard of Care
VOC	Vaso-occlusive crisis

2 EXECUTIVE SUMMARY

In accordance with the request of the G-BA of September 18, 2025, Vertex submitted v2.0 of the study protocol and statistical analysis plan (SAP) for the Exagamglogene autotemcel (Exa-cel) routine practice data collection (*Anwendungsbegleitende Datenerhebung*, AbD) on October 16, 2025. In this version, the AbD was designed as a prospective, non-interventional, site-facing comparative study wholly run by Vertex as the GPOH sickle cell disease (SCD) registry declined to participate in the AbD as the G-BA requirements were deemed non-feasible within the registry. This was confirmed by the registry to the G-BA in writing in January 2026 and predominantly based on the interventional character of the AbD, fixed data collection schedules and necessary interventions for eligibility assessment beyond routine care.

Subsequently, the G-BA adjusted the AbD requirements to allow for implementation of the AbD with the GPOH registry (*GPOH-Register Sichelzellkrankheit)* and avoidance of parallel structures, informing Vertex in writing on February 10, 2026. Key adjustments include the acceptance of vaso-occlusive crises (VOCs) leading to hospitalization for the VOC endpoints, waiver of the collection of patient-reported outcomes and the possibility to restrict the population to patients aged ≥12 to <21 years, among others. Based on these updated requirements, the GPOH SCD registry has confirmed their intention to participate should the AbD be feasible. In principle, both the GPOH SCD registry and Vertex welcomed these adjustments as they allow the technical implementation of the AbD with the GPOH registry.

However, Vertex would like to **reiterate our concerns regarding methodological requirements and the required sample size for the AbD. In brief the number of Exa-cel eligible patients available in Germany is too low to meet the required sample size for the AbD. Furthermore, it appears highly unlikely that the study will meet the commitments to provide real-world evidence on the performance of Exa-cel vs. standard of care** (SoC) in Germany to inform future benefit assessments within a reasonable timeframe.

Vertex continues to be committed to engage and implement a plan to successfully deliver the Exa-cel AbD and for that reason, Vertex outlines in this summary the key aspects that will prevent the successful conduct of the study, which are expanded later in this document:

- **Insufficient number of patients:** There are not enough patients to inform the comparative study given sample size requirements. **Vertex maintains that the AbD is not feasible due to the very limited number of eligible patients.** Even without the age restriction, a minimum sample size of 100 patients would be required to allow adequate confounder control, as also acknowledged by IQWiG, and to generate robust comparative evidence for the purpose of a future benefit assessment. A sample of 100 patients would correspond to enrollment of approximately 30% to 76% of the entire Exa-cel eligible SCD population in Germany of 130 to 330 patients, which is not considered operationally feasible. In addition, fewer than 100 potentially eligible patients are currently recorded in the GPOH SCD registry. With restriction of the study population to patients aged ≥12 to <21 years, the number of potentially eligible registry patients is reduced to less than 30, further confirming the infeasibility of the proposed AbD to provide robust and reliable comparative results under the current methodological and sample size requirements.
- **Study duration:** The AbD would not generate comparative results before 2034 earliest. Vertex maintains that the proposed AbD is also infeasible within a timeframe relevant to

the benefit assessment. Study set-up alone is expected to require at least 8 months, including contracting with the registry and participating centers, obtaining ethics committee approval, and implementing updates to the registry database. Post set-up, the study would require a 2-year patient identification window, an estimated 1-year interval from the decision to treat with Exa-cel to completion of the washout period after the last RBC transfusion for post-transplant management (T60), and a minimum follow-up period of 3 years per patient after T60. On this basis, the AbD would not generate outcome data before 2034 at the earliest, such that a benefit assessment informed by these data would not be possible before mid-2034. [redacted]. Overall, the proposed AbD would extend substantially beyond the timelines requested by the G-BA and would therefore fail to inform a future benefit assessment in a relevant and timely manner.

- **Methodology:** To adequately inform a future benefit assessment, appropriate study design in the real-world setting should be implemented. The prevention of VOCs (freedom from VOCs) and the reduction of VOCs are the main treatment goals of Exa-cel. Exa-cel can only exert its effect once infused and engraftment achieved, therefore this is when Exa-cel effectiveness can be compared to SoC appropriately. It is important to understand the clinical course of patients selected for Exa-cel that undergo mobilization, apheresis and conditioning prior to infusion, which is why we recommend capturing data for this period separately. Therefore, Vertex maintains the current approach to assess all endpoints for Period 1 and 2 separately.

Vertex continues to be committed to engage and implement a plan to successfully deliver the Exa-cel AbD and for that reason, Vertex outlines in the present document the key aspects that will prevent the successful conduct of the study. To overcome these concerns, Vertex is proposing a research protocol that balances requirements vs operationalization to increase the likelihood of positive feasibility and operationalization, and high-quality evidence generation to inform future benefit assessments. **This proposed approach, however, does not overcome the fact there is an insufficient number of patients in Germany for the AbD.**

3 ABD FEASIBILITY CONSIDERING ADJUSTED REQUIREMENTS

In accordance with the G-BA request dated 18 September 2025, Vertex submitted version 2.0 of the study protocol and SAP for the routine practice data collection (Anwendungsbegleitende Datenerhebung, AbD) for Exagamglogene autotemcel (Exa-cel) on 16 October 2025. In this version, the AbD was designed as a prospective, non-interventional, site-based comparative study to be fully operated by Vertex through a newly established data platform. This approach was adopted because the GPOH SCD registry declined participation in the AbD, having concluded that the G-BA requirements were not feasible to implement within the registry

The registry based this on the following key aspects:

- **Interventional character of the AbD**: Central elements of the AbD were seen as a clinical intervention due to stipulation to collect clinical data and patient-reported outcomes (PROs) according to a fixed visit schedule as well as the obligatory assessment of a patient's eligibility for a hematopoietic stem cell transplant (HSCT) for patients both in the Exa-cel and SoC arms.
- **Frequency of data collection:** The registry collects data from participating centers annually. Real-time adverse event reporting as well as any kind of source data verification is not foreseen in agreements between the registry and participating centers.

Upon withdrawal of the GPOH SCD registry, G-BA requested version 2.0 of the protocol and SAP to reflect a site-facing study operated by Vertex requiring the creation of a novel data platform for collection of clinical data. This would have created a parallel structure alongside the GPOH SCD registry.

On February 10, 2026, the G-BA informed Vertex that creating parallel structures alongside existing registries is not preferable. As a result, the G-BA revised the AbD requirements to allow the AbD to be conducted within the registry. Vertex expects the changes to be published by the G-BA.

To discuss the feasibility of the AbD considering the new G-BA requirements, representatives of the GPOH SCD registry and Vertex met in Heidelberg on 16th April 2026. Detailed meeting minutes, signed by both parties, were shared confidentially with the G-BA (1).

Overall, the GPOH SCD registry representatives confirmed their intention to participate should the AbD be feasible. **Nevertheless, substantial practical limitations and concerns remain, both with regard to the feasibility of the study and its proportionality to the expected utility of the data collected for future benefit assessments**.

4 INSUFFICIENT NUMBER OF PATIENTS IN GERMANY FOR THE REQUIRED SAMPLE SIZE IN THE AbD

In its letter dated February 10, 2026 (2), the G-BA provides the option of restriction of the age-related inclusion criterion to patients below 21 years of age to facilitate the AbD with the registry. The recruitment of adults 21 years and older may be omitted.

Vertex welcomes this change as it acknowledges the pediatric nature of the GPOH SCD registry and has therefore implemented this change in the updated study protocol and SAP.

Nevertheless, irrespective of this age restriction, there is an insufficient number of eligible patients in Germany, as well as within the GPOH registry, to conduct a comparative study, as described below.

4.1 Sample size and available patients aged ≥12 years

Before limiting the sample size calculation and consideration of Exa-cel eligible patients to age ≥12 to <21 years, it is informative to consider the Exa-cel indicated population of those aged ≥12 years.

According to the Medicinal Products Directive / Annex XII (Arzneimittel-Richtlinie/Anlage XII) for Exa-cel, the number of patients (N) in Exa-cel's indication is assumed to range between 130 and 330 individuals (mean: 230) (3). Vertex notes that analysis of the primary endpoint, *freedom from VOCs requiring hospitalization*, over a period of three years from T60, applying the intention-to-treat (ITT) principle, would require a sample size of 258 patients (N=86 for Exa-cel and N=172 for the comparator therapy) in order to generate robust comparative evidence for the purpose of the benefit assessment. This is based on an assumed Exa-cel response rate of 75.9%, an assumed SoC response rate of 25.0% and including all patients in Period 2 regardless of follow-up time and imputing T60 for patients that did not receive Exa-cel as well as for their matched SoC counterparts. This sample size exceeds the estimated total number of patients in Germany, thereby precluding the feasibility of the AbD and, consequently, the generation of comparative evidence for a future benefit assessment. The sample size estimation is provided in Table 1 of Appendix I. The calculation is based on data from the reference study CLIMB-121 in SCD and on IQWiG assumptions regarding the responder rate in the comparator arm (25%) [2].

Vertex highlighted this to the G-BA in a letter dated March 2, 2026. In its response, the G-BA argued that the 25% response rate of VOC freedom in the SoC arm is likely to be overestimated. The G-BA references an assumed response rate of 16% for VOC freedom in the SoC arm, which leads to an estimated sample size of 141 patients even if an Exa-cel response rate as low as 63.5% is assumed. This sample size is "within the lower bound of the expected annual patient numbers in Germany" (4), presumably referencing the total patient number of 130 to 330 patients. This number is still, however, above the lower estimate and requires an unrealistic proportion of patients to enroll in a study.

It is important to note that the total number of patients of 130-330 patients, as stated in the G-BA's resolution from September 18, 2025 (3), neither describes the incidence nor the number of already identified patients. Rather, it refers to the estimated total number of patients with SCD living in Germany who are, in principle, eligible for treatment with Exa-cel.

A calculation of the number of patients at German treatment centers participating in the GPOH SCD registry who may be eligible for treatment with Exa-cel (see Table 2 in Appendix II), based on information provided by the GPOH registry and applying the G-BA's calculation approach, results in an estimate of only 92 to 101 patients and are likely to be overestimated (see Table 2 in Appendix II).

In view of the limited number of potentially eligible patients and the restricted availability of data within the GPOH registry, the AbD cannot be conducted successfully, even in the indicated population of those aged ≥12 years.

4.2 Exa-cel eligible patients with restriction to patients ≥ 12 to < 21 years of age

While Vertex welcomes the restriction to patients aged ≥12 to < 21 years, as it reflects the pediatric nature of the GPOH registry, it further reduces the number of available patients to a degree, at which even appropriate confounder control is no longer ensured and where there is no possibility to generate robust comparative evidence for the purpose of a future benefit assessment.

Applying the G-BA-used framework described in 4.1 onto the overall prevalence of SCD patients in Germany results in an estimated total number of Exa-cel-eligible patients in Germany aged ≥12 to <21 years of 40 to 98 patients (see Table 3 in Appendix III). Only approximately 25-27 Exa-cel-eligible patients of this age group are projected to be included within the GPOH registry (see Table 4 in Appendix IV).

These numbers are significantly below the minimum requirement defined by IQWiG in the AbD study concept for adequate confounder control, where IQWiG states (5):

„Für Szenarien mit einer Stichprobengröße unter 100 Patientinnen und Patienten ist zu beachten, dass in der Regel bei einer Studiengröße von weniger als 100 Patientinnen und Patienten keine adäquate Confounderkontrolle durchgeführt werden kann und somit ungeachtet des Ergebnisses der orientierenden Fallzahlschätzung eine Stichprobengröße von mindestens 100 Patientinnen und Patienten für die AbD erforderlich ist."

Even under the assumption of a full enrollment of all patients with SCD living in Germany who are aged ≥12 to <21 years of age and eligible for treatment with Exa-cel — an assumption that is not feasible in practice — the achievable sample size of less than 30 patients would still fail to meet IQWiG's own minimum requirement of 100 patients to account for adequate confounder control or be able to generate robust comparative evidence for the purpose of a future benefit assessment.

Regardless of the age cohort considered, or assumptions used in the sample size calculation, it is clear there are insufficient number of patients in Germany to inform a comparative study and generate robust comparative evidence for the purpose of a future benefit assessment.

5 STUDY DURATION

5.1 Study duration

The AbD would not generate comparative results before 2034.

In its resolution from December 21, 2023, effective as of January 15, 2025, the G-BA requests final AbD analyses latest six years after the resolution coming into effect, i.e. January 15, 2031 (6). There are significant concerns regarding the AbD to be reasonably feasible within this, or even with a slightly extended, timeframe. Even with optimal procedural assumptions, Vertex does not believe that a final data analysis will be available before the end of 2033 to early 2034, thus rendering the study unfit for its purpose to inform a new benefit assessment.

1. Assuming a G-BA resolution in August 2026 for the AbD and a G-BA-determined start of the AbD in September 2026, to be performed as per protocol version 3.0, Vertex and the GPOH registry anticipate registry preparation, contracting of centers and ethics approvals to take approximately 8 months. Therefore, the start of data collection is realistically assumed in June 2027. Of note: it is unlikely that all GPOH SCD centers will have been contracted by the registry by this point.
2. As defined in the study protocol, a patient identification period is required to identify eligible individuals. Vertex views the start of the identification period, defined as assignment of an index date to the first patient, as start date of the AbD, i.e., when all following criteria are satisfied:
    a. all necessary regulatory and contractual requirements are fulfilled (see above)
    b. the registry eCRF has been updated to allow prospective documentation
    c. the first Exa-cel therapy decision for a patient who has consented to the AbD is documented

    The identification period is set to two years and would therefore end in June 2029, the earliest.
3. The period between treatment decision for Exa-cel and the completion of the necessary washout period after last RBC transfusion for post-transplant support (T60) is estimated to be around 12 months for each Exa-cel patient.
    a. After treatment consent, single case applications to the medical services are likely to be submitted by the majority of centers, which can take several weeks to approve.
    b. Thereafter patients need to undergo 8 weeks of washout from disease modifying therapy (HU) prior to mobilization and cell collection (and often more than one such cycle needed).
    c. Manufacturing and the extensive required quality control before release can take several months before the drug can be delivered to the treatment center.
    d. Prior to myeloablation, another minimum of 8 weeks is required for preparation of the patient (i.e. exchange transfusions) and only thereafter a patient is infused with Exa-cel.
    e. After myeloablation and infusion, patients require RBC transfusions for post-transplant support and a washout period of 60 days is required after their last RBC transfusion (T60). [redacted]

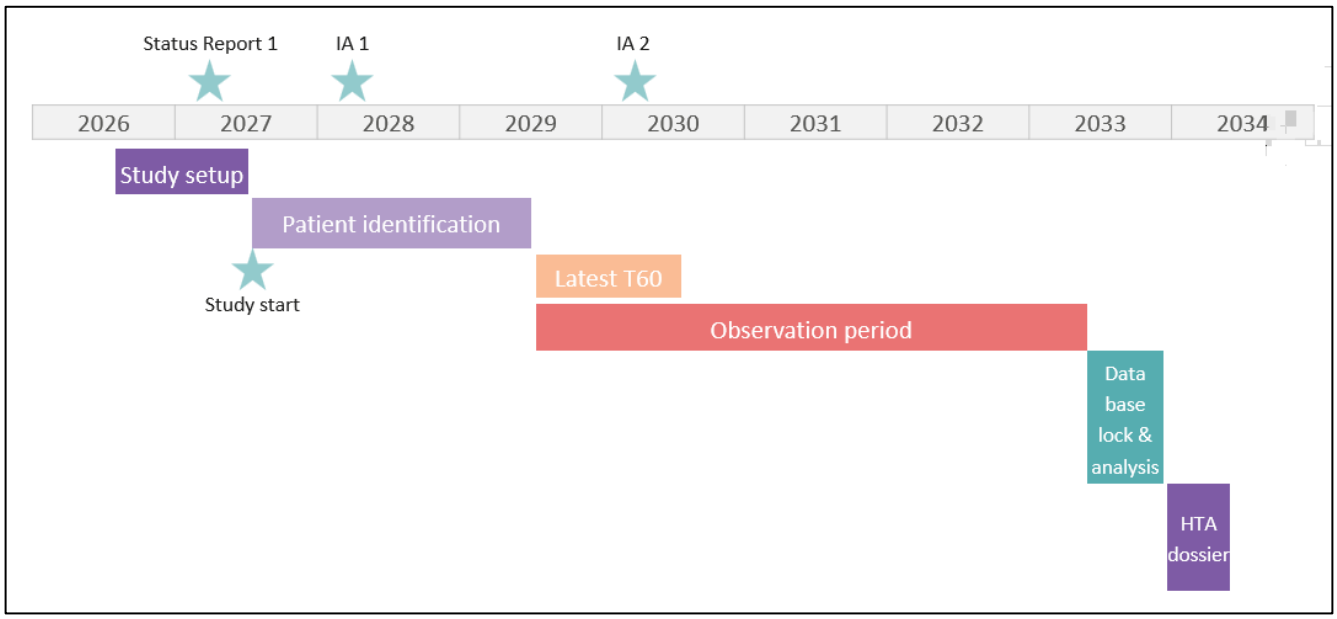
    Assuming the last Exa-cel patient with a treatment decision for Exa-cel in June 2029 is included into the AbD, this patient's T60 is assumed to occur around June 2030.
4. For every patient three years of follow-up are required to satisfy the G-BA's requirement regarding the primary endpoint "VOC freedom over 36 months", which is assessed from T60 onwards. Therefore, a patient with a therapy decision at the end of identification period, in the best case, would conclude the study in June 2033.

The timelines described are illustrated in Figure 1 below.

An additional six months can be estimated for source data verification and data cleaning before database lock and data analysis. Preparation of the benefit dossier is anticipated to take appr. 3 months, leading to final submission of the AbD data appr. April 2034, instead of January 2031. [redacted]

Considering this, execution within the G-BA-requested timelines is unfeasible and an AbD significantly running beyond G-BA-requested timelines to support the future benefit assessment of Exa-cel is highly likely. Vertex therefore considers the AbD not only unfeasible but disproportionate, as it will not be able to fulfil its intended purpose of a future benefit assessment based on comparative data.

Figure 1: Anticipated AbD timelines



5.2 Data availability for status reports or interim analyses

Based on the above, it cannot be reasonably expected that meaningful status updates or interim analyses can be provided for 6 months, 18 months or even 36 months after AbD start, if the AbD start is defined as the time of G-BA resolution (as is the current practice).

Data collection is planned prospectively; the patient identification window will start after the study is fully set up and the first patient has a therapy decision for Exa-cel. Therefore, it cannot be expected that any included Exa-cel patient will have been infused at the time of the first planned interim analysis 18 months after the time of G-BA resolution. Thus, neither sample size re-calculation nor a futility analysis will be possible at that time.

The second interim analysis is planned 36 months after G-BA resolution. At this time, it is anticipated that the identification window will be closed. None of the co-primary endpoints will have sufficient data to allow for a final sample size re-calculation.

Overall, meaningful assessments cannot be made on the AbD status or preliminary results over the first 18 months after study start, as defined by G-BA. Therefore, no meaningful decisions can be made with regards to timeline adjustments or overall study continuation.

6 ANALYSIS CONSIDERATIONS

To adequately inform a future benefit assessment, appropriate study design in the real-world setting should be implemented. In the protocol and SAP submitted to G-BA on May 21, 2026, Vertex maintains its position that the appropriate approach of analyzing Exa-cel effectiveness needs to consider separate by period analyses and an appropriate estimand handling strategy. Details are laid out below.

6.1 Separate by period analyses instead of one analysis over the entire observation period (ITT approach)

Except for the endpoint “VOC freedom”, the G-BA is requesting that analyses are conducted over the entire observation period per the ITT principle using the Full Analysis Set (FAS), i.e. not separately for the two treatment periods as proposed by Vertex.

There is significant concern about this approach as treatment with Exa-cel can only exert its effect on VOCs after the infusion of Exa-cel has taken place and its effect is only clearly measurable after a washout period of 60 days after the last RBC transfusion for post-transplant management has been completed (T60); the 60-day washout period is based on well-known and studied viability of transfused erythrocytes (7).

Estimating the treatment effect of both periods combined is a simplification that is not appropriate for cell and gene therapies such as Exa-cel which have long pre-treatment periods to prepare the patient for treatment. The following are specific concerns:

Interpretation of results:

Estimating the Exa-cel effect over both periods combined creates an averaged estimate that is representative neither of Period 1 where patients are undergoing mobilization, apheresis, conditioning and infusion nor Period 2 after which patients are treated.

As an example, assume

- Period 1 duration one year
- Period 2 duration three years
- Estimate over both periods combined (observation period): annualized rate of one VOC

This could be both due to four VOCs in Period 1 and zero in Period 2 as well as one VOC in each year of Period 1 and Period 2, making a real difference in patient’s lives.

This difficulty in interpretation was also already highlighted by registry representatives during the scientific advice meeting with G-BA (8).

The same issue applies to interpretation of safety analyses as the different steps of Exa-cel have different safety profiles.

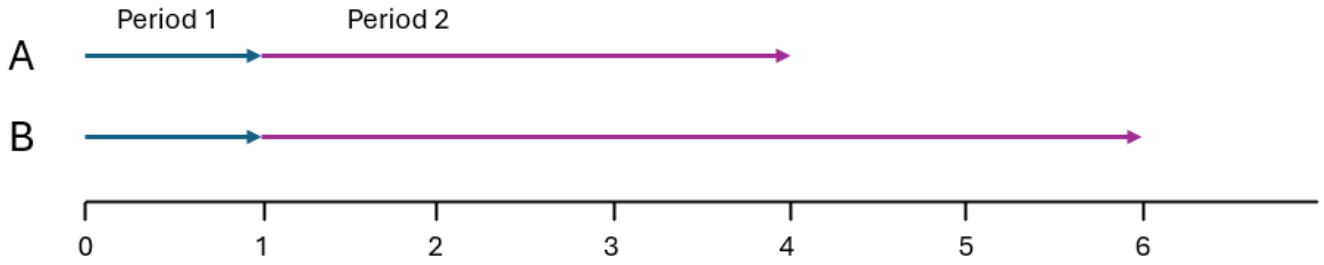
Dependence of results on study duration:

Estimating the Exa-cel effect over both periods combined, basically creates a weighted average of the effect with the weights reflecting period duration.

As shown from CLIMB-131 long term follow-up data (up to six years), the Exa-cel effect remains stable over time, while SoC effect is expected to remain stable or get worse over time.

As shown in Figure 2, if we estimate the effect of Exa-cel in a study of four years (scenario A) we will estimate the effect as $\frac{1}{4} * Period1\ effect + \frac{3}{4} * Period2\ effect$, while if we estimate the effect of Exa-cel in a study of seven years (scenario B) we will estimate the effect as $\frac{1}{7} * Period1\ effect + \frac{6}{7} * Period2\ effect$, resulting in different effect estimates solely based on study duration.

Figure 2 Scenarios of effect estimation based on study duration



Given that patients will still be ongoing after four years, estimating the effect solely on Period 2 will provide an estimate closer to real life expectation of Exa-cel treatment.

Conclusions

The prevention of VOCs (freedom from VOCs) and the reduction of VOCs are the main treatment goals of Exa-cel. Exa-cel can only exert its effect once infused and engraftment achieved, therefore this is when Exa-cel effectiveness can be compared to SoC appropriately. It is important to understand the clinical course of patients selected for Exa-cel that undergo mobilization, apheresis and conditioning prior to infusion, which is why we recommend capturing data for this period separately. Therefore, Vertex maintains the current approach to assess all endpoints for Period 1 and 2 separately.

6.2 Estimand handling strategy for Exa-cel treatment switch

The G-BA is requesting the implementation of the treatment policy strategy as primary estimand to assure analysis of all patient-relevant endpoints per ITT principle.

As outlined in the supplement for the protocol for a routine practice data collection of Exa-cel in SCD, Version 1.0, submitted to G-BA on June 13, 2025, the treatment policy strategy is inappropriate.

According to International Council for Harmonisation (ICH) E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials Page 5/19 EMA/CHMP/ICH/436221/2017:

"The principles outlined in this addendum are relevant whenever a treatment effect is estimated, or a hypothesis related to a treatment effect is tested, whether related to efficacy or safety. While the main focus is on randomised clinical trials, the principles are also applicable for single arm trials and observational studies."

According to the addendum the treatment effect to be tested has to be precisely defined:

"It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated."

Further, the addendum defines for treatment policy strategy:

"The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest".

Using treatment policy strategy for intercurrent event "Therapy decision for Exa-cel" translates into the following clinical question of interest:

Question of interest: Is Exa-cel therapy superior to SoC independent of whether SoC patients receive Exa-cel or not?

This clinical question is not aligned with the purpose of the AbD. The SoC treatment effect in this case is confounded with the treatment effect of Exa-cel. This is especially concerning as we cannot exclude the possibility of SoC patients switching to Exa-cel during the course of the AbD, especially given the small eligible population in Germany for Exa-cel, and more so with passing time and after the end of the patient identification period. Even though no estimation can be provided on how many SoC patients could switch to Exa-cel, it is anticipated that a large number of SoC patients will consider Exa-cel during the projected eight years of the study duration.

In addition, as patients, who are eventually treated with Exa-cel, will no longer be treated with SoC, we consider "treatment with Exa-cel" as irreversible crossover to the intervention arm. This type of crossover is not an acceptable option for a randomized clinical trial, which the AbD is trying to emulate. In a randomized clinical trial such crossovers would be excluded as treatment options per protocol.

Therefore, the use of treatment policy strategy for the intercurrent event of "therapy decision for Exa-cel" is not in line with the principles outlined in ICH E9 addendum.

From a medical perspective, it should be noted that following treatment policy for these patients would render the results of the SoC group uninterpretable. The most obvious aspect is that the necessary myeloablation will negatively affect the safety profile of the SoC group; in addition, the exchange transfusions during the mobilization procedures as well as the Exa-cel treatment effects after engraftment would skew the effectiveness outcomes of the SoC group.

To be able to follow the goal outlined for the AbD in the best possible way, the following is applied:

- Use hypothetical strategy for intercurrent event of "therapy decision for Exa-cel" for primary endpoint annualized VOC rate as well as secondary effectiveness endpoints
- For safety endpoints, evaluate data from SoC patients after Exa-cel therapy decision descriptively as a separate group.

Vertex has implemented treatment policy strategy for the intercurrent event "therapy decision for Exa-cel" for primary endpoint of VOC freedom as the impact on analysis is considered limited.

6.3 T60 imputation

The purpose of Period 2 analyses is to estimate the effect of Exa-cel after Exa-cel infusion. From that perspective, it is counterproductive to impute an arbitrary T60 date for Exa-cel patients that were never infused with Exa-cel. Therefore, an imputation strategy for T60 for these patients is not provided.

7 APPENDICES

7.1 Appendix I – Sample size estimation of VOCs leading to hospitalization over 3 years for patients ≥12 years old

Sample size estimation for endpoint of freedom from VOCs leading to hospitalization over 3 years starting from T60 analyzed in all patients starting Period 2 with T60 imputed for Exa-cel patients not being treated with Exa-cel is depicted in Table 1.

Table 1: Sample size estimation of VOCs leading to hospitalization over 3 years from T60 (FAS Period 2, T60 imputed) for patients ≥12 years old

Parameter	Assumption
Estimate	Risk Ratio
Analysis method	Log binomial regression model
Power	80%
Alpha	0.05 (two-sided)
Shifted null hypothesis	2.0
Allocation ratio	1:2
Exa-cel response rate	75.9%
SoC response rate	25.0%
Evaluable patients*	224 (75 on Exa-cel, 149 on SoC)
Drop-out rate (in Period 1)	12.5%
Total sample size	258 (86 on Exa-cel, 172 on SoC)

*Calculated using the nBinomial function from the gsDesign package in R.

In the reference studies **CLIMB-121/131,** which is assumed to be representative of the study population in the AbD as the same KCO criteria are applied, 17 of 63 patients did not reach Period 2. Of the 46 patients who received Exa-cel and reached Period 2, 4 of 46 experienced a vaso-occlusive crisis requiring hospitalization. One patient (1 of 46) died, and 13 patients were still ongoing.

Assuming that 1 of these 13 ongoing patients would need to be classified as a non-responder, the estimated response rate for these 46 patients is **40/46**.

For the 17 discontinued patients, it is assumed that 7 patients discontinue the study before an imputed T60, and 10 patients remain in the study but receive SoC therapy.

In an analysis in which only patients who discontinue the study before their theoretical T60 are excluded (**FAS Period 2, T60 imputed**), the estimated response rate is **75.9%**. This calculation is based on the following formula:

$$(46 \times 40/46 + 10 \times 0.25)/(46 + 10) = 75.9\%$$

Under this scenario, the study discontinuation rate in Period 1 is approximately **12.5%**.

To demonstrate a benefit of Exa-cel over SoC therapy with a statistical power of at least 80%, a total of **N = 258** patients would need to be enrolled (**N = 86** for Exa-cel and **N = 172** for comparator therapy). This calculation is based on a shifted null hypothesis of **2.0** for freedom from VOCs requiring hospitalization, taking into account all patients who do not discontinue the study before their (imputed or actual) T60.

If, however, all patients who initiate the study (**FAS**) were to be included in the analysis, the response rate for Exa-cel would need to be assumed to be even lower, which would result in a higher required sample size.

7.2 Appendix II – Number of Exa-cel-eligible patients aged 12 years or older within the GPOH SCD registry

The number of patients recorded in the GPOH SCD registry who may be enrolled in an AbD can be estimated using the following steps (the detailed calculation is presented in Table 2):

1. Number of patients recorded in the GPOH Registry: As of May 2026, 1,239 patients were recorded in the GPOH SCD registry (1,441 recorded patients, of whom 202 were lost to follow-up or died) [1].
2. Number of patients potentially eligible for Exa-cel: Applying the calculation approach used by the Federal Joint Committee (G-BA) (as of 18 September 2025) results in an estimate of 92 to 101 patients at German treatment centers affiliated with the GPOH SCD registry who are, in principle, eligible for Exa-cel (including patients not covered by statutory health insurance). This number is below the minimum number of patients required for the conduct of the AbD.
3. According to the GPOH SCD registry, 71.3% of patients in the registry were <12 years old at time of registration into the registry[1]. This indicates that the percentage of patients aged ≥ 12 years in the calculation below is a substantial overestimation, indicating the overall number of Exa-cel eligible patients in German treatment centers within the GPOH registry is substantially overestimated as well.
4. Availability for the AbD: Not all patients will consent to participate in the AbD or be able to participate. It must therefore be assumed that fewer than the 100 patients required for adequate confounder adjustment will be available for the AbD.[1]

Table 2: Calculation of patient numbers in relevant German treatment centers within the GPOH registry aged 12 years or older *(all assumptions used in steps 2 to 5 are identical to those applied by the G-BA (9).)*

	Calculation step	Number of patients
1	Number of patients in the GPOH SCD Registry[1]	1,239
2	Number of patients aged ≥12 years (min; max: 74.1%; 75.8%)	918 – 939
3	Number of patients with ≥2 VOCs per year (23.25%)	213 - 218
4	Number of patients eligible for the treatment procedure (54.0%)	115 – 118
5	Number of patients for whom no HLA-compatible related hematopoietic stem cell donor is available (min; max: 80.0%; 86.0%)	92 - 101

1) Information from GPOH SCD registry provided to Vertex as of May 2026.

7.3 Appendix III – Prevalence of Exa-cel-eligible patients aged ≥12 to <21 years in Germany

Table 3: Calculation of prevalence of Exa-cel-eligible patients aged ≥12 to <21 years *(all assumptions used in steps 2 to 5 are identical to those applied by the G-BA (9).)*

	Calculation step	Number of patients
1	Number of sickle cell patients in Germany	2,000 – 4,558
2	Number of patients aged ≥12 to <21 years (19.96%)[1]	399 – 910
3	Number of patients with ≥2 VOCs per year (23.25%)	93 – 211
4	Number of patients eligible for the treatment procedure (54.0%)	50 – 114
5	Number of patients for whom no HLA-compatible related hematopoietic stem cell donor is available (min; max: 80.0%; 86.0%)	40 - 98

1) Calculation based upon registry data from Kunz et al., 2021(10). Age distribution provided by author upon request. Age group 18-25 years (15.10%) was approximated linearly for age group 18 to 20 years (result: 5.66%).

7.4 Appendix IV – Number of Exa-cel-eligible patients aged ≥12 to <21 years within the GPOH SCD registry

The calculation from Table 2 has been replicated for patients aged ≥12 to <21 years based on the absolute number of patients aged ≥12 years to <21 years in the GPOH SCD registry.

Table 4: Calculation of patient numbers in relevant German treatment centers within the GPOH registry aged ≥12 to <21 years *(all assumptions used in steps 2 to 4 are identical to those applied by the G-BA (9).)*

	Calculation step	**Number of patients**
1	Number of patients in the GPOH Registry for Sickle Cell Disease	1,239
2	Number of patients aged ≥12 years to <21 years (19.96%)[1]	247
3	Number of patients with ≥2 VOCs per year (23.25%)	58
4	Number of patients eligible for the treatment procedure (54.0%)	31
5	Number of patients for whom no HLA-compatible related hematopoietic stem cell donor is available (min; max: 80.0%; 86.0%)	25- 27

1) Calculation based upon registry data from Kunz et al., 2021 (10). Age distribution provided by author upon request. Age group 18-25 years (15.10%) was approximated linearly for age group 18 to 20 years (result: 5.66%).

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