## 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 registry-based study required by G-BA

**Date of Protocol:** 13-June-2025

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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 according to the approved indication for Exa-cel comprises patients 12 years of age and older 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 morbidity (including pain, chronic organ damage, cerebrovascular events and the need for RBC transfusions), mortality and safety (including rates of serious adverse events [SAEs] and specific adverse events [AEs]).

The study is a non-interventional, prospective, non-randomized, comparative registry-based 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 one year 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 required 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 required Vertex to conduct a routine practice data collection (AbD) comparing Exagamglogene autotemcel (Exa-cel) with patient-individualized treatment for patients 12 years of age and older 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 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 morbidity, including pain, chronic organ damage, cerebrovascular events and the need for red blood cell (RBC) transfusions, as well as mortality (i.e. annualized death rate). The safety objectives are to compare rates of serious adverse events (SAEs) and specific adverse events (AEs). |
| **Data Sources** | This study will use clinical data from routine patient care as documented in the patients' medical files. Data will be entered into the GPOH registry, which will be amended to fulfill AbD requirements. 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 who have consented to transfer data to the registry. |

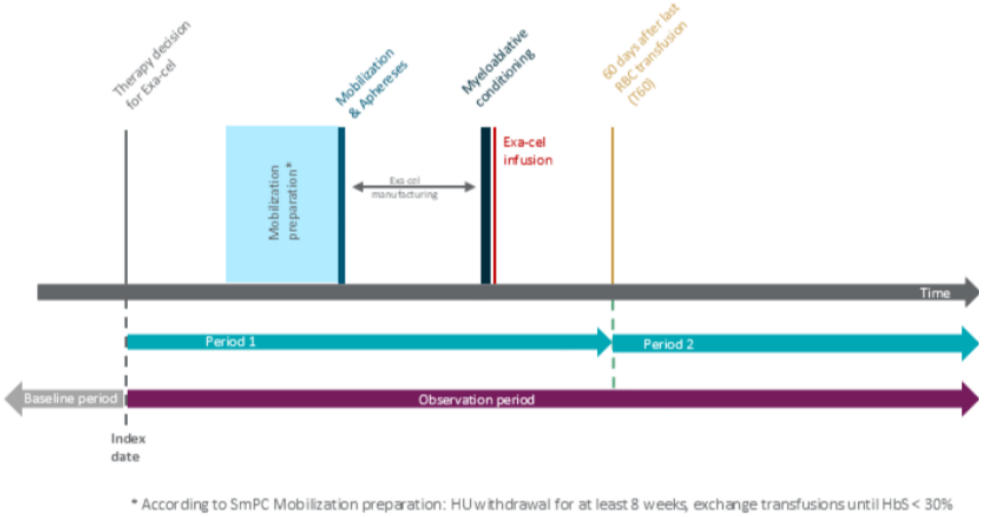
**Study Design**

The study begins with a patient identification period planned to last 2 years. Therapy decision for Exa-cel, as defined by informed consent and reimbursement confirmation, during this time window will trigger each respective patient to be included in the study. Their index date will be set as the date of therapy decision for Exa-cel.

As soon as an Exa-cel patient no longer requires RBC transfusions for more than 60 days post-transplant (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 censoring, whichever comes first), is defined as Period 1. The period from T60 to the end of the study (or censoring) 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.**




**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.

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 according to the assessment of the treating physician
4. An HLA-matched related HSC donor is not available (discretion of treating physician)
5. ≥12 years of age at index date
6. Number of VOCs at least in the year before index date is available in the patient's file
7. Receives patient-individualized treatment with hydroxycarbamide and / or chronic RBC transfusions at index date
8. Provided written, signed informed consent for their data to be included in the study
9. For Exa-cel patients only: Reimbursement approved by health insurance provider

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

1. Treatment with Exa-cel 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
2. Patient is not eligible for full myeloablative conditioning according to the assessment of the treating physician

**Treatment**

- Exagamglogene autotemcel

**Comparator**

- Hydroxycarbamide
- Chronic RBC transfusions

**Endpoints**

**Primary:**

***Morbidity:***

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

**Secondary:**

***Morbidity:***

- Annualized VOC rate in Period 1
- Proportion of patients with prescription of non-opioid analgesics during Period 1 and in 6-month intervals during period 2, all types and by type (WHODRUG preferred name)
- Proportion of patients with prescription of opioid analgesics during Period 1 and in 6-month intervals during Period 2, all types and by type (WHODRUG preferred name)
- Proportion of patients with
    - Newly occurring chronic organ damage by period, all types and by type
    - Worsened chronic organ damage by period, all types and by type
    - Improvement of chronic organ damage by period, all types and by type
- Proportion of patients with new cerebrovascular events or new pathological transcranial Doppler measurements of intracerebral blood flow by period, all types and by type
- Proportion of patients requiring RBC transfusions for the treatment of complications of SCD by period, all types and by type (acute / chronic)

***Mortality:***

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

***Safety:***

- Proportion of patients with SAEs by period
- Annualized rate of SAEs by period
- Proportion of patients with specific AEs by period
- Annualized rate of specific AEs by period

**Study Size**

The estimated sample size for a powered comparative analysis of the co-primary endpoint VOC freedom is a minimal number of 75 eligible patients (1:2 allocation, i.e., 25 patients in the Exa-cel group, 50 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]). This calculation is based on assumed response rates of 93% for Exa-cel and 25% for the comparator group as proposed by G-BA. To account for an assumed 25% rate of patients with a decision for

Exa-cel treatment who do not receive Exa-cel or who die or are lost to follow-up after receiving Exa-cel, inclusion of at least 33 Exa-cel patients for this endpoint analysis is targeted.

The study design is set up to include SCD patients from the GPOH SCD registry who are treated at specific transplant centers, have signed informed consent for the study, who fulfill all inclusion and none of the exclusion criteria and who have a therapy decision for Exa-cel or are Standard of Care (SoC) patients sufficiently similar to Exa-cel patients (as identified by the matching algorithm) during the identification period. A sample size of at least 100 patients (including 33 patients on Exa-cel) is considered appropriate and was also stipulated by G-BA.

**Statistical Methods**

All endpoints will be analyzed comparatively (Exa-cel group vs. patient-individualized treatment group) 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 potential confounding in all comparative analyses.

**Planned Analyses**

Two interim analyses including futility analyses regarding the required sample size will be conducted 18 months and 36 months after study start. 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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# 7 LIST OF ABBREVIATIONS

| 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*) |
| EoS | End of study |
| Exa-cel | Exagamglogene autotemcel |
| CD | Cluster of differentiation |
| CI | Confidence interval |
| CRISPR-Cas9 | Clustered regularly interspaced short palindromic repeats/CRISPR-associated 9 |
| DNA | Deoxyribonucleic acid |
| eCRF | Electronic case report form |
| FAS | Full Analysis Set |
| G-BA | Federal Joint Committee (*Gemeinsamer Bundesausschuss*) |
| GDPR | General Data Protection Regulation |
| GPOH | Society of Pediatric Oncology and Hematology (*Gesellschaft für Pädiatrische Onkologie und Hämatologie*) |
| GvHD | Graft-versus-host-disease |
| Hb | Hemoglobin |
| HbA | Hemoglobin A |
| 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 |
| HPFH | Hereditary persistance of fetal hemoglobin |
| HSC(T) | Hematopoietic stem cell (transplantation) |
| HSPC | Hematopoietic stem and progenitor cell |
| HU | Hydroxycarbamide (Hydroxyurea) |
| IA | Interim analysis |
| 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 (Kompetenz-Centrum Onkologie der Medizinischen Dienste) |
| LIC | Liver iron concentration |

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|---|---|
| LVEF | Left ventricular ejection fraction |
| MACNU Design | Modified Active Comparator New-User (MACNU) Design |
| MAH | Marketing Authorization Holder |
| MED | Mediterranean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDAT | Medical data |
| MUD | Matched unrelated donor |
| NI | Non-interventional |
| NYHA | New York Heart Association |
| PICO | Population, Intervention, Comparator, Outcome |
| PNUD | Prevalent New User Design |
| PS | Propensity score |
| PT | Preferred term |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCD | Sickle cell disease |
| SCT | Stem cell transplantation |
| SD | Standard deviation |
| SEA | Southeast Asia |
| SoC | Standard of Care |
| TCD | Transcranial Doppler |
| uACR | Urine albumin-creatinine ratio |
| VOC | Vaso-occlusive crisis |

# 8 RESPONSIBLE PARTIES

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# 9 REVISION HISTORY

Not applicable for this version of the document.

# 10 INTRODUCTION

## 10.1 Background

Sickle cell disease (SCD) encompasses a range of inherited red blood cell disorders that arise from a point mutation in the *HBB* gene, which codes for the β-globin chain of the adult hemoglobin (Hb) (1). 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 red blood cells (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 (2).

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 (3).

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 (4). 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 (5-7).

SCD is common throughout large areas of sub-Saharan Africa, the Middle East, and India (8). 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 (9). In Germany, the prevalence of SCD in 2019 was estimated to be approximately 3,160 patients (10). First results from the nationwide newborn screening established in Germany in 2021 show an incidence of 80-160 newborns affected by SCD per year (11, 12). 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 (13-17).

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 (3). 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 (18).

The only curative therapy currently available for patients with SCD is allogenic hematopoietic stem cell transplantation (HSCT). The gold standard for allogenic 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 (19). Graft failure or graft-versus-host-disease (GvHD) and infections are major risks associated with allogenic 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 vast 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 (20-22).

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 required Vertex to conduct a non-randomized, prospective, comparative, registry-based study comparing Exa-cel with existing therapy alternatives for patients with SCD, with the decision becoming effective with market entry (23, 24).

## 10.2 Study Rationale

This study is planned in accordance with the G-BA resolution on the requirement of an AbD for patients with SCD treated with Exa-cel compared to patient-individualized treatment (23, 24). 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 (23, 24).

# 11 STUDY OBJECTIVES AND ENDPOINTS

The aim of this non-interventional 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 years and older 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<br>• Chronic red blood cell (RBC) transfusions |
| **Outcome** | Objectives and endpoints of this study are presented in detail in Table 2. |

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, and
- To compare the proportion of VOC-free patients over 36 months between Exa-cel and Standard of Care (SoC).

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 (25).

Definitions for all relevant time periods for the study are contained in section 12.2.

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

**Table 2: Objectives and endpoints**

| Objective | Endpoint |
|---|---|
| ***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 |

| Objective | Endpoint |
|---|---|
| ***Secondary*** | |
| *Morbidity* | |
| To compare the annualized rate of VOCs | Annualized VOC rate in Period 1 |
| To compare pain medication prescriptions for SCD management over time | • Proportion of patients with prescription of non-opioid analgesics during Period 1 and in 6-month intervals during Period 2, all types and by type (WHODRUG preferred name)<br>• Proportion of patients with prescription of opioid analgesics during Period 1 and in 6-month intervals during Period 2 all types and by type (WHODRUG preferred name) |
| To compare the proportion of patients with newly occurring or worsened chronic organ damage or improvement of chronic organ damage | Proportion of patients with<br>• Newly occurring chronic organ damage by period; all types and by type<br>• Worsened chronic organ damage by period; all types and by type<br>• Improvement of chronic organ damage by period; all types and by type<br>The following events are considered as relevant chronic organ damage in SCD patients:<br>• Aseptic osteonecrosis<br>• Cardiomyopathy<br>• Retinopathy<br>• Hepatopathy<br>• Pulmonary hypertension<br>• Osteoporosis<br>• Nephropathy<br>• Leg ulcer<br>• Alloimmunization<br>• Siderosis |
| To compare the proportion of patients with new cerebrovascular events | Proportion of patients with new cerebrovascular events by period, all types and by type:<br>• Stroke (ischemic, hemorrhagic)<br>• De novo pathologic intracerebral blood flow as measured by transcranial doppler sonography |
| To compare need for RBC transfusions | Proportion of patients requiring RBC transfusions by period, all types and by type (acute / chronic) |

| Objective | Endpoint |
|---|---|
| *Mortality* | |
| To compare the annualized death rate | Proportion of patients who died by period<br>Annualized death rate by period |
| *Safety* | |
| To compare the occurrence of SAEs | Proportion of patients with SAEs by period<br>Annualized rate of SAEs by period |
| To compare the occurrence of specific AEs | Proportion of patients with specific AEs by period<br>Annualized rate of specific AEs by period<br>The following are defined as specific AEs:<br>• Bleeding<br>• Infection |
| a: For definitions of analysis periods, see section 12.2 | |

# 12 RESEARCH METHODS

## 12.1 Data Sources and Data Collection

The data source for this study are clinical data from routine patient care as documented in the patients' medical files. Data will be entered into the GPOH 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 12.5). 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 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, 45 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 proportion of adult patients is expected to increase during the AbD, as G-BA requires all healthcare providers (physicians, medical care centers and facilities, hospitals) that provide Exa-cel, to be included in the study and therefore in the GPOH SCD registry (26). This is expected to lead to participation of more "adult centers".

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. The data are transferred 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 are offered inclusion in this study. 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 guidance by G-BA (28) and in the checklist for individual cost coverage requests with the medical services of the German payers (KCO checklist) (29). Similar criteria will be applied for all participating centers because the evaluation of a patient's eligibility according to the selection criteria (see section 12.3) as well as the decision for or against a prescription of Exa-cel require transplant expertise.

The GPOH SCD registry is regarded by G-BA as a suitable primary data source if specific limitations are addressed.

## 12.2 Study Design

This is a prospective, non-interventional, observational, non-randomized, comparative, registry-based study using data recorded in the GPOH registry. Individuals will be identified within the GPOH SCD registry. The consent patients have already provided to the registry does not cover all elements required for the present study. Therefore, an additional informed consent is needed for every patient for the use of their data for the purposes of this study.

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 in the study. SCD treatment can consist of Exa-cel or any of the comparators hydroxycarbamide 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 12.4.2). From the index date onwards, data from both Exa-cel and SoC patients will be collected as part of routine clinical practice in the GPOH SCD registry 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 (25)). T60 was utilized within the pivotal Exa-cel study CTX001-121 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.

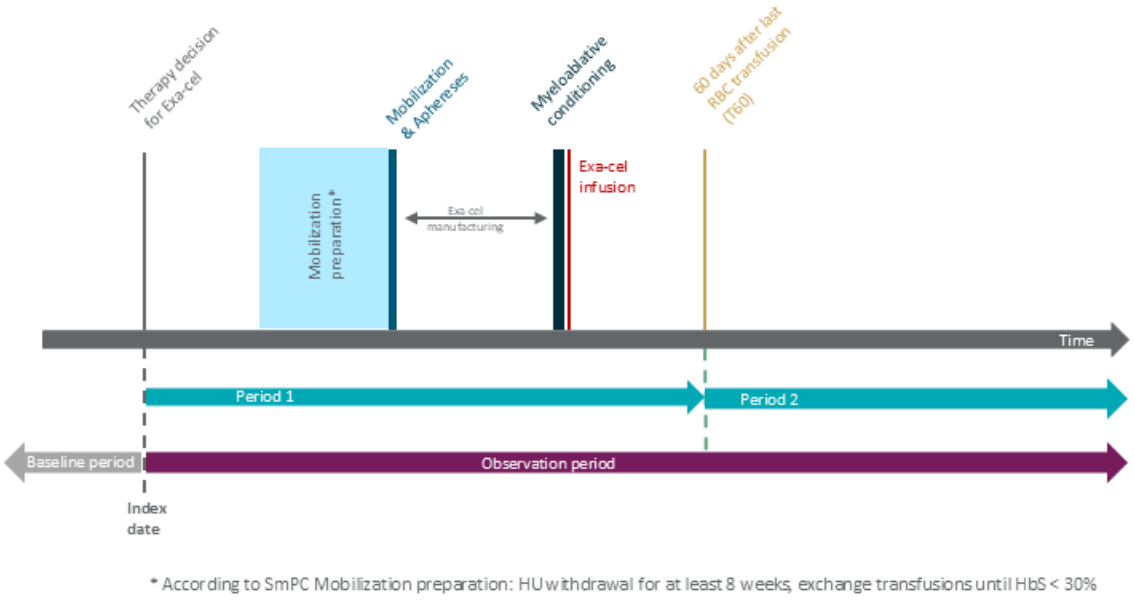


**Figure 1: Overview of Exa-cel treatment from therapy decision to end of study and time periods relevant for the AbD at a patient level.**

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 | Eligible patients will be identified between AbD start and 2 years after that, i.e., their index date, as defined below, falls within a 2-year period after AbD start. |
| Index date | For Exa-cel patients, the index date is defined as the date of therapy decision for Exa-cel (treatment consent and reimbursement approved).<br>For SoC patients, the index date is defined as the index date of the Exa-cel patient they were matched to. |
| 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).<br>For a SoC patient, T60 is defined as the same T60 date of the matched Exa-cel patient. If the matched Exa-cel patient does not have a T60 date, the SoC patient will also not be assigned a T60 date. |

| Time period / study date | Definition |
|---|---|
| Baseline period | The one-year period prior to the index date is defined as the baseline period for each patient. |
| Observation period | The observation period is defined as the period from the index date to the end of the study or censoring. 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 to censoring, whichever comes first, is defined as Period 1. |
| Period 2 | The period from T60 to the end of the study or censoring 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 censored at time of death, informed consent withdrawal, or loss to follow-up. During the observation period, intercurrent events such as treatment decision for Exa-cel or any other HSCT for SoC patients may occur. This will not impact data collection, which will continue as part of routine clinical practice in the GPOH SCD registry. Information on how intercurrent events will be considered in effect estimation is included in section 13 of this protocol and in the statistical analysis plan (SAP).

### 12.3 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.

#### 12.3.1 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 according to the assessment of the treating physician
4. An HLA-matched related HSC donor is not available (discretion of treating physician)

5. ≥12 years of age at index date
6. Number of VOCs at least in the year before index date is available in the patient's file
7. Receives patient-individualized treatment with hydroxycarbamide and / or chronic RBC transfusions at index date
8. Provides written, signed informed consent for inclusion in the study
9. For Exa-cel patients only: reimbursement approved by health insurance provider

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

Only Exa-cel patients with confirmed reimbursement will be considered in this study, as otherwise Exa-cel cannot be deemed available to the respective patient, in line with inclusion criterion 9.

SCD patients may receive an allogenic stem cell transplantation (SCT) from an HLA-MUD. However, as treatment with Exa-cel is not recommended for patients with a history of allogenic or autologous SCT per label, MUD-SCT patients cannot receive Exa-cel. Including patients who have already had a MUD-SCT would thus violate the positivity assumption. Therefore, such patients will not be included in the study.

Patients included into the study may have a treatment decision for MUD-SCT or any other SCT after index date. How this change in treatment is handled in the analysis is described in section 13 of this protocol and in the SAP.

### 12.3.2 Exclusion Criteria

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

1. Treatment with Exa-cel 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
2. Patient is not eligible for full myeloablative conditioning according to the assessment of the treating physician

## 12.4 Patient Identification

### 12.4.1 Patient Identification Period

A minimum follow-up time of 36 months starting 60 days after the last RBC transfusion for post-transplant management is planned for each individual. 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 is defined as a two-year time window beginning at AbD start.

Patients for whom an Exa-cel therapy decision (treatment consent and reimbursement approved) 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, all sufficiently similar (in terms of age, 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 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 (for details see explanation of MACNU design in section 12.4.2).

In case SoC patients may have a therapy decision for Exa-cel after the patient identification period, they will remain in the comparator group for analysis. Details on how a treatment switch to Exa-cel after the patient identification period or a decision for allogenic HSCT after inclusion into the SoC group will be handled in the analysis of endpoints are described in section 13 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.

### 12.4.2 Modified Active Comparator New-User Design

The inclusion and exclusion criteria of this study (see section 12.3) 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

It is anticipated that external factors, especially selection criteria based on disease severity, will be utilized by medical services of payers (German: Medizinischer Dienst) for individual cost coverage requests in the real-life situation in Germany. In addition, the label per se narrows the population to those patients who are sufficiently fit to undergo an HSCT and are able to undergo full myeloablation. While ostensibly being eligible for Exa-cel treatment per the label wording, due to these external imposed factors, the majority of patients on SoC will in practice not be considered for potential treatment with Exa-cel. Therefore, it is not medically justified to include all patients currently enrolled in the GPOH SCD registry to this study; instead, 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 the inclusion criteria, already on continuous SCD SoC treatment (HU 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 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) (30). 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 the selection of SoC patients with similar disease severity characteristics to the Exa-cel patients, which is essential to ensure comparable treatment cohorts. The flow chart in Figure 2 illustrates the MACNU design.

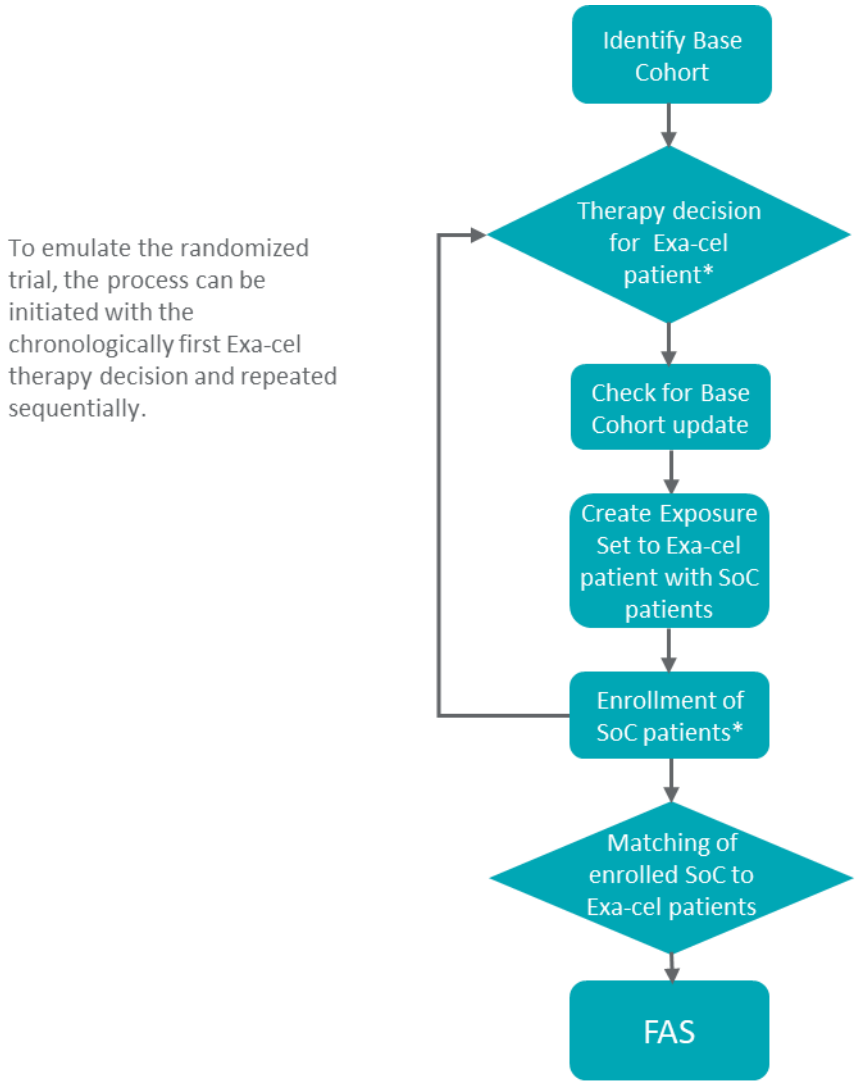


**Figure 2: Flow chart of the MACNU design**

*Therapy decision has to fall into 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 is explained step-by-step below.

The following steps of the MACNU design are initiated with the first chronological Exa-cel patient included into the study.

**Current base cohort**

Every time a therapy decision for Exa-cel is made within the patient identification period, all eligible SoC patients in the GPOH SCD registry (also including those patients who are already in the study), are screened to define the base cohort to that date.

**Creation of exposure sets:**

An exposure set is a subset of patients from the current base cohort at the time a decision is made for a given patient to receive Exa-cel therapy. The exposure set includes SoC patients with similar characteristics to the Exa-cel patient, where similarity is based on age, number of VOCs in the year prior to the index date and chronic treatment with RBC transfusions.

The choice of these variables is based on the principal idea of the MACNU design of selecting SoC patients with similar disease severity to Exa-cel patients:

- Age is an important determinant of an SCD patient's health status and thus disease severity, especially regarding accumulated comorbidities and complications due to the progression of SCD. The proposed age strata take this into account as well as the stipulations by G-BA's ATMP quality guidance for Exa-cel (28) and the checklist for individual cost coverage requests with the medical services of the German payers (KCO checklist) (29): These stipulations govern whether a therapy decision is made by a pediatric or an adult hematologist, as well as require special considerations and justifications for the use of Exa-cel beyond the age of 35 years. Therefore, age is a crucial factor for the therapy decision, health state of the patient and, thus, expected outcome of any SCD therapy.
- The number of VOCs 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 to treatment and supportive measures. The number of past VOCs is also a well-known risk factor for the occurrence of future VOCs. Furthermore, the number of VOCs in the patient's recent past is decisive for certain therapy decisions (e.g. the need for starting or intensifying chronic RBC transfusions) and is a factor to be considered for therapy decision for Exa-cel according to the KCO checklist (29).
- 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. They clearly affect therapy decisions and are major criteria to be considered as stipulated by G-BA's ATMP quality guidance for Exa-cel as well as the KCO checklist (28, 29).

Once the decision has been made to treat a patient with Exa-cel, all SoC patients from the base cohort who have comparable patient characteristics (as per selection process described below) with regard to the three stratification factors at the time of the index date of the Exa-cel patient are assigned to that Exa-cel patient to form an exposure set.

Patients identified to be suitable for the exposure set and not already included in the study are asked to provide their informed consent for their registry data to be used in this study.

*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.*

The creation of exposure sets is a stepwise approach using the following 3 variables for stratification of the SoC patients in the base cohort:

- Treatment with chronic RBC transfusions (yes / no) at therapy decision for the Exa-cel patient
- Number of VOCs during the baseline period defined as the year before therapy decision for the Exa-cel patient, categorized as 0, 1-2, ≥3
- Age (in years) at therapy decision for the Exa-cel patient categorized as 12-21, 22-35, ≥36

On the basis of these criteria (3 variables with 2, 3 & 3 categories), 18 strata (i.e., 2 x 3 x 3) are formed.

The steps to create the exposure set for a specific Exa-cel patient are as follows:

1. Create strata based on the above stratification variables and assign all SoC patients from the current base cohort into one of the strata
2. Identify the stratum for the Exa-cel patient
3. Check if there are at least 3 SoC patients in the Exa-cel stratum; if not, a stepwise approach will be applied to identify further patients:
    a. Criterion "age" will be eliminated. The strata will be re-formed accordingly, and patients will be re-assigned (resulting in 6 strata).
    b. If the stratum containing the Exa-cel patient still contains less than 3 SoC patients after step a, the process will be stopped and the 0-2 SoC patients in that stratum will be accepted.

Eligible SoC patients in the exposure set will be included in the study, subject to informed consent. Preference is given to patients for whom data from the past year is available in the GPOH SCD registry. Before accepting a stratum with fewer than 3 patients (see step "b" above), patients with data entry of ≥1 to <3 years in the past will also be considered. Data from the past year from these patients should be entered into the GPOH SCD registry database as soon as possible.

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. An 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 Informed consent form (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 the 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 age and number of VOCs as continuous variables) 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.

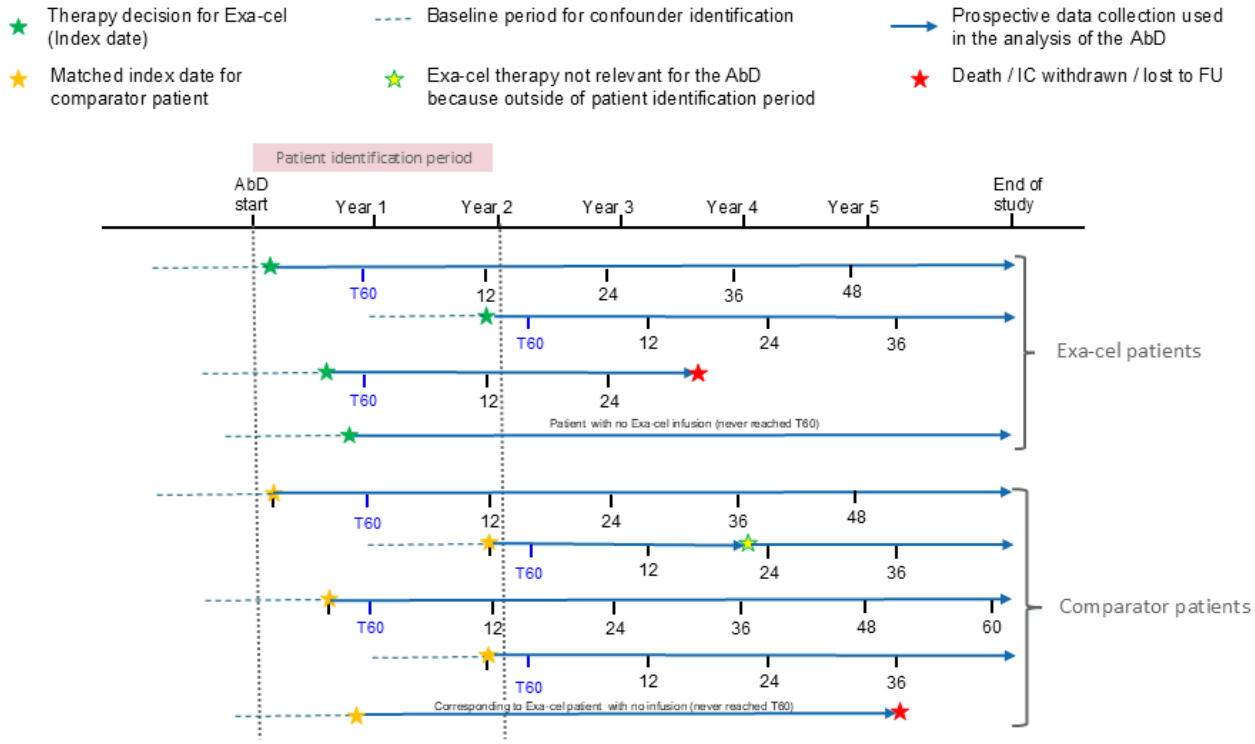


**Figure 3: Exemplary treatment patterns, formation of exposure sets and allocation to Exa-cel and comparator group**

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 or censoring due to death, withdrawal of informed consent 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 end of study or censoring due to death, withdrawal of informed consent, 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')

**Alternative approach for the MACNU design described above**

The first planned interim analysis will have a data cut-off date at approximately the halfway point of the patient identification period (12 months after study start), the scope of this interim analysis is outlined in the SAP. A futility analysis (see section 14) will examine whether, at this time, a sufficient number of SoC patients have been included to achieve the final sample size goal (outlined in section 13.5) at the end of the patient identification period by continuing the described MACNU design.

If the number of SoC patients specified for the futility analysis has not been reached at interim analysis 1, the MACNU design will be modified from this point onwards: Once a new Exa-cel patient is identified, the updated base cohort and all subsequent updated base cohorts will only include those SoC patients in the GPOH SCD registry who are not yet included in another exposure set, i.e. have not yet been included into 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 aims to ensure that a sufficient number of SoC patients will be included in the study.

## 12.5 Variables

For each individual, patient demographic and clinical characteristics as well as a broad range of safety and effectiveness outcomes are or will be collected in the GPOH SCD registry (Table 4). For patients included in the AbD, data will be collected according to Table 4. Wherever possible, the operationalization employed in the GPOH SCD registry will be adopted. The baseline value of a variable is the closest measurement before or at index date during the one-year baseline period.

**Table 4: Variables and their operationalization within the GPOH SCD registry**

| Variable | Operationalization |
|---|---|
| **Demographics and Baseline characteristics*** | |
| Sex | Male / female |
| Age (years)** | Date of birth |
| Body height | cm |
| Body weight | kg |
| Genotype | Diagnosis / subtype:<br>HbSS, HbSC, HbSß0 Thal, HbSß+ Thal, HbS/OArab, HbS/D Punjab, HbS/C Harlem, HbC/S Antilles, HbS/Quebec-CHORI, HbA/S Oman, HbS/E, HbA/Jamaica Plain, HbS/HPFH, other |
| Age at diagnosis | Date of diagnosis – date of birth |

| Variable | Operationalization |
|---|---|
| Prior and concomitant diseases<br>• Nephropathy **<br>• Chronic pain**<br>• Hepatopathy**<br>• Pulmonary hypertension**<br>• Cerebrovascular event (prior stroke, neurological deficit)**<br>• Alloimmunization**<br>• Siderosis (iron overload)**<br>• Cardiomyopathy<br>• Osteoporosis<br>• Proliferative retinopathy<br>• Pulmonary hypertension<br>• Ulcus cruris<br>• Gallstones<br>• Aseptic osteonecrosis (incl. status post-surgical correction)<br>• „Other underlying diseases“ | Yes / no (unless otherwise specified)<br><br>Medical Dictionary for Regulatory Activities (MedDRA) coded |
| Smoking regularly | Yes / no |
| Alpha-thalassemia | Yes / no (if yes α 3,7 homozygous, α 3,7 heterozygous, α 4,2 homozygous, α 4,2 heterozygous, α 20,5 homozygous, α 20,5 heterozygous, SEA homozygous, SEA heterozygous, MED homozygous, MED heterozygous, α triplication, α1 mutation homozygous, α1 mutation heterozygous. Other) |
| Modifiers of fetal hemoglobin (HbF) synthesis | Yes / no (if yes BCL11A rs 766432 homozygous, BCL11A rs 766432 heterozygous, HMIP rs 9399137 homozygous, HMIP rs 9399137 heterozygous, Gamma-Globin-Promotor Xmnl-Polymorphism homozygous, Gamma-Globin-Promotor Xmnl-Polymorphism heterozygous) |
| Total hemoglobin (Hb) | mmol/dL |
| Sickle cell hemoglobin (HbS) level | % of total Hb |
| HbF level | % of total Hb |

| Variable | Operationalization |
|---|---|
| VOCs ** | Number of VOCs over 12 months prior to index date<br>VOC defined as hospitalization with overnight stay for any of the following:<br>• Priapism: no, yes, unknown<br>• Splenic sequestration(s): no, yes, unknown<br>• Acute chest syndrome(s) (ACS): no, yes, unknown / number of ACSs<br>• Pain crises: no, yes, unknown / number of hospital days |
| Chronic transfusion therapy** | Yes / no<br><br>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), mean HbS level prior transfusions (%) |
| Iron chelation | Yes / no;<br><br>Among patients with „yes": Desferroxamine yes / no, Deferasirox yes / no, phlebotomy yes / no |
| HU therapy ongoing at index date | Yes / no,<br>Among patients with "yes": dose (mg/kg*d), indication (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)<br>Among patients with "no": date of discontinuation, 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 |
| Eligibility for HSCT according to the assessment of the treating physician*** | Yes / no<br>If no: reason |
| An HLA-matched related HSC donor is not available (discretion of treating physician)*** | Yes / no |

| Variable | Operationalization |
|---|---|
| Concomitant pain medication***<br>• Non-opioid analgesics<br>• Opioid analgesics | Pain medication will be coded via WHODRUG |
| Chronic organ damage<br>• Aseptic osteonecrosis<br>• Cardiomyopathy<br>• Retinopathy<br>• Hepatopathy<br>• Pulmonary hypertension<br>• Osteoporosis<br>• Nephropathy<br>• Leg ulcer<br>• Alloimmunization<br>• Siderosis | Yes / no for each |
| Patient eligible for AbD (all inclusion and none of the exclusion criteria fulfilled)*** | Yes / no |
| **Variables for morbidity endpoints** | |
| VOCs leading to hospitalization | Number of VOC defined as hospitalization with overnight stay for any of the following:<br>• Priapism: no, yes<br>• Splenic sequestration(s): no, yes<br>• Acute thorax syndrome(s) (ACS): no, yes, / number of ACSs, number of days on ventilation<br>• Pain crises: no, yes, number, number of days in hospital |
| RBC transfusions:<br>• Acute RBC transfusion<br>• Chronic RBC transfusions | Number, total volume of transfusions (ml), type (exchange transfusion, erythrocyte apheresis, on top transfusion) |
| Eligibility for hematopoietic stem cell (HSC) transplantation, per the discretion of the physician (ongoing assessment) | Yes / no |

| Variable | Operationalization |
|---|---|
| Chronic organ damage:<br>• De novo diagnosis<br>• Worsening<br>• Improvement<br>for the following<br>1. Aseptic osteonecrosis<br>2. Cardiomyopathy<br>3. Retinopathy<br>4. Hepatopathy ***<br>5. Pulmonary hypertension<br>6. Osteoporosis<br>7. Nephropathy<br>8. Leg ulcer<br>9. Alloimmunization<br>10. Siderosis<br><br>Organ damage will be coded via MedDRA preferred term (PT) | Categorial collection (yes / no)<br>For worsening and improvement, changes in the following variables will be considered, corresponding to the numbered types in the left-hand cell:<br>1. Change in Ficat / ARCO classification<br>2. Change in left ventricular ejection fraction (LVEF) category and / or change in New York Heart Association (NYHA) class<br>3. Change in visus<br>4. Change *** to be determined with registry e.g. Child-Pugh Score***<br>5. Change in NYHA class and / or change in 6-minute walk test<br>6. Change in DXA T-Score category<br>7. Change in eGFR category and / or change in Urine albumin-creatinine ratio (uACR) category<br>8. Change to be determined with registry***, no quantitative measures<br>9. Change to be determined with registry***, no quantitative measures<br>10. Change in liver iron concentration (LIC) (mg/g) category as per German diagnostic and treatment guidelines (31)<br>Definitions of meaningful change for worsening and improvement are listed in the SAP for the types listed above. |
| Occurrence of cerebrovascular events<br>- Stroke (ischemic, hemorrhagic ***)<br>- De novo pathologic flow in transcranial doppler | Categorial collection (yes / no)<br>- For stroke: Symptoms (headache, seizure, paresis, sensory, speech impediment, impaired consciousness, silent / no overt clinical manifestation, other), days on ventilation, outcome (resolved, persistent neurological deficit, death)<br>- For TCD: pathological yes / no |

| Variable | Operationalization |
|---|---|
| **Variables for safety endpoints including mortality** | |
| Serious adverse events (SAE):*** | • Term (coded via MedDRA PT)<br>• Start date, stop date, ongoing<br>• Seriousness (death, life threatening, disability / incapacity, hospitalization, congenital abnormality, required intervention to prevent life-threatening event)<br>• CTCAE grade<br>• Relatedness / causality assessment (underlying condition, medicinal product coded with WHODRUG, other)<br>• Medication changed due to event (yes / no)<br>• Outcome (resolved yes / no) |
| Specific AE Bleeding***<br>o Epistaxis (MedDRA PT epistaxis)<br>o Skin / cutaneous soft tissue (MedDRA PT skin haemorrhage)<br>o Oral / gingival (MedDRA PT gingival bleeding)<br>o Vaginal (MedDRA PT vaginal haemorrhage)<br>o Gastrointestinal (MedDRA PT gastrointestinal haemorrhage)<br>o Hematuria / urethral (MedDRA PT hematuria)<br>o Intracranial (MedDRA PT haemorrhage intracranial)<br>o Catheter / device-related (MedDRA PT catheter site haemorrhage)<br>o Other (MedDRA PT hemorrhage) → free text field for description | Categorial collection (yes / no)<br>• Seriousness (yes / no, if yes: death, life threatening, disability/incapacity, hospitalization, congenital abnormality, required intervention to prevent life-threatening event)<br>• Start date, stop date, ongoing<br>• CTCAE grade<br>• Relatedness / causality assessment (underlying condition, medicinal product coded with WHODRUG, other)<br>• Required treatment with blood transfusions (yes / no)<br>• Outcome |

| Variable | Operationalization |
|---|---|
| Specific AE Infection***<br>o Nasopharyngeal / sinusitis (MedDRA PT upper respiratory tract infection)<br>o Oral (MedDRA PT oral infection)<br>o Pulmonary (MedDRA PT pneumonia)<br>o Bloodstream / sepsis (MedDRA PT sepsis)<br>o Skin (MedDRA PT skin infection)<br>o Vaginal (MedDRA PT vaginal infection)<br>o Gastrointestinal (MedDRA PT gastrointestinal infection)<br>o Catheter / device related (MedDRA PT device related infection)<br>o Other or unknown (MedDRA PT infection); free text field for description | Categorial collection (yes / no)<br>• Seriousness (yes / no, if yes: death, life threatening, disability / incapacity, hospitalization, congenital abnormality, required intervention to prevent life-threatening event)<br>• Start date, stop date, ongoing<br>• CTCAE grade<br>• Relatedness / causality assessment (underlying condition, medicinal product coded with WHODRUG, other)<br>• Causative organism<br>o Viral infection (MedDRA PT viral infection)<br>o Bacterial infection (MedDRA PT bacterial infection)<br>o Fungal infection (MedDRA PT fungal infection)<br>o Other (MedDRA PT infection)<br>• Required treatment with antibiotic / antifungal / antiviral medication (yes / no)<br>• Outcome |

| Variable | Operationalization |
|---|---|
| **Variables for Exa-cel therapy*** ** | |
| Exa-cel therapy<br>1. Mobilization (incl. preparation)<br>2. Apheresis<br>3. Conditioning<br>4. Infusion<br>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<br>2. Number of cycles, start date of each apheresis cycle<br>3. Conditioning agent, date start of conditioning, dose, posology (qd, q6, other), total AUC<br>4. Date of infusion, total Exa-cel dose infused<br>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 (SoC only) | Yes / no; start / stop date, dose (mg/kg*d); reason for discontinuation |
| Iron chelation | Yes / no;<br>Among patients with „yes“: Desferroxamine yes / no, Deferasirox yes / no, phlebotomy yes / no |

| Variable | Operationalization |
|---|---|
| **Variables for SCT from a MUD (Patients switching from SoC to MUD SCT)*** ** | |
| SCT from a MUD (SoC group only)<br>1. Mobilization (incl. preparation, may be done for back-up cell collection)<br>2. Apheresis (may be done for back-up cell collection)<br>3. Conditioning<br>4. SCT<br>5. Post-SCT | The number of patients going through each step will be reported.<br>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<br>2. Number of cycles, start date of each apheresis cycle<br>3. Conditioning agents, date start of conditioning, dose<br>4. Date of transplantation<br>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 SCT 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 SCT without administration of platelet transfusions for 7 days), date hospital discharge), post-SCT immuno-suppression (coded via WHODRUG, start date, stop date, dose)<br>Post-transplant immunosuppression: drug used, dose, start date, end date |

| Variable | Operationalization |
|---|---|
| **Variables for discontinuation of documentation** | |
| Reason for discontinuation of documentation | • Date of last contact: mm/dd/yyyy<br>• Reason for discontinuation of documentation: Care at non-participating institution, consent to inclusion in the registry or in the AbD withdrawn, LFU: lost contact or moved away unknown, deceased<br>• Date of death: mm/dd/yyyy<br>• 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 sickle cell disease, probable cause unrelated to sickle cell disease<br>Description: free text entry |

* Baseline characteristics are taken in the year before or at therapy decision
** Confounder variables
*** Currently not part of the GPOH SCD registry data base – fields need to be added

# 13 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.

## 13.1 General Considerations

**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 13.3) 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 during the baseline 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. The FAS will be used for all analyses of morbidity, mortality and safety except the co-primary endpoint of VOC freedom.

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

**Overall analysis strategy**
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 via the aforementioned adjustment method.

All endpoints except VOC freedom (co-primary endpoint) will be analyzed separately for Period 1 and 2 as defined in section 12.2 on Study Design. VOC freedom over 36 months will be analyzed for Period 2 only. For analyses in Period 2, patients will be included only if they have a defined T60 date.

Serious adverse events (SAEs) and specific adverse events (AEs) during Period 1 will additionally be analyzed split into the following sub-periods for Exa-cel patients:

- 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 other SCT), AEs 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.

For the objective comparing pain medication prescriptions for SCD management over time, the proportion of patients with prescription of non-opioid and opioid analgesics in Period 2 will be compared in 6-month intervals.

## 13.2 Analysis Strategy

**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 any transplantation (Exa-cel, MUD-SCT, other) (SoC group only)
- HSCT is no longer appropriate, e.g. at the discretion of the physician, the individual is no longer eligible for full myeloablative conditioning (for Period 2, SoC group only)
- Change of SoC therapy (SoC group only)

Table 5 summarizes the analysis strategy for the primary endpoint **VOC freedom (in Period 2)** within the estimand framework.

**Table 5: 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 |

| **VOC freedom, Period 2** | **Primary Estimand** |
|---|---|
| Handling of ICE | |
| Therapy decision for any transplantation (Exa-cel, MUD-SCT, other)[a] | Treatment policy |
| Change of SoC therapy[a] | Treatment policy |
| HSCT no longer appropriate[a] | Treatment policy |
| ***Analysis (Estimator)*** | |
| Confounder[b] adjustment method | Calculation of weights based on PS |
| Analysis model | Logistic regression including weights |
| a: Potential ICE for SoC group only<br>b: 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 are handled via Treatment Policy approach: Once an ICE occurs, no censoring happens, and patients continue to be observed until 36 months after T60. Treatment groups will be compared via risk ratio, estimated from a weighted logistic regression model.

Table 6 summarizes the analysis strategy for the primary endpoint **annualized VOC rate in Period 2** within the estimand framework.

**Table 6: 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 any transplantation (Exa-cel, MUD-SCT, other)[a] | Hypothetical[b] |
| Change of SoC therapy[a] | Treatment policy |
| HSCT no longer appropriate[a] | Treatment policy |
| **Analysis (Estimator)** | |
| Confounder[c] adjustment method | Calculation of weights based on PS |
| Analysis model | Negative binomial regression including weights |
| a: Potential ICE for SoC group only<br>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.<br>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 ICEs “change of SoC therapy” and “HSCT no longer appropriate” will be handled using Treatment Policy:

data starting from that ICE will continue to be used in the analysis. For the ICE "therapy decision for any transplantation", 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. As this analysis is conducted only in Period 2, patients who do not have a defined time point T60 will not be included in the analysis. The Hypothetical approach is used for the ICE of therapy decision for any transplantation in the SoC arm, as it is expected that any other transplantation, especially Exa-cel itself, 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, it is no longer possible to estimate the treatment effect of Exa-cel over SoC.

### Secondary Objectives

Table 7 summarizes the analysis strategy for the secondary endpoint **annualized VOC rate for Period 1** within the estimand framework.

**Table 7: 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 (Index date to the earlier of T60 or EoS or censoring) |
| Population-level summary | Rate ratio |
| Handling of ICE | |
| Therapy decision for any transplantation (Exa-cel, MUD-SCT, other)[a] | Hypothetical[b] |
| Change of SoC therapy[a] | Treatment policy |
| HSCT no longer appropriate | Treatment policy |
| ***Analysis (Estimator)*** | |
| Confounder[c] adjustment method | Calculation of weights based on PS |
| Analysis model | Negative binomial regression including weights |
| a: Potential ICE for SoC group only<br>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.<br>c: Missing values in confounders will be imputed using Multiple Imputation. | |

Annualized VOC rate during Period 1 will be analyzed analogue to Period 2. The ICEs "change of SoC therapy" and "HSCT no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICE "therapy decision for any transplantation", 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.

For the remaining secondary analyses, endpoints will be evaluated on the FAS. Endpoints where a proportion of patients having an event is compared between treatment groups (e.g. proportion of patients with newly identified or worsened chronic organ damage, proportion of patients with SAEs etc.) will use the risk ratio derived from a weighted logistic regression model as a population-level summary. 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 as a population-level summary. For further details on the analysis and handling of ICEs, see the SAP.

## 13.3 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 endpoint, all steps in the PS procedure to obtain an adjusted effect estimate will be conducted on both 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 (32) 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 (33).

The following ten confounders that are relevant in the context of statistical evaluation of endpoints in a registry-based study were identified and will be considered for PS weighting:

- Iron overload
- Chronic renal insufficiency
- Chronic pain
- Hepatopathy
- Pulmonary hypertension
- Cerebrovascular risk
- Number of VOCs
- Age
- Chronic transfusion therapy
- Alloimmunization

The operationalization of these confounders is described in section 12.5.

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 logistic regression 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 sensitivity analysis, the risk ratio is estimated on the FAS36 instead.

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 patients in Period 2, the rate ratio with 95% CI will be estimated via negative binomial regression with treatment as the independent variable and including the PS weights.

The effect estimates are then pooled across all imputed datasets. The rate ratio is tested against the shifted null hypothesis $H_0$: rate ratio=2.0. Superiority of Exa-cel is shown if the lower bound of the 95% CI is >2.0.

For the **secondary endpoints**, the risk ratio or the rate ratio will be estimated via weighted logistic regression 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, unweighted comparison will be performed instead.

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.

## 13.4 Subgroup Analysis and Sensitivity 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.

Subgroup analyses will be performed for the following baseline characteristics:

- Age (in years) at index date (12-21 vs. 22-35 vs. ≥36)
- 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.

No sensitivity analyses are planned.

## 13.5 Sample Size Consideration

Because of the intended potential functional cure of the Exa-cel therapy, the primary goal is to prevent patients suffering from VOCs. As an approximation of the appropriate number of cases for the AbD, G-BA proposed to assume response rates of 93% for Exa-cel and 25% in the comparator group for the primary endpoint "VOC freedom over 3 years". As a formal requirement by G-BA and the Institute for Quality and Efficiency in Health Care *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen,* IQWiG*)*, the lower bound of a 95% CI of the risk ratio has to be larger than 2.0 (shifted null hypothesis). Assuming a 1:2 ratio between intervention and comparator group, a power of 80% would require 75 patients in total (25 in the Exa-cel group and 50 in the comparator group) for the analysis.

From past experience, it is anticipated that 25% of SCD patients with a therapy decision for Exa-cel will not receive Exa-cel due to several reasons. To account for this and for Exa-cel patients who died or are lost to follow-up after Exa-cel infusion, the target inclusion to support at least 80% power would be at least 33 Exa-cel patients.

As the study is being conducted in a real-world observational setting, the actual number of individuals per group depends on real-world utilization. The study design is set up to include all SCD patients from the GPOH SCD registry, treated at a center contributing to the AbD, who sign informed consent, who fulfill all of the inclusion criteria and none of the exclusion 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. This study set up is anticipated to have at least 70 comparator patients. A sample size of at least 100 patients is appropriate for a sufficiently powered comparative analysis of both primary endpoints and was stipulated by G-BA as needed to adjust for all identified confounders in the statistical analysis.

# 14 PLANNED REPORTS

The following status reports, interim reports and final report are planned according to the requirements in the resolution by G-BA (Table 8). All dates refer to the study start date, which will be defined by G-BA.

**Table 8: Planned reports to G-BA**

| Report | Date | Content |
|---|---|---|
| Status report 1 | 6 months after study start<br>Data cut: 4 months after study start | Information on patient inclusion; presented in the status report template (34) |
| Interim report 1<br>and status report 2 | 18 months after study start<br>Data cut: 12 months after study start | Interim analysis results including disposition, baseline characteristics and descriptive safety analysis by period; presented in module 4 of the dossier template (35)<br>Futility analysis regarding the required sample size<br>Information on patient inclusion; presented in the status report template (34) |
| Interim report 2<br>and status report 3 | 36 months after study start<br>Data cut: 30 months after study start | Interim analysis results including disposition, baseline characteristics and descriptive analyses for secondary morbidity endpoints during Period 1 as well as descriptive safety analysis by period presented in module 4 of the dossier template (35)<br>Futility analysis regarding the required sample size<br>Information on patient inclusion; presented in the status report template (34) |
| Status report 4 | 54 months after study start<br>Data cut: 48 months after study start | Information on patient inclusion; presented in the status report template (34) |
| Final report | Expected one year after EoS | Final analysis presented in module 4 of the dossier template (35) |

Status reports 1 through 4 will include information on number of patients included in the study.

According to G-BA, a sample size reassessment based on the interim data is to be included in the first interim report (23, 24). As the sample size calculation is based on the endpoint proportion of VOC-free patients, this is not feasible. Observation for that endpoint for each Exa-cel patient starts at 60 days after the last RBC transfusion for post-transplant management (T60). This date may not be reached for many (or any) patients 6 months after study start; especially since patients are assigned to the Exa-cel group if the treatment

decision for Exa-cel is made in the first 2 years after study start and manufacturing time needs to be taken into account. Accordingly, no sample size recalculation will take place during the first interim analysis.

A futility analysis will be conducted at the first interim analysis 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 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. In addition, for Exa-cel patients T60 may take some months to be reached after study start, therefore the number of patients with a T60 date in the Exa-cel group will be examined.

At the first interim analysis (IA1), the alternative approach for the MACNU design (see section 12.4.2) will be applied if the number of Exa-cel patients is according to expectations, and the probability of including at least 67 SoC patients until the end of the study is less than 80%, i.e.,

$Exa_{IA1} > int(33 * \frac{time_{afterIA1}}{time_{untilIA1}})$ and $SoC_{IA1} < 67$ and $\sum_{i=0}^{66-SOC_{IA1}} \left(\frac{\lambda^i e^{-\lambda}}{i!}\right) < 0.8$

with

- $SoC_{IA1}$ = number of SoC patients at IA1 readout
- $Exa_{IA1}$ = number of Exa-cel patients at IA1 readout
- $\lambda = \min(SoC_{IA1}, 3 * Exa_{IA1}) * \frac{time_{afterIA1}}{time_{untilIA1}}$ rate at which we include SoC patients up to IA1 readout
- $time_{untilIA1}$ = time (months) from study start until IA1
- $time_{afterIA1}$ = time (months) from IA1 until end of 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.

At the second interim analysis (IA2), the final number of included patients is compared against the initial sample size assessment. Continued conduct of the study based on the futility assessment will be discussed with G-BA.

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

# 15 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 when they reach the age of majority, or by data being entered into the database incompletely or with a delay.

Center staff are required to track missing data (e.g. via the family doctor, if possible) and 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 17 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.

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 judgement 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 13 of this protocol and detailed in the SAP.

# 16 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

## 16.1 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.

## 16.2 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 formAg.

## 16.3 Patient Information and Informed Consent

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. 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.

## 16.4 Patient Privacy

The patient data collected as part of the study is documented by the treating center directly via the Internet in the MARVIN-RDE system and stored in the MARVIN-RDE database on XClinical company servers. The data are given a pseudonym (numerical code, MARVIN ID) 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. XClinical guarantees legally compliant storage, backup and validation, especially the protection of the data against loss and against access by unauthorized persons. 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.

## 16.5 Reporting of Safety Information to the Sponsor

The reporting procedures defined below by this non-interventional study protocol are applicable to study patients receiving 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.

### 16.5.1 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
  - Life-threatening
  - Requires hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability / incapacity (substantial disruption of the ability to conduct normal life functions)
  - Congenital anomaly or birth defect
  - Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., a new hematologic malignancy diagnosis).

## 16.6 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 9.

**Table 9: 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. |

## 16.7 AE Reporting Procedure

All AEs observed in patients receiving 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.

This 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 AEs 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) and non-serious AEs in a timely manner (e.g., no later than 30 days 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

## 16.8 Pregnancy Reporting

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

# 17 DATA MANAGEMENT / REPORTING OF DATA

## 17.1 Data Entry / Data Capture

Data management for the AbD is conducted by the GPOH SCD registry. Therefore the same electronic data capture system will be used for the AbD; 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. For the purposes of the AbD, in addition to data fields already incorporated in the GPOH SCD registry, supplementary eCRFs are planned in MARVIN.

For the AbD, data collection for each patient is planned starting at the time of inclusion in the study, and then encounter-based, with quarterly data collection deemed feasible. To facilitate data entry, documentation aids are available.

## 17.2 Data Quality Assurance

As the AbD will be implemented within 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 and will be outlined in a separate data management plan. Discrepancies are clarified with the documenting center and implausible data are corrected.
Source data verification will be implemented for patient data within the AbD as per G-BA stipulation and details will be outlined in a separate Data Monitoring Plan. These measures increase the likelihood of high data quality.

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# 19 SIGNATURE PAGE

## 19.1 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

## 20 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 |
|---|---|---|

***VERTEX PHARMACEUTICALS INCORPORATED***

**Supplement for Study Protocol / Statistical Analysis Plan for a Routine Practice Data Collection („Anwendungsbegleitende Datenerhebung“) of Exagamglogene autotemcel (Exa-cel) in sickle cell disease (SCD)**
**Version 1.0**

# Table of Contents

# 1 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AbD | Routine practice data collection (*Anwendungsbegleitende Datenerhebung*) |
| ACS | Acute thorax syndrome |
| ATC | Authorized Treatment Center |
| BPI | Brief pain inventory |
| CHMP | Committee for Medicinal Products for Human Use |
| EMA | European Medicines Agency |
| Exa-cel | Exagamglogene autotemcel |
| 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) |
| IA1 | Interim analysis 1 |
| 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 (*Kompetenz-Centrum Onkologie der Medizinischen Dienste*) |
| LF | Long form |
| MACNU | Modified Active Comparator New-User |
| MSA | Master Service Agreement |
| MUD | Matched unrelated donor |
| PRO | Patient reported outcome |
| RBC | Red blood cell |
| SAP | Statistical analysis plan |
| SCD | Sickle cell disease |
| SCT | Stem cell transplantation |
| SF-36 | Short form 36 |
| SmPC | Summary of product characteristics |
| SoC | Standard of Care |
| VOC | Vaso-occlusive crisis |

## 2 [redacted]

[redacted]

## 3 [redacted]

[redacted]

# 4 HANDLING OF MUD-HSCT PATIENTS

## 4.1 G-BA position

Niederschrift: Die allogene Stammzelltransplantation mit einer HLA-kompatiblen, nicht-verwandten Stammzellspende stellt in Einzelfällen eine mögliche, relevante Therapieoption dar und wird daher als Bestandteil der patientenindividuellen Therapie im Vergleichsarm erachtet.

Daher sind auch Patientinnen und Patienten, die eine MUD-Spende erhalten, im Rahmen der AbD zu erfassen.

The G-BA is requesting inclusion of allogenic stem cell transplantation (SCT) from a human leucocyte antigen (HLA)-matched, unrelated donor (MUD) into the comparator arm.

## 4.2 Vertex position

According to the Exa-cel summary of product characteristics (SmPC), patients with a history of allogenic hematopoietic stem cell transplantation (HSCT) are not recommended for treatment with Exa-cel. However, according to the inclusion criterion (see synopsis) "Participant receives patient-individualized treatment (see "comparator treatment") at index date" to MUD-SCT patients implies they have already received a MUD-SCT at index date. As therapy with Exa-cel is not recommended in patients with prior allogenic or autologous SCT per label, MUD-SCT patients cannot receive Exa-cel. This contradicts the positivity assumption of all eligible patients. Therefore, MUD-SCT is not an individualized treatment option for patients included in the comparator group.

SoC patients included in the AbD and receiving a MUD-SCT later will stay in the study and therapy decisions for a MUD-SCT during the AbD will be handled as intercurrent events.

Vertex therefore excludes allogenic SCT from an HLA-matched MUD from the comparator arm definition.

# 5 SENSITIVITY ANALYSES FOR VOC FREEDOM STARTING FROM THERAPY DECISION

## 5.1 G-BA position

Niederschrift: Lediglich für den Endpunkt Vermeidung vasookklusiver Krisen kann in den Studienunterlagen begründet werden, ab welchem Zeitpunkt nach der Infusion mit Exagamglogen Autotemcel von einer Vermeidung vasookklusiver Krisen ausgegangen werden kann und daher eine sinnvolle Betrachtung des Endpunktes möglich ist. Daraus ergibt sich jedoch nicht, dass für diesen Endpunkt der Zeitpunkt des Beobachtungsbeginns gewählt werden kann. Eine Sensitivitätsanalyse nach dem ITT-Prinzip für den gesamten Studienzeitraum sollte durchgeführt werden.

The G-BA is requesting analyses of all patient-relevant endpoints per intention-to-treat (ITT)-principle. Only for the endpoint "VOC freedom over 36 months" a justified deviation is possible, and the

observation period may start from a defined point in time after Exa-cel infusion. However, the G-BA is requesting a sensitivity analysis per ITT principle for the entire study period.

### 5.2 Vertex position

For Vertex, sensitivity analyses provide value to assess the stability of an effect. With the requested sensitivity analysis, we would not be able to assess the stability of the effect of Exa-cel after actual Exa-cel infusion.

Analyzing vaso-occlusive crisis (VOC) freedom over 36 months from therapy decision onwards means inclusion of the period from therapy decision to 60 days after last red blood cell transfusion for transplant management (point in time when the Exa-cel effect is measurable). This approach is inappropriate to test stability of effect and lacks face validity given that a patient will be counted as a non-responder once they experience a single VOC in the 36 months from therapy decision. Therefore, it can be expected that the inclusion of the time prior to the expected effect of Exa-cel will artificially increase the non-response rate over 36 months, even if no VOCs occur from the onset of the Exa-cel effect. The effect that would be measured in such a sensitivity analysis will be mostly influenced by the time prior to the Exa-cel effect and only marginally influenced by the Exa-cel effect itself. This would preclude an evaluation of the clinical benefit and stability of effect of treatment with Exa-cel.

Therefore, this sensitivity analysis is not considered in the study.

## 6 PRIMARY ANALYSIS PERIOD FOR ANNUALIZED VOC RATE

### 6.1 G-BA position

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| Niederschrift: Das IQWiG bestätigt, dass die annualisierte Rate als primäre Analyse gemäß dem ITT-Prinzip über den gesamten Zeitraum ausgewertet werden soll. Dies liegt darin begründet, dass Patientinnen und Patienten ggf. Risiken in Kauf nehmen, wenn eine Therapieentscheidung für Exa-Cel getroffen wird. Es steht dem pharmazeutischen Unternehmer frei, Sensitivitätsanalysen vorzunehmen. Die zeitliche Parallelität zwischen Vergleichs- und Interventionsarm sollte beachtet werden. |

Following Institute for Quality and Efficiency in Health Care *(Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen,* IQWIG) recommendation, the G-BA is requesting to analyze annualized VOC rate primarily over the entire observation period. This is due to the fact that, once the therapy decision for Exa-cel is made, patients may potentially be exposed to related risks. The company is free to additionally provide relevant sensitivity analyses. Comparable observation periods between comparator and intervention arms are to be considered.

### 6.2 Vertex position

Vertex agrees with IQWIG on the need for comparable observation periods and therefore defining a timepoint comparable to “60 days after last red blood cell (RBC) transfusion for transplant management” (T60) for the SoC arm. For each SoC patient, this time point is defined in the study

protocol as the same calendar T60 date of the matched Exa-cel patient. If the matched Exa-cel patient does not have a T60 date, the SoC patient will also not be assigned a T60 date.

This results in the definition of the following study periods:

- Baseline period: one year before index date (time of therapy decision for Exa-cel patients and matched same calendrical index date for matched SoC patient)
- Period 1: index date until T60 or end of study or censoring, whatever comes first
- Period 2: T60 until end of study or censoring
- Observation period: index date to end of study or censoring

As already detailed by [redacted] during the G-BA advice meeting from 26 February 2025, it is very difficult to properly interpret the analysis of annualized VOC rate over the entire observation period (Period 1 & 2 combined).

Example: Assume Period 1 lasts for 1 year and Period 2 lasts for 3 years. Further assume a patient has 4 VOCs in Period 1 and no VOCs in Period 2. Then, for the entire observation period on average, the patient suffers from 1 VOC per year. This is both a misinterpretation of what happens in year 1 as well as in years 2-4.

Therefore, Vertex proposes to analyze annualized VOC rate for both Periods 1 and 2 separately. For the proposed analyses, the ITT principle is followed with respect to including all patients and the entire observation period while still being able to adequately measure the clinical benefit of Exa-cel and therefore ensure ability to interpret the analysis in terms of Exa-cel effect.

# 7 DEFINITION OF ANALYSIS PERIODS FOR ALL PATIENTS

## 7.1 G-BA position

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| Niederschrift: Ebenso ist für Patientinnen und Patienten mit Therapieentscheidung für Exagamglogen Autotemcel, die keine Infusion erhalten haben, ein entsprechender Zeitpunkt zu wählen. |

Accordingly, for patients with therapy decisions for Exa-cel, who did not receive an Exa-cel infusion, a corresponding time point (T60) should be selected.

## 7.2 Vertex position

As Period 2 is used for assessment of effectiveness after Exa-cel infusion, Vertex does not believe a T60 should be artificially defined for patients with therapy decision for Exa-cel, who did not receive the infusion. To do so would strongly bias the analysis providing an estimate of effect mostly based on an observation period with non-existent data of Exa-cel effect.

Further, selecting a time point “60 days after last RBC transfusion for transplant management” with the absence of Exa-cel transfusion (non-existent data), violates absolute face validity.

Given the methodological limitations and the futility of this analysis in providing G-BA with evidence on the real-world performance of Exa-cel, Vertex has not addressed this approach in the study protocol.

# 8 ESTIMAND HANDLING STRATEGY FOR INTERCURRENT EVENT OF TREATMENT WITH EXA-CEL IN SOC ARM

## 8.1 G-BA position

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| Niederschrift: Patientinnen und Patienten mit Therapieentscheidung für eine allogene hämatopoetische Stammzelltransplantation oder für Exagamglogen Autotemcel nach dem Rekrutierungszeitraum sollten im Vergleichsarm bis zum Studienende weiter beobachtet werden und mit diesem Beobachtungszeitraum in die Auswertung eingehen. Im Rahmen einer Sensitivitätsanalyse ist die Zensierung dieser Patientinnen und Patienten zum Zeitpunkt des Behandlungswechsels denkbar. |

Patients with therapy decision for an allogenic HSCT or Exa-cel after the patient identification period should be observed in the SoC arm until end of study and be analyzed in SoC arm as well. Censoring of such patients at time of treatment change is possible as sensitivity analysis.

## 8.2 Vertex position

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 on 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 transferring to Exa-cel during the course of the AbD, more so with

passing time and after the end of the patient identification period; however, at the current time, no estimation can be provided on how many patients would undergo such a transfer.

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, Vertex believes that 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, Vertex proposes to:

- 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.

# 9 MACNU DESIGN OPERATING CHARACTERISTICS

## 9.1 G-BA position

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| Niederschrift: Der pharmazeutische Unternehmer sollte sicherstellen, dass eine alternative Strategie zum Einschluss von Patientinnen und Patienten des Vergleichsarms als auch eine alternative Festlegung des Indexdatums vorliegt, falls der Ansatz mit dem MACNU-Verfahren in der vorliegenden Datensituation nicht zu einer angemessenen Fallzahl führt oder die vollständige Erhebung der Confounder und Endpunkte vor dem Hintergrund des entstehenden Aufwands nicht angemessen erscheint. |

The pharmaceutical company needs to ensure that an alternative strategy is available to include patients in the SoC arm and define their index date in case the patient inclusion algorithm as per Modified Active Comparator New-User (MACNU) design does not result in an appropriate sample size or the operational effort in collecting data for confounders and endpoint is not appropriate.

## 9.2 Vertex position

Vertex has simplified the MACNU mechanism, conducted relevant simulations to better understand the characteristics of the newly developed MACNU design and implemented a futility criterion in the protocol to adapt the MACNU design if needed.

### 9.2.1 Updated MACNU design

Stratification factor "Treatment with Hydroxyurea" was removed from the matching algorithm, reducing the number of possible strata from 48 to 24 and simplifying the steps if the exposure set for a specific Exa-cel patient would contain less than 3 patients.

With the comparator treatments reduced to "chronic red blood cell transfusions" and "hydroxyurea", all patients need to be either on chronic RBC transfusions or on hydroxyurea or on both. If patients do receive chronic RBC transfusions, the impact of hydroxyurea supplementation on VOC rate is expected to be limited. Therefore, those two stratification factors were merged to one, either with or without chronic RBC transfusions.

A detailed explanation of the updated MACNU design is available in the protocol.

### 9.2.2 Simulation Results

[redacted]

### 9.2.3 Futility Criterion in Protocol

The futility criterion applied at interim analysis 1 (IA1) was adapted as follows:

1) If the probability of recruiting at least 67 SoC patients until the end of the study is less than 80%, i.e., $P(SoC_{final} < 67) < 0.8$ with $SoC_{final}$ = number of SoC patients after patient identification period, the MACNU design will be updated to only consider new SoC patients for matching (SoC patients not already recruited into the study).

   Assuming SoC / Exa-cel recruitment ratio remains the same throughout the patient identification period and Exa-cel recruitment rate is the same after IA1 as it is until IA1, then using a Poisson distribution of „SoC patient“ events we have:

   $P(k\ events) = \frac{\lambda^k e^{-\lambda}}{k!}$ or

   $P(< k\ events) = \sum_{i=0}^{k-1} \frac{\lambda^i e^{-\lambda}}{i!}$

Rephrasing the stopping criteria and assuming $SoC_{IA1} < 67$ we have

$$P(SOC_{final} < 67) = P(SOC_{New} < 67 - SOC_{IA1}) = \sum_{i=0}^{66-SOC_{IA1}} \frac{\lambda^i e^{-\lambda}}{i!}$$

This results in the following rule:

The MACNU design after IA1 will be updated if Exa-cel patients is according to expectations, and our probability of recruiting at least 67 SoC patients until the end of the study is less than 80%, i.e.,

$$\boldsymbol{Exa_{IA1} > int(33 * \frac{time_{afterIA1}}{time_{untillA1}})} \textbf{ and } \boldsymbol{SoC_{IA1} < 67} \textbf{ and } \boldsymbol{\sum_{i=0}^{66-SOC_{IA1}} \left(\frac{\lambda^i e^{-\lambda}}{i!}\right) < 0.8}$$

with

- $SoC_{IA1}$ = number of SoC patients at IA1 readout
- $Exa_{IA1}$ = number of Exa-cel patients at IA1 readout
- $\lambda = \min(SOC_{IA1}, 3 * Exa_{IA1}) * \frac{time_{afterIA1}}{time_{untillA1}}$ rate at which we recruit SoC patients up to IA1 readout
- $time_{untillA1}$ = time (months) from study start until IA1
- $time_{afterIA1}$ = time (months) from IA1 until end of patient identification period

2) In case of unexpectedly high number of SoC patients matched to a small number of Exa-cel patients up until IA1, $\lambda$ is capped at $3 * Exa_{IA1} * \frac{time_{afterIA1}}{time_{untillA1}}$ to avoid overestimating the rate of SoC patients per Exa-cel patient expected after IA1.

3) If Exa-cel recruitment is lower than expected, it will be discussed with G-BA how to proceed.

# 10 ANALYSIS OF SECONDARY ENDPOINTS OF MORBIDITY AND MORTALITY

## 10.1 G-BA position

Niederschrift: Der pharmazeutische Unternehmer plant die Endpunkte überwiegend als Anteil an Patientinnen und Patienten mit Ereignis auszuwerten. Das ist sachgerecht und sollte in den Studienunterlagen für alle sekundären Endpunkte, insbesondere auch für die Mortalität festgelegt werden. Auswertungen als annualisierte Raten, die der pharmazeutische Unternehmer bei den sekundären Endpunkten zu vasookklusiven Krisen, Mortalität und Nebenwirkungen plant, sind verzichtbar.

[…]

Der Auswertungszeitraum muss in beiden Behandlungsarmen einheitlich ab dem Indexdatum beginnen und den gesamten Studienzeitraum abdecken.

The pharmaceutical company plans to evaluate the endpoints mostly as proportion of patients with events. This is as expected and should be described like this in the study documents for all secondary endpoints, especially also for mortality. Analysis using annualized rates as proposed by the pharmaceutical company for secondary endpoints for VOC, mortality and adverse events are permissible.

The analysis time period for both treatment arms should start at index date and cover the entire observation period.

### 10.2 Vertex position

Vertex agrees that the number and proportion of patients is relevant for all analyses and will present these for all endpoints.

Vertex, however, considers annualized rates a more relevant estimate for mortality and morbidity endpoints as all patients will be observed until end of study and length of treatment periods will be different between patients.

While matched SoC patients will in general have a similar observation period as their matched Exa-cel patient, there will be a different number of SoC patients matched to each Exa-cel patient, which means there may be an imbalance in number of patients compared to overall observation time between Exa-cel arm and SoC arm.

As annualized rate puts the number of events in relation to the observation time, Vertex considers the annualized rate a worthwhile addition to the proportion of patients with events and the number of events and would therefore not abstain from this estimate.

Regarding the analysis time period, for the same reasons as specified for annualized VOC rate, Vertex proposes to analyze secondary endpoints for Period 1 and Period 2 separately.

## 11 MEASURES TO INCREASE REPRESENTATION OF ADULT PATIENTS IN EXA-CEL AND SOC ARM

The G-BA is requesting information on planned measures to increase the share of adult patients in the AbD. [redacted]

For SoC patients, the matching mechanism of the MACNU design will assure appropriate matching of patients of similar age.

# 12 EXCLUSION OF ANTITHROMBOTIC MEDICATION IN CONCOMITANT MEDICATION

## 12.1 G-BA position

> Niederschrift: Die vom pharmazeutischen Unternehmer vorgesehene Dokumentation deckt nicht alle der vom G-BA beispielhaft benannten Begleitmedikationen ab, es fehlen die Behandlung mit Analgetika und antithrombotische Therapien. Antithrombotische Therapien bei Gefäßverschlüssen werden derzeit nicht im GPOH-Register dokumentiert.
>
> […]
>
> In den Studienunterlagen ist daher […] eine inhaltliche Begründung vorzulegen, warum auf die Erfassung dieser Begleitmedikationen verzichtet werden kann.

The G-BA is requesting antithrombotic medication within collection of concomitant medication. Antithrombotic medication is currently not being collected in the GPOH registry and therefore not included in the study protocol.

## 12.2 Vertex position

Antithrombotic medication is not a regularly used therapy in sickle cell patients and is not standard of care in the prevention of VOCs. It is neither mentioned nor recommended in the GPOH guideline sickle cell disease (2) and registry representatives / clinical experts confirmed this during the AbD scientific advice meeting (3).

# 13 VOC OPERATIONALIZATION

## 13.1 G-BA Position

> Niederschrift: In den Tragenden Gründen des Beschlusses vom 21. Dezember 2023 wird in der Operationalisierung der vasookklusiven Krisen neben der Hospitalisierung ausschließlich auf die Behandlung in der Notfallambulanz abgestellt und nicht auf jegliche Behandlung im ambulanten Sektor. Es ist vom pharmazeutischen Unternehmer konkret für die Behandlung in der Notfallambulanz darzulegen, warum nicht von einer messsicheren Erfassung auszugehen ist.
>
> […]
>
> Die Erfassung der Milzsequestration und Priapismen sollte unabhängig von einer Hospitalisierung / Behandlung in der Notfallambulanz erfolgen. […] Dies ist vom pharmazeutischen Unternehmer zu prüfen und darzulegen, wie eine messsichere Erhebung von Ereignissen unabhängig von einer Hospitalisierung ermöglicht werden kann, beispielsweise über regelmäßige gezielte Abfragen.

The G-BA is requesting collection of the individual components of the composite endpoint of VOCs as following:

- Pain crises & acute thorax syndrome: If leading to hospitalization or emergency room admission
- Splenic sequestration & priapism: Collection independently of hospitalization or emergency room admission

Deviations from this request need to be assessed and justified by the pharmaceutical manufacturer.

## 13.2 Vertex Position

The operationalization of data collection on VOCs is a composite endpoint of the following four components:

- Pain crises
- Acute thorax syndrome
- Splenic sequestration
- Priapism

As confirmed by the registry in the AbD scientific advice meeting on 26 February 2025 (3), in the real-world setting in Germany the adjudication of events is not common practice, and adequate and accurate documentation of VOCs can only be achieved utilizing hospitalization with overnight stay as a proxy. Only when a patient has been hospitalized, there is a high probability for the documenting center (who is participating in the GPOH registry) to have knowledge (e.g. a written report) of the event. According to the GPOH registry, patients themselves do not proactively inform the centers participating in the registry about VOCs, regardless of treatment in an inpatient, emergency room or outpatient setting; usually patients (especially SoC patients, are seen by various specialists and general practitioners or manage non-severe pain crises at home). Therefore, only severe pain crises leading to hospitalization are accurately collected in the GPOH registry.

Other methods of documentation, e.g. digital documentation through an app-based solution, are not adequate, as confirmed by the GPOH registry's statement in the AbD scientific advice meeting. While patients in the intervention arm will be subject to intense medical observation at the transplant center (the documenting center) and any of the above VOC components are likely to be seen, patients in the SoC will very likely not be seen by the documenting center more frequently than once per year and the documenting center usually does not receive extensive documentation from other physicians the patient is seeing. Thus, only for VOC events leading to hospitalization an adequate documentation is possible which can allow for source data verification.

Specific considerations per VOC component are explained below:

1) Pain crises: A pain crisis will not always be recognized or documented adequately in the outpatient or emergency room setting. This is true especially if the patient cannot, e.g. due to language barriers, adequately inform the treating physician about their disease or symptoms. Additionally, adequate documentation of emergency room treatment cannot always be assumed, i.e. the treatment site documenting for the registry would need to rely on anamnestic measures of the patient. Therefore, adequate assessment and documentation of a pain crisis is

not possible, as a correct diagnosis cannot be assured. An operationalization as "pain crisis leading to hospitalization" is a more conservative and more certain definition, as a certain severity of the pain crisis is given, and adequate documentation can be relied on. This operationalization is already established in the GPOH registry and is therefore adequate.

2) Acute chest syndrome (ACS): An ACS is always linked to a hospitalization with overnight stay or emergency room admission. For an ACS to be captured by the GPOH registry, an adequate documentation (German: "Entlassungsbrief") to the documenting treatment center is required. This will only be the case of a hospitalization with overnight stay, which are the only events the GPOH registry captures.
3) Splenic sequestration: Splenic sequestrations are usually linked to a transfusion and therefore to a hospitalization with overnight stay. An outpatient or emergency room treatment are not realistic and therefore not captured by the GPOH registry.
4) Priapism: The GPOH registry confirmed that self-limiting priapism is usually not reported due to a sense of shame of the patients. Lasting priapism usually leads to a hospitalization with overnight stay and can only be adequately captured by the GPOH registry in this case. This was confirmed by the GPOH registry in the G-BA scientific advice meeting (3).

Vertex therefore continues to believe, in agreement with the GPOH registry and as confirmed during the scientific advice meeting, that all components of VOCs need to be linked to a hospitalization with overnight stay.

# 14 COLLECTION OF PROS

## 14.1 G-BA position

Niederschrift: Eine abschließende Bewertung inwieweit eine Forderung der Erhebung von PRO-Daten im konkret vorliegenden Fall unverhältnismäßig wäre, kann erst im Rahmen der Überprüfung der Studienunterlagen erfolgen. Bei Einreichung der Studienunterlagen sollte der pharmazeutische Unternehmer insbesondere auf folgende Aspekte genauer eingehen:

- Beschreibung, welche konkreten Fragebögen für eine mögliche Umsetzung der PRO-Erhebung in Betracht gezogen wurden und in welchen Sprachen bzw. für welche Altersgruppen diese Fragebögen verfügbar sind
- Beschreibung welche konkreten Aspekte der Implementierung der PRO-Erhebung in der gewählten Datenquelle entgegenstehen
- Darstellung welche alternativen Möglichkeiten der Erhebung von PROs außerhalb des Registers evaluiert wurden und eine Diskussion der festgestellten Limitationen in Bezug auf die Umsetzbarkeit

The G-BA is requesting collection of patient-reported outcomes (PROs). Vertex is asked to provide details and justification on the following aspects:

- Which questionnaires could be considered for a potential PRO-collection and for which languages and age groups these are available

- Which concrete aspects hinder implementation of PRO-collection in the selected data source, i.e. the GPOH registry
- Which alternative possibilities for PRO collection outside of the registry could be considered and which limitations might hinder feasibility

## 14.2 Vertex position

Vertex has assessed the collection and analysis of PROs and discussed its perspective with the GPOH registry. In a joint assessment, Vertex and the GPOH registry conclude, that the effort required to implement PROs would be disproportionate in the context of the AbD, also considering the target enrollment of at least 33 Exa-cel patients, and there are methodological limitations with regards to implementation of PROs as well as analysis.

PRO Implementation

The implementation of PROs is hindered by aspects related to the indication. The majority of sickle cell disease (SCD) patients treated in Germany come from African or Arab countries, where a broad variety of languages are spoken (4, 5). The patient information and consent forms of the GPOH registry are available in German, English, French and Arabic. It can therefore be assumed that patients included in the registry, and therefore potentially eligible for the AbD, speak one of the aforementioned languages (German, English, French and Arabic). Appropriate surveys would therefore need to be available and validated for all patients in one of those languages. This was already noted as a major problem for the practical implementation in the expert exchange ("*Fachaustausch*") for the AbD (6).

Furthermore, the Exa-cel indication includes patients aged 12 years and older. Therefore, different, appropriately validated questionnaires would have to be used for the age groups 12 to 18 years and >18 years. These would also need to be validated in all required languages.

Per G-BA request, Vertex has conducted a review of potentially relevant PROs in SCD, including information on their availability and validation in relevant languages and for different age groups. Beyond the above listed languages, Turkish was considered as an additional potentially relevant language. Only PRO instruments for children aged 12 years and older, adolescents and adults are considered relevant.

PRO instruments were identified from the pivotal clinical trial for Exa-cel (CLIMB-121, NCT03745287) as well as from previous benefit assessments of medicinal products for the indication SCD (Crizanlizumab, Voxelotor).

For reasons of readability, the detailed assessment of each identified PRO can be found in the separate report "Exa-cel AbD: Patient-reported outcomes (PROs) in the indication sickle cell disease" (7).

In summary, the detailed assessment has shown that no single questionnaire can be used consistently across age groups in the AbD due to lack of validation or lack of validated translations. In the AbD scientific advice meeting (3), the IQWiG confirmed that PRO instruments need to be validated in a language understandable by the patient. Therefore, none of the identified questionnaires is fully utilizable for the AbD due to limitations in terms of age, language and / or validation.

Another specific characteristic in SCD is the main symptom of recurrent, acute VOCs, which are linked to severe pain and a reduced quality of life (2). As the potentially relevant questionnaires only

consider short time periods, they can only record those VOCs, that occurred within the time period of the questionnaire. E.g., the questionnaire "brief pain inventory" (BPI) in its short form (SF) covers only the last 24 hours; the long form (LF) only the last 7 days. The SF-36 for quality of life assessment partially covers the acute situation and partially the preceding four weeks (8, 9). The different anticipated incidence of acute VOCs in both treatment arms will result in significant bias as especially in patients in the SoC arm, who only receive symptomatic treatment, a higher incidence of VOCs can be expected. These would therefore be underreported, overestimating these patients' quality of life.

This issue was already discussed in the benefit assessment of crizanlizumab in SCD, where the G-BA agreed upon the limited validity of PRO results due to the use of SF-36 and BPI-LF questionnaires at pre-defined time points, as "only a fraction of the surveys coincided by chance with the occurrence of a VOC" (10).

Alternatively, a large number of fixed data collection points (e.g. weekly) would need to be scheduled to continuously collect pain symptom progression and quality of life over the observation period. In practice, this would involve disproportionate effort both for patients and treatment centers and is not feasible, as per assessment of Vertex and the GPOH registry.

PRO Assessment

Per G-BA request, the below describes which concrete aspects hinder the implementation of PROs in the selected data source, i.e. the GPOH registry.

First, the willingness to complete PRO questionnaires must be considered low, especially for study participants in the comparator arm. Even in interventional clinical studies in SCD, low response rates were observed, which continued to decline throughout the observation, so that corresponding endpoints have not yet been used by the G-BA for the benefit assessment (10, 11). Accordingly, it seems unrealistic to expect sufficiently high response rates, as are usually required in benefit assessments, in an AbD spanning multiple years.

This assessment was confirmed by the GPOH registry in the expert exchange ("*Fachaustausch*") (6) and confirmed once more in the scientific advice meeting. In the scientific advice meeting, the GPOH registry stated, that a response in PRO questionnaires especially in the comparator arm will be hindered additionally by cultural differences and language barriers. The registry even gave the example that some patients who don't have confirmed residence permit / asylum status are extremely reluctant to provide anything in writing due to fear of any mistake may jeopardize their residence status. In contrast, Exa-cel patients will likely be compliant with regards to their response, as they are potentially cured and closely observed in their treatment centers (3).

In addition, Exa-cel and the comparator treatment are very different treatment approaches as Exa-cel is a curative treatment and the comparator treatment, at best, slows down disease progression and cure cannot be achieved. Self-assessment of quality of life will therefore be biased and due to lack of blinding, a bias towards Exa-cel can be expected. Furthermore, different outcomes can be assumed within the comparator arm itself, as patients experience different levels of stress from their therapy (oral intake of hydroxycarbamide vs. regular red blood cell transfusions). The different treatment modalities further complicate the interpretation of results.

The inclusion of patients aged 12 years and older into a study running at least 3 years in light of age-specific questionnaires (age group 12-18 years and >18 years) results in additional hurdles. The separate evaluation of adults and children or adolescents would lead to lower case numbers in the analysis, making it more difficult to derive a statistically significant treatment effect. For patients

reaching the age of 18 within the study period it will need to be determined whether they should switch to the adult version of the respective questionnaire. In this case, no baseline value (informed consent or treatment decision) would be available for this version of the questionnaire, which would distort the analysis. A pooled evaluation of pediatric and adult questionnaires would also be highly biased.

An additional aspect, that was raised during the expert exchange, is the dependence of many SCD patients on pain medication such as opioids (6). Chronic opioid therapy or its discontinuation can have unexpected, sometimes paradoxical effects on the subjective perception of pain, which is not necessarily linked to SCD. As a result, the effects of treatment on pain perception in these patients cannot reliably be measured using PROs.

To summarize, there is a high probability that the combination of low response rates and reduced certainty of results due to bias would ultimately lead to the PRO data collected not being taken into account in the assessment of the AbD results.

Alternative possibilities of PRO collection and analysis

Collection and analysis of PROs are hindered by the aspects laid out above:

- Limitations of PRO collection due to inappropriate questionnaires: None of the identified questionnaires is fully utilizable for the AbD due to limitations in terms of age, language and / or validation.
- Limitations due to analysis of outcomes: Expected low response rates, bias due to different willingness of patients to respond depending on treatment arm, challenges linked to age and opioid use.

These limitations apply for data collection and analysis of the data within the GPOH registry, where PRO collection is currently not implemented. However, the same limitations continue to apply using an external third party for PRO collection, e.g. in a trust center-based model. Therefore, such a model would not increase the feasibility of PRO collection.

Summary

There are numerous challenges associated to the collection and analysis of PROs in SCD patients; consequently, the GPOH registry does not collect any PRO data to date, supported by statements from registry representatives. The same issues apply when considering a trust-center based model.

The implementation of PRO collection and analysis in the GPOH registry, if at all possible, would be associated with considerable additional effort of the registry, AbD-participating centers and patients. In light of a questionable gain in knowledge, it is Vertex' view that this additional effort is disproportionate and implementation of PRO collection is inappropriate also considering the target enrollment of at least 33 Exa-cel patients.

# 15 CONSIDERATION OF ACUTE VS. CHRONIC RBC TRANSFUSIONS IN COMPARATOR ARM

## 15.1 G-BA Position

> Niederschrift: Die Geschäftsstelle unterstreicht, dass bei einer fehlenden (medizinischen) Eignung für die im Vergleichsarm genannten Therapieoptionen die Positivität nicht erfüllt ist. Die Vergleichbarkeit der Patientenpopulationen im Vergleichs- und im Komparatorarm muss für die Datenauswertung gegeben sein.
>
> […]
>
> Das IQWiG erläutert, dass der Begriff „Eignung bzw. Nicht-Eignung für eine Transfusionstherapie“ in den Studienunterlagen detailliert dargelegt werden sollte. Patientinnen und Patienten, für die eine Transfusionstherapie grundsätzlich geeignet ist, sie diese aber wegen einer (momentan) fehlenden Indikation nicht erhalten, könnten im Vergleichsarm der AbD eingeschlossen werden.

The G-BA is requesting that positivity, i.e. patients need to be eligible for the intervention as well as one of the comparator treatments, needs to be fulfilled. This includes a chronic red blood cell transfusion program.

## 15.2 Vertex Position

Transfusions in SCD are necessary to treat certain acute complications but can also be part of a long-term therapy concept. Transfusions are associated with potentially serious side effects, particularly due to the risk of alloimmunization, hemosiderosis and the transmission of infections, and should therefore only be used with caution and a clear indication. Blood transfusions are also not indicated for the primary treatment of pain crises (2) The cited guideline clearly states that transfusions are either given for emergency situations or electively; elective transfusions are further divided under “occasional” and as part of a chronic transfusion program.

When chronic transfusions are indicated, they can prevent the occurrence of VOCs and other severe complications of SCD; therefore, patients on a chronic transfusion program are part of the SoC Arm of the AbD.

Patients who are not receiving hydroxycarbamide (Hydroxyurea, HU) therapy for any reason and are not on a chronic transfusion program are merely relying on supportive measures, which cannot be considered standard of care in the prevention of VOCs and therefore do not fulfil the requirement of inclusion into the control arm of the AbD. Even if such patients have received acute transfusions for emergency situations, or elective occasional transfusions in the past, they are not receiving any accepted treatment to prevent VOCs.

The registry representatives stated that there may be singular cases where patients within the approved Exa-cel indication cannot be treated with HU for various reasons (e.g. compliance issues or toxicity) and have no indication for chronic transfusions (3). However, it seems highly unlikely that such patients would be prioritized for treatment with Exa-cel, especially as the Medical services of the German payers (*Kompetenz-Centrum Onkologie der Medizinischen Dienste*, KCO) assessment list for

Exa-cel stipulates that prescribers should show proof that all existing therapeutic measures have been fully utilized (12). Thus, inclusion of such patients into the SoC Arm would violate the positivity assumption, as these patients would likely not be approved to receive Exa-cel by the medical services. As these would be only singular cases, exclusion of such patients would not jeopardize the enrollment success of the AbD.

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*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 registry-based study required by G-BA

**Version:** Version 1.0

**Version Date of SAP:** 13 June 2025

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# 3 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 |
| EoS | End of study |
| Exa-cel | Exagamglogene autotemcel |
| FAS | Full Analysis Set |
| FS | Fine stratification |
| G-BA | Federal Joint Committee (*Gemeinsamer Bundesausschuss*) |
| GPOH | Society of Pediatric Oncology and Hematology (*Gesellschaft für Pädiatrische Onkologie und Hämatologie*) |
| Hb | Hemoglobin |
| HbA | Hemoglobin A |
| HbF | Fetal hemoglobin |
| HbS | Sickle cell hemoglobin |
| HbSC | Hemoglobin SC |
| HbSS | Hemoglobin SS |
| HLA | Human leukocyte antigen |
| HPFH | Hereditary persistance of fetal hemoglobin |
| HSC(T) | Hematopoietic stem cell (transplantation) |
| 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)* |
| LIC | Liver iron concentration |
| LVEF | Left-ventricular ejection fraction |
| MACNU Design | Modified Active Comparator New-User Design |
| MED | Mediterranean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple imputation |
| MUD | Matched unrelated donor |
| NYHA | New York Heart Association |
| OW | Overlap weighting |
| PICO | Population, Intervention, Comparator, Outcome |

| Abbreviation | Definition |
|---|---|
| PS | Propensity score |
| PT | Preferred term |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCD | Sickle cell disease |
| SCT | Stem cell transplantation |
| SD | Standard deviation |
| SEA | Southeast Asia |
| SMD | Standardized mean difference |
| SoC | Standard of Care |
| TCD | Transcranial doppler |
| uACR | Urine albumin-creatinine ratio |
| VOC | Vaso-occlusive crisis |

# 4 MODIFICATIONS TO STATISTICAL ANALYSIS

Not applicable for this version of the document.

# 5 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®) required 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 13 June 2025, Version 1.0.

This AbD is a non-interventional, prospective, non-randomized, comparative study in patients with severe sickle cell disease (SCD). Patients' medical data will be entered into the German Society of Pediatric Oncology and Hematology (GPOH) registry, which will be amended to fulfill AbD requirements. The GPOH SCD registry is an independent multicenter, clinical and epidemiological registry including patients with SCD irrespective of disease severity in Germany who have consented to transfer data to the registry. 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.

# 6 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 and recurrent vaso-occlusive crises (VOCs). Information on **P**opulation, **I**ntervention, **C**omparator and **O**utcome (PICO) are outlined in Table 1.

**Table 1: PICO scheme of the present study**

| | |
|---|---|
| **Population** | Patients aged 12 years and older 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<br>• Chronic red blood cell (RBC) transfusions |
| **Outcome** | Objectives and endpoints of this study are presented in detail in Table 2. |

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, and
- To compare the proportion of VOC-free patients over 36 months, between Exa-cel and Standard of Care (SoC).

For the comparison of the proportion of VOC-free patients over 36 months, it is appropriate that the 36-month period starts from 60 days after last red blood cell (RBC) transfusion for post-transplant management.
The following table provides an overview of the specific objectives and endpoints in this study.

**Table 2: Objectives and endpoints**

| Objective | Endpoint |
|---|---|
| ***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 |

| Objective | Endpoint |
|---|---|
| ***Secondary*** | |
| *Morbidity* | |
| To compare the annualized rate of VOCs | • Annualized VOC rate in Period 1 |
| To compare pain medication prescriptions for SCD management over time | • Proportion of patients with prescription of non-opioid analgesics during Period 1 and in 6-month intervals during Period 2, all types and by type (WHODRUG preferred name)<br>• Proportion of patients with prescription of opioid analgesics during Period 1 and in 6-month intervals during Period 2, all types and by type (WHODRUG preferred name) |
| To compare the proportion of patients with newly occurring or worsened chronic organ damage or improvement of chronic organ damage | Proportion of patients with<br>• Newly occurring chronic organ damage by period; all types and by type<br>• Worsened chronic organ damage by period; all types and by type<br>• Improvement of chronic organ damage by period; all types and by type<br>The following events are considered as relevant chronic organ damage in SCD patients:<br>• Aseptic osteonecrosis<br>• Cardiomyopathy<br>• Retinopathy<br>• Hepatopathy<br>• Pulmonary hypertension<br>• Osteoporosis<br>• Nephropathy<br>• Leg ulcer<br>• Alloimmunization<br>• Siderosis |
| To compare the proportion of patients with new cerebrovascular events | Proportion of patients with new cerebrovascular events by period, all types and by type:<br>• Stroke (ischemic, hemorrhagic)<br>• De novo pathologic intracerebral blood flow as measured by transcranial doppler (TCD) sonography |

| Objective | Endpoint |
|---|---|
| To compare need for RBC transfusions | Proportion of patients requiring RBC transfusions by period; all types and by type (acute / chronic) |
| *Mortality* | |
| To compare the annualized death rate | Proportion of patients who died by period<br>Annualized death rate by period |
| *Safety* | |
| To compare the occurrence of SAEs | Proportion of patients with SAEs by period<br>Annualized rate of SAEs by period |
| To compare the occurrence of specific AEs | Proportion of patients with specific AEs by period<br>Annualized rate of specific AEs by period<br>The following are defined as specific AEs:<br>• Bleeding<br>• Infection |
| a: For definitions of analysis periods, see section 8.2 | |

# 7 OVERALL STUDY DESIGN AND POPULATION

This is a prospective, non-interventional, observational, non-randomized, comparative, registry-based study using data recorded in the GPOH registry. Individuals will be identified within the GPOH SCD registry during a two-year patient identification period; an additional informed consent is needed for every patient for the use of their data for the purposes of this study. Target inclusion is at least 100 patients, including at least 33 Exa-cel patients. For details regarding sample size considerations, see protocol section 13.5.

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. All eligible patients with a therapy decision for Exa-cel during the patient identification period will be offered inclusion in the study. Index date for Exa-cel patients will be set at the time of therapy decision. Eligible patients on patient-individualized treatment within the GPOH SCD registry will be included using the *Modified Active Comparator New-User* (MACNU) design: Once a new Exa-cel patient is identified, the base cohort consisting of eligible SoC patients in the GPOH SCD registry at that Exa-cel patient's index date is updated, and those SoC patients deemed to be sufficiently similar to that Exa-cel patient based on characteristics related to SCD disease severity are asked to provide their informed consent. At the end of the patient identification period, treatment group assignment is final. Patients in the SoC group with treatment decision for Exa-cel after patient identification will remain part of the SoC group. Each SoC patient is matched to the most similar Exa-cel patient using time-conditional propensity scores to determine their index date, which will be set to the same date as that of the Exa-cel patient. For more details regarding the MACNU design, see protocol section 12.4.2.

Patients will be observed during two consecutive time periods. Period 1 starts at index date and ends at T60 (see section 8.2 for definition) or end of study or censoring (death, withdrawal of consent or loss of follow-up), whichever comes first. Period 2 starts at T60 and ends at end of study or censoring, whichever comes first.

# 8 STATISTICAL ANALYSIS

## 8.1 General Considerations

**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.

All objectives will compare patients in the Exa-cel group to patients in the patient-individualized treatment (SoC) group 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 8.8.

**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. If only the day is missing, 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. For partial dates with both month and day missing, a partial start date will be imputed as the first day of the first month of the year, and a partial stop date as the last day of the last month of the year.

Missing values in confounding variables used in PS estimation will be imputed using multiple imputation. The specific methods are described in detail in section 8.8.1. For missing values in endpoints, see the respective estimand framework in section 8.7.

## 8.2 Time Periods and Time Points Relevant to Analysis

Table 3 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 8.7 for each endpoint where they apply.

**Table 3: 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 | Eligible patients will be identified between AbD start and 2 years after that, i.e., their index date, as defined below, falls within a 2-year period after AbD start. |

| Time period / study date | Definition |
|---|---|
| Index date | For Exa-cel patients, the index date is defined as the date of therapy decision for Exa-cel (treatment consent and reimbursement approved).<br>For SoC patients, the index date is defined as the index date of the Exa-cel patient they were matched to. |
| 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).<br>For an SoC patient, T60 is defined as the same T60 date of the matched Exa-cel patient. 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 one-year period prior to the index date is defined as baseline period for each patient. |
| Observation period | The observation period is defined as the period from the index date to the end of the study or censoring. 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 to censoring, whichever comes first, is defined as Period 1. |
| Period 2 | The period from T60 to the end of the study or censoring 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. |

## 8.3 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. The FAS will be used for all analyses of morbidity, mortality and safety except for the co-primary endpoint of VOC freedom.

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

## 8.4 Baseline Characteristics

Baseline characteristics will be summarized based on the FAS, using descriptive statistics. They comprise basic demographic characteristics, disease and past treatment characteristics and all confounders that were identified systematically using a literature review and expert input. The baseline value of a variable is defined as the closest measurement before or at index date during the one-year baseline period.

Baseline characteristics will include the following:

**Table 4: Demographics and baseline characteristics**

| Variable | Operationalization |
|---|---|
| Sex | Male / female |
| Age (years)* | Date of birth |
| Body height | cm |
| Body weight | kg |
| Genotype | Diagnosis / subtype:<br>HbSS, HbSC, HbSß0 Thal, HbSß+ Thal, HbS/OArab, HbS/D Punjab, HbS/C Harlem, HbC/S Antilles, HbS/Quebec-CHORI, HbA/S Oman, HbS/E, HbA/Jamaica Plain, HbS/HPFH, other |
| Age at diagnosis (years) | Date of diagnosis - date of birth |
| Prior and concomitant diseases<br>• Nephropathy*<br>• Chronic pain*<br>• Hepatopathy*<br>• Pulmonary hypertension*<br>• Cerebrovascular event (prior stroke, neurological deficit)*<br>• Alloimmunization*<br>• Siderosis (iron overload)*<br>• Cardiomyopathy<br>• Osteoporosis<br>• Proliferative retinopathy<br>• Pulmonary hypertension<br>• Ulcus cruris<br>• Gallstones | Yes / no (unless otherwise specified) |

| Variable | Operationalization |
|---|---|
| • Aseptic osteonecrosis (incl. status post-surgical correction)<br>• „Other underlying diseases“ | Medical Dictionary for Regulatory Activities (MedDRA) coded |
| Smoking regularly | Yes / no |
| Alpha-thalassemia | Yes / no (if yes α 3,7 homozygous, α 3,7 heterozygous, α 4,2 homozygous, α 4,2 heterozygous, α 20,5 homozygous, α 20,5 heterozygous, SEA homozygous, SEA heterozygous, MED homozygous, MED heterozygous, α triplication, α1 mutation homozygous, α1 mutation heterozygous. Other) |
| Modifiers of fetal hemoglobin (HbF) synthesis | Yes / no (if yes BCL11A rs 766432 homozygous, BCL11A rs 766432 heterozygous, HMIP rs 9399137 homozygous, HMIP rs 9399137 heterozygous, Gamma-Globin-Promotor Xmnl-Polymorphism homozygous, Gamma-Globin-Promotor Xmnl-Polymorphism heterozygous) |
| Total hemoglobin (Hb) | mmol/dL |
| Sickle cell hemoglobin (HbS) level | % of total Hb |
| HbF level | % of total Hb |
| VOCs* | Number of VOCs over 12 months prior to index date<br>VOC defined as hospitalization with overnight stay for any of the following:<br>• Priapism: no, yes, unknown<br>• Splenic sequestration(s): no, yes, unknown<br>• Acute thorax syndrome(s) (ACS): no, yes, unknown / number of ACSs<br>• Pain crises: no, yes, unknown / number of hospital days |
| Chronic transfusion therapy* | Yes / no<br>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 apharesis, on top transfusion) mean HbS level prior transfusions (%) |

| Variable | Operationalization |
|---|---|
| Iron chelation | Yes / no<br>Among patients with "yes": desferroxamine yes / no, deferasirox yes / no, phebotomy yes / no |
| HU therapy ongoing at index date | Yes / no<br>Among patients with "yes": dose (mg/kg*d), indication (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)<br>Among patients with "no": date of discontinuation, 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 |
| Chronic organ damage<br>• Aseptic osteonecrosis<br>• Cardiomyopathy<br>• Retinopathy<br>• Hepatopathy<br>• Pulmonary hypertension<br>• Osteoporosis<br>• Nephropathy<br>• Leg ulcer<br>• Alloimmunization<br>• Siderosis | Yes / no for each |

* Confounder variables, see also section 8.8.1

Baseline characteristics will be summarized by treatment group with the descriptive summary statistics listed in section 8.1.

## 8.5 Concomitant Medications

Concomitant pain medication use during the study (non-opioid analgesics, opioid analgesics) will be analyzed as a secondary morbidity endpoint (see section 8.7.2.).

## 8.6 Treatment Exposure

Treatment exposure to any study medication - patient-individualized treatment and Exa-cel - will be described on the FAS. Treatments that patients in both groups can receive (e.g. RBC transfusions or hydroxycarbamide before an Exa-cel patient completes Exa-cel treatment) 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 5: Treatment exposure**

| **Variable** | **Operationalization** |
|---|---|
| RBC transfusions<br>• Acute RBC transfusion<br>• Chronic RBC transfusions | Number, total volume of transfusions (ml), type (exchange transfusion, erythrocyte apheresis, on top transfusion) |
| HU therapy (SoC only) | Yes / no; start / stop date, dose (mg/kg*d); reason for discontinuation |
| Iron chelation | Yes / no;<br><br>Among patients with „yes“: Desferroxamine yes / no, Deferasirox yes / no, phlebotomy yes / no |
| SCT from a MUD (SoC group only)<br>1. Mobilization (incl. preparation, may be done for back-up cell collection)<br>2. Apheresis (may be done for back-up cell collection)<br>3. Conditioning<br>4. SCT<br>5. Post-SCT | The number of patients going through each step will be reported.<br>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<br>2. Number of cycles, start date of each apheresis cycle<br>3. Conditioning agents, date start of conditioning, dose<br>4. Date of transplantation<br>5. Date patient weaned off from post-transplant RBC transfusions, date neutrophil engraftment achieved |

| Variable | Operationalization |
|---|---|
| | (3 consecutive measurements of absolute neutrophil count (ANC) ≥500 cells/µL on 3 different days after SCT 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 SCT without administration of platelet transfusions for 7 days), date hospital discharge), post-SCT immuno-suppression (coded via WHODRUG, start date, stop date, dose)<br>6. Post-transplant immunosuppression: drug used, dose, start date, end date |
| Exa-cel therapy<br>1. Mobilization<br>2. Apheresis<br>3. Conditioning<br>4. Infusion<br>5. Post-infusion | The number of patients going through each step will be reported.<br>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<br>2. Number of cycles, start date of each apharesis cycle<br>3. Conditioning agent, date start of conditioning, dose, posology (qd, q6, other), total AUC<br>4. Date of infusion, total Exa-cel dose infused<br>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) |

| Variable | Operationalization |
|---|---|
| Discontinuation from Exa-cel therapy journey before infusion | Date and reason for discontinuation |

## 8.7 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 to be used as weights in the comparative analyses
2) Comparative, PS-adjusted analysis for all endpoints

Section 8.8 provides details on PS and weight calculation.

### 8.7.1 Primary Endpoints

The co-primary endpoints are VOC freedom and annualized VOC rate during Period 2.

VOCs are defined as hospitalization with overnight stay for priapism, splenic sequestration(s), acute thorax syndrome or pain crises.

For VOC freedom, the treatment groups will be compared regarding the proportion of patients who are VOC-free over 36 months starting at T60 (Period 2). For the annualized VOC rate, the treatment groups will be compared for Period 2.

The following **intercurrent events (ICEs)** will be considered during the analysis:

- Therapy decision for any transplantation (Exa-cel, matched unrelated donor [MUD]-SCT, other) (SoC group only)
- Hematopoietic stem cell (HSC) transplantation is no longer appropriate, e.g. at the discretion of the physician, the individual is no longer eligible for full myeloablative conditioning (SoC group only)
- Change of SoC therapy (SoC group only)

Table 6 summarizes the analysis strategy for the primary endpoint **VOC freedom over 36 months in Period 2** within the estimand framework.

**Table 6: 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) |

| **VOC freedom, Period 2** | **Primary Estimand** |
|---|---|
| Population-level summary | Risk ratio |
| Handling of ICE | |
| Therapy decision for any transplantation (Exa-cel, MUD-SCT, other)[a] | Treatment policy |
| Change of SoC therapy[a] | Treatment policy |
| HSCT no longer appropriate[a] | Treatment policy |
| ***Analysis (Estimator)*** | |
| Confounder[b] adjustment method | Calculation of weights based on PS |
| Analysis model | Logistic regression including weights |
| a: Potential ICE for SoC group only<br>b: Missing values in confounders will be imputed using multiple imputation. | |

For the primary endpoint VOC freedom over 36 months, starting from T60 is of primary interest, i.e. during Period 2. As recommended by G-BA, ICEs are handled via Treatment Policy approach: once an ICE occurs, no censoring happens and patients continue to be observed until 36 months after T60. Treatment groups will be compared via risk ratio, estimated from a weighted logistic regression model.

Table 7 summarizes the analysis strategy for the primary endpoint **annualized VOC rate for Period 2** within the estimand framework.

**Table 7: 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 any transplantation (Exa-cel, MUD-SCT, other)[a] | Hypothetical[b] |
| Change of SoC therapy[a] | Treatment policy |
| HSCT no longer appropriate[a] | Treatment policy |

| **Annualized VOC rate, Period 2** | **Primary Estimand** |
|---|---|
| **Analysis (Estimator)** | |
| Confounder[c] adjustment method | Calculation of weights based on PS |
| Analysis model | Negative binomial regression including weights |
| a: Potential ICE for SoC group only<br>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.<br>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 ICEs "change of SoC therapy" and "HSCT no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICE "therapy decision for any transplantation", 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. As this analysis is conducted only for Period 2, patients who do not have a defined time point T60 will not be included in the analysis.

### 8.7.2 Secondary Endpoints

All secondary endpoints will be evaluated on the FAS.

Table 8 summarizes the analysis strategy for the secondary endpoint **annualized VOC rate for Period 1** within the estimand framework.

**Table 8: 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 (Index date to the earlier of T60 or EoS or censoring) |
| Population-level summary | Rate ratio |
| Handling of ICE | |
| Therapy decision for any transplantation (Exa-cel, MUD-SCT, other)[a] | Hypothetical[b] |
| Change of SoC therapy[a] | Treatment policy |
| HSCT no longer appropriate | Treatment policy |

| **Annualized VOC rate, Period 1** | **Primary Estimand** |
|---|---|
| ***Analysis (Estimator)*** | |
| Confounder[c] adjustment method | Calculation of weights based on PS |
| Analysis model | Negative binomial regression including weights |
| a: Potential ICE for SoC group only<br>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.<br>c: Missing values in confounders will be imputed using multiple imputation. | |

Annualized VOC rate during Period 1 will be analyzed analogously to Period 2. The ICEs "change of SoC therapy" and "HSCT no longer appropriate" will be handled using Treatment Policy: Data starting from that ICE will continue to be used in the analysis. For the ICE "therapy decision for any transplantation", 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.

Regarding the estimand strategy of other 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 logistic regression model as a population-level summary. 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 as a population-level summary.

ICEs for other secondary endpoints are defined the same as for annualized VOC rate. The ICEs "change of SoC therapy" and "HSCT no longer appropriate" will be handled using Treatment Policy. For the ICE "therapy decision for any transplantation", the Hypothetical approach is used: Only data up to the ICE will be used for analysis.

For descriptive safety analysis, occurrence of serious adverse event (SAEs) and specific adverse events (AEs) will be evaluated in three groups:

1. Exa-cel group: AEs occurring during the specified time periods in Table 9 for patients in the Exa-cel group
2. SoC group: AEs occurring during the specified time periods in Table 9 up to therapy decision for any transplantation (Exa-cel, MUD-SCT or other)
3. SoC group with therapy decision for any transplantation: AEs occurring during the specified time periods in Table 9 starting at therapy decision for any transplantation

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

**Table 9: 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 |
| Proportion of patients with prescription of non-opioid analgesics (all types and by type[a]) | Type of analgesic will be coded via WHODRUG preferred name. | Period 1, in 6-month intervals during Period 2 |
| Proportion of patients with prescription of opioid analgesics (all types and by type[a]) | | |
| Proportion of patients with newly occurring chronic organ damage (all types and by type[a]) | The following events are considered as relevant chronic organ damage in SCD patients:<br>1. Aseptic osteonecrosis<br>2. Cardiomyopathy<br>3. Retinopathy<br>4. Hepatopathy<br>5. Pulmonary hypertension<br>6. Osteoporosis<br>7. Nephropathy<br>8. Leg ulcer<br>9. Alloimmunization<br>10. Siderosis<br>Organ damage will be coded via MedDRA preferred term. Worsening and improvement are defined as following, corresponding to the numbered types above:<br>1. Change in Ficat / ARCO classification (stages 0 to IV, where move to a higher stage corresponds to worsening)<br>2. Change in LVEF category: >50% (normal), 40-49% (mild impairment), 30-39% (moderate impairment), <30% (severe impairment); and / or change in NYHA class (I-IV, where move to a higher class corresponds to worsening) | Period 1, Period 2 |
| Proportion of patients with worsened chronic organ damage (all types and by type[a]) | | |
| Proportion of patients with improvement of chronic organ damage (all types and by type[a]) | | |

| Endpoint | Operationalization | Analysis Time Periods |
|---|---|---|
| | 3. Change in logMAR visus of at least 0.2 in one eye (increase corresponds to improvement), any occurrence of central artery occlusion, ablatio or bleeding will count as worsening / no improvement<br>4. Change to be determined with registry e.g. Child-Pugh Score<br>5. Change in NYHA class (I to IV, where move to a higher class corresponds to worsening) and / or change in 6-minute walk test<br>6. Change in DXA T-Score category: >-1 (normal), -1 to -2.5 (osteopenia), <-2.5 (osteoporosis)<br>7. Change in eGFR category: >90 ml/min (normal), 60-89 ml/min (mild impairment), 45-59 (moderate impairment I), 30-44 ml/min (moderate impairment II), 15-29 ml/min (severe impairment), <15 ml/min (renal failure); and/or change in uACR category: <30 mg/g (normal), 30-<300 mg/g (microalbuminuria), 300-3000 mg/g (macroalbuminuria), ≥3000 mg/g (proteinuria)<br>8. Change to be determined with registry, no quantitative measures<br>9. Change to be determined with registry, no quantitative measures<br>10. Change in liver iron concentration (LIC) (mg/g) category (no indication for chelation therapy, chelation therapy indicated, risk for severe organ siderosis) as per German diagnostic and treatment guidelines (1); thresholds depend on method used for determining LIC<br>A patient counts as having worsened / improved organ damage of a specific type if the above defined change occurs during the specified analysis time period, compared to the baseline value of the parameter, scale or classification. | |

| Endpoint | Operationalization | Analysis Time Periods |
|---|---|---|
| Proportion of patients with new cerebrovascular events (all types and by type[a]) | Types include:<br>• Stroke (ischemic, hemorrhagic)<br>• De novo pathologic flow in transcranial doppler | Period 1, Period 2 |
| Proportion of patients requiring RBC transfusions (all types and by type[a]) | Types include:<br>• Acute RBC transfusion<br>• Chronic RBC transfusions | Period 1, Period 2 |
| ***Mortality*** | | |
| Proportion of patients who die | Derived via date of death recorded in the registry. | Period 1, Period 2 |
| Annualized death rate | | |
| ***Safety*** | | |
| Proportion of patients with SAEs | SAEs[c] are any AEs that meet any of the following criteria:<br>• Results in death<br>• Life-threatening<br>• Requires hospitalization or prolongation of existing hospitalization<br>• Results in persistent or significant disability / incapacity<br>• Congenital anomaly or birth defect<br>• Requires intervention to prevent life-threatening event | Period 1, Period 2<br>Period 1 will be additionally split into[b]:<br>• Time from index date to start of mobilization<br>• Mobilization & apheresis<br>• End of last apheresis to conditioning<br>• Conditioning<br>• Exa-cel infusion to 60 days after last RBC transfusion (T60) |
| Annualized rate of SAEs | | |
| Proportion of patients with specific AEs | Specific AE Bleeding[d]:<br>• Epistaxis (MedDRA PT epistaxis)<br>• Skin / cutaneous soft tissue (MedDRA PT skin haemorrhage)<br>• Oral / gingival (MedDRA PT gingival bleeding)<br>• Vaginal (MedDRA PT vaginal haemorrhage)<br>• Gastrointestinal (MedDRA PT gastrointestinal haemorrhage)<br>• Hematuria / urethral (MedDRA PT hematuria)<br>• Intracranial (MedDRA PT haemorrhage intracranial)<br>• Catheter / device related (MedDRA PT catheter site haemorrhage) | |
| Annualized rate of specific AEs | | |

| Endpoint | Operationalization | Analysis Time Periods |
|---|---|---|
| | • Other (MedDRA PT hemorrhage) → free text field for description<br>Specific AE Infection[d]:<br>• Nasopharyngeal / sinusitis (MedDRA PT upper respiratory tract infection)<br>• Oral (MedDRA PT oral infection)<br>• Pulmonary (MedDRA PT pneumonia)<br>• Bloodstream / sepsis (MedDRA PT sepsis)<br>• Skin (MedDRA PT skin infection)<br>• Vaginal (MedDRA PT vaginal infection)<br>• Gastrointestinal (MedDRA PT gastrointestinal infection)<br>• Catheter / device related (MedDRA PT device related infection)<br>• Other or unknown (MedDRA PT infection) free text field for description | |
| a: Analysis by type will be descriptive only.<br>b: Descriptive only for patients in the Exa-cel group.<br>c: For SAEs, descriptive analyses regarding criteria, CTCAE grade, type (MedDRA PT), relatedness to Exa-cel treatment and outcome will additionally be performed.<br>d: Components of the specific AEs Bleeding and Infection will be analyzed descriptively. | | |

## 8.8 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.

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 both analysis sets (FAS and FAS36) independently of each other.

### 8.8.1 Confounders and Missing Values in Confounders

The following ten confounders relevant for this AbD were identified systematically using a literature review and expert input, and their expected level of impact on specific endpoints are ranked:

**Table 10: Confounders relevant for adjusted analysis**

| Rank, VOC endpoints | Rank, other endpoints | Confounder | Operationalization Used in Adjustment |
|---|---|---|---|
| 9 | 1 | Iron overload | Categorical (yes / no) |
| 8 | 2 | Chronic renal insufficiency | Categorical (yes / no) |
| 4 | 3 | Chronic pain | Categorical (yes / no) |
| 7 | 4 | Hepatopathy | Categorical (yes / no) |
| 6 | 5 | Pulmonary hypertension | Categorical (yes / no) |
| 5 | 6 | Cerebrovascular risk | Categorical (yes / no) |
| 1 | 7 | Number of VOCs | Continuous (number of VOCs recorded in baseline period) |
| 3 | 8 | Age | Continuous (in years) |
| 2 | 9 | Chronic transfusion therapy | Categorical (yes / no) |
| 10 | 10 | Alloimmunization | Categorical (yes / no) |

Details regarding definition of these confounders are listed in section 8.4 on baseline characteristics. All confounders are measured at baseline.

Details on the methodological approach of confounder identification can be found in the report attached as a reference (2).

To adjust for these confounding factors, they will be included in PS estimation. **Multiple imputation (MI)** will be performed on each analysis set to impute missing baseline values.

For MI, the within-method will be used, as recommended in literature (3, 4). Using the MI method, m=50 datasets will be created where in each dataset, the missing baseline confounder values will be imputed. The MI model used to impute missing values will include all confounding variables.

The general terms “analysis population” and “imputed dataset” will be used for both FAS and FAS36 to describe the methodology going forward to avoid redundancy.

The following steps in confounder adjustment will be performed on each imputed dataset, and on each dataset, the treatment effects will be estimated. Only then the different effect estimates will be combined.

### 8.8.2 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. All identified 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 the PS model does not converge, drop confounder ranked as "10" and rerun the PS model. If the PS model still does not converge two separate PS models will be run depending on the endpoint.

- For VOC-related endpoints, use the respective ranking of the remaining 9 confounders (see Table 10) and drop the lowest ranked confounder in the list of included confounders. Repeat this process until the PS model does converge. If no confounders are left, an unadjusted comparison will be performed instead.
- For non-VOC-related endpoints, use the respective ranking of the remaining 9 confounders and drop the lowest ranked confounder in the list of included confounders (Table 10). Repeat this process until the PS model does converge. If no confounders are left, an unadjusted comparison will be performed instead.

Consequently, for VOC-related and non-VOC-related endpoints different PS will be used in the following analyses steps.

### 8.8.3 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.

The overlap in PS distributions between groups will be quantified as the areal overlap percentage of the PS densities. The median overlap percentage across imputed datasets will be calculated and discussed.

### 8.8.4 Propensity Score Weighting

After PS estimation, PS weights are then 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) (5, 6).

The mathematical distinction between IPTW and OW also coincides with a difference in interpretation (6). 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 propensity scores) 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 (7).

OW was also found to be superior to fine stratification (FS) in terms of balancing covariates bias and precision (8).

### 8.8.5 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 logistic 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 patients in Period 2, the rate ratio with 95% CI will be estimated via negative binomial regression with treatment as the independent variable and including the PS weights.

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=2.0. Superiority of Exa-cel is shown if the lower bound of the 95% CI is >2.0.

For the **secondary endpoints**, the risk ratio or the rate ratio will be estimated via weighted logistic regression or negative binomial regression respectively, as described in section 8.7.2. No testing against a shifted null hypothesis will be performed.

If any model for effect estimation does not converge, unweighted comparison will be performed instead. If the unweighted model also doesn't converge, only descriptive statistics will be presented.

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.

## 8.9 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 logistic 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.

Subgroup analyses will be performed for the following baseline characteristics:

- Age (in years) at index date (12-21 vs. 22-35 vs. ≥36)
- 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.

## 8.10 Sensitivity Analyses

No sensitivity analyses are planned.

# 9 PLANNED ANALYSES

The following status reports, interim reports and final report are planned according to the requirements in the resolution by G-BA (Table 11). All dates refer to the study start date which will be defined by G-BA.

**Table 11: Planned reports to G-BA**

| Report | Date | Content |
|---|---|---|
| Status report 1 | 6 months after study start<br>Data cut: 4 months after study start | Information on patient inclusion; presented in the status report template (9) |
| Interim report 1<br>and status report 2 | 18 months after study start<br>Data cut: 12 months after study start | Interim analysis results including disposition, baseline characteristics and descriptive safety analysis by period; presented in module 4 of the dossier template (10)<br>Futility analysis regarding the required sample size<br>Information on patient inclusion; presented in the status report template (9) |
| Interim report 2<br>and status report 3 | 36 months after study start<br>Data cut: 30 months after study start | Interim analysis results including disposition, baseline characteristics and descriptive analyses for secondary morbidity endpoints during Period 1 as well as descriptive safety analysis by period presented in module 4 of the dossier template (10)<br>Information on patient inclusion; presented in the status report template (9) |
| Status report 4 | 54 months after study start<br>Data cut: 48 months after study start | Information on patient inclusion; presented in the status report template (9) |
| Final report | Expected one year after EoS | Final analysis presented in module 4 of the dossier template (10) |

Status reports 1 through 4 will include information on number of patients included in the study.

According to G-BA, a sample size recalculation based on the interim data is to be included in the first interim report (11, 12). As the sample size calculation is based on the endpoint proportion of VOC-free patients, this is not feasible: Observation for that endpoint for each Exa-cel patient starts at 60 days after the last RBC transfusion for post-transplant management (T60). This date may not be reached for many (or any) patients 6 months after study start; especially since patients are assigned to the Exa-cel group if the treatment decision for Exa-cel is made in the first 2 years after study start and manufacturing time needs to be taken into account. Therefore, no sample size recalculation will take place during the first interim analysis.

A futility analysis will be conducted at the first interim analysis to assess whether the study will meet the required sample size for final analysis using the MACNU design for enrollment. The futility analysis will examine the total number of patients enrolled in the study and the number of patients in each of the SoC and Exa-cel groups in the FAS at that time. In addition, the number of patients with a T60 date in each treatment group will be presented.

At the first interim analysis (IA1), the alternative approach for the MACNU design (see section 12.4.2 of the protocol) will be applied if the number of Exa-cel patients is according to expectations, and the probability of recruiting at least 67 SoC patients until the end of the study is less than 80%, i.e.,

$Exa_{IA1} > int(33 * \frac{time_{afterIA1}}{time_{untilIA1}})$ and $SoC_{IA1} < 67$ and $\sum_{i=0}^{66-SOC_{IA1}} \left(\frac{\lambda^i e^{-\lambda}}{i!}\right) < 0.8$

with

- $SoC_{IA1}$ = number of SoC patients at IA1 readout
- $Exa_{IA1}$ = number of Exa-cel patients at IA1 readout
- $\lambda = \min(SoC_{IA1}, 3 * Exa_{IA1}) * \frac{time_{afterIA1}}{time_{untilIA1}}$ rate at which SoC patients are recruited up to IA1 readout
- $time_{untilIA1}$ = time (months) from study start until IA1
- $time_{afterIA1}$ = time (months) from IA1 until end of 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.

At the second interim analysis (IA2), the final number of recruited patients is compared against the initial sample size assessment. Continued conduct of the study based on the futility assessment will be discussed with G-BA.

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.

At IA2, descriptive analysis by group for all secondary morbidity endpoints for Period 1 will be performed. Period 1 in this interim analysis ends at the earlier of T60 (if defined), censoring (death, lost to follow-up or withdrawal of informed consent) or date of datacut for IA2. In addition, descriptive analysis of safety endpoints by group will be performed at IA2.

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.

## 10 REFERENCES


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# 11 LIST OF APPENDICES

## 11.1 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.