

Managed Access Agreement

Exagamglogene autotemcel for treating sickle cell disease [TA1044]

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Innovative Medicines Fund – Data Collection Arrangement

Exagamglogene autotemcel for treating sickle cell disease (TA1044)

Company name: Vertex (the company)

Primary source(s) of data collection: CLIMB SCD-121 and CLIMB-131 **Secondary**

source(s) of data collection: Post-authorisation safety study (PASS) with data collected in the European Society for Blood and Marrow Transplantation (EBMT) registry

NICE Agreement Manager	[REDACTED]
NHSE Agreement Manager	[REDACTED]
Vertex Agreement Manager	[REDACTED]

1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for the treatment of sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) who have β^S/β^S , β^S/β^0 or β^S/β^+ , for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available (TA1044). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.

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2 Commencement and period of agreement

- 2.1 This data collection arrangement shall take effect on publication of the MAA.
- 2.2 Estimated dates for data collection, reporting and submission for a guidance update are as below:

Table 1

End of data collection (primary source)	██████
Data available for the development of company submission	██████
Anticipated company submission to NICE for a guidance update	June 2029

- 2.3 Vertex anticipate the results from the additional data collected during the Innovative Medicines Fund period will be incorporated into an evidence submission and the updated economic model by June 2029. Vertex anticipates that a period of time will be required after data availability to allow for data cleaning, verification, analysis and incorporation into the updated economic model for the evidence submission.
- 2.4 Vertex acknowledge their responsibility to adhere as closely as possible to the timelines presented in this document.
- 2.5 NICE will, as far as is practicable, schedule the guidance update into the technology appraisal work programme to align with the estimated dates for the end of data collection.

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- 2.6 The NICE guidance update will follow the process and methods applicable to guidance updates that are in place at the time the invitation to participate in the guidance update is issued. These may be different from the process and methods applicable to guidance updates when this technology entered into the managed access agreement.
- 2.7 As part of the managed access agreement, the technology will continue to be available through the Innovative Medicines Fund after the end of data collection and while the guidance is being updated. This assumes that the data collection period ends as planned and the guidance update follows the standard timelines.
- 2.8 The company is responsible for paying all associated charges for a guidance update. Note that this includes the 'change fee' if the Company does not provide sufficient notice to NICE regarding changes to the evaluation timelines. Please refer to the [NICE website and Charging Procedure](#) for further information.
- 2.9 The company must inform NICE and NHS England (NHSE) in writing of any anticipated changes to the estimated dates for data collection and reporting at the earliest opportunity.
- 2.10 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE.
- 2.11 If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example, due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:

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- Where capacity allows, NICE will explore options to reschedule the guidance update date to align with the earlier reporting timelines.
- It may be necessary to amend the content of the final real-world data report (for example if planned outputs will no longer provide meaningful data).

2.12 If data collection is anticipated to conclude later than the estimated dates for data collection, the company should note:

- The company must submit a written request to NICE and NHSE, with details of the extension requested, including an explanation of the factors contributing to the request.
- It may be necessary for the company to mitigate the impact of any delay, and reduce any risks of further delays.

2.13 Vertex acknowledge their responsibility to provide an evidence submission for this technology to NICE under all circumstances following a period of managed access. This evidence submission should contain all data laid out in this document. Note: Vertex have agreed to be responsible for providing the results from the Burden of Illness (BoI) study and to provide a systematic literature review as a part of their resubmission.

2.14 In the event that Vertex do not make a submission to NICE for the purpose of updating the guidance, NICE and NHSE will require the company to agree to submit the clinical evidence collected during the managed access period, and to participate in an engagement meeting convened by NICE with attendance from NHSE, patient and professional group stakeholders, with the company presenting the clinical evidence collected during the

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managed access period and an explanation of the decision to proceed with withdrawal of the guidance.

2.15 NICE and NHSE may consider the data collection arrangement no longer valid, and withdraw the technology from the Innovative Medicines Fund for the following, non-exhaustive, grounds:

- The primary sources of data are delayed, without reasonable justification.
- The primary sources of data are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation.

3 Monitoring arrangements

3.1 NICE will convene a Managed Access Oversight Group (MAOG) with mandatory attendance from NICE, NHSE and Vertex. Other parties may be invited to attend the MAOG, such as the relevant registry, patient groups and advocates, clinical experts and other relevant parties.

3.2 The MAOG exists to oversee the operation of all aspects of the MAA and to address issues that may arise throughout the MAA term. The MAOG is responsible for monitoring the implementation of the MAA and for recommending actions to support its operation and will meet regularly throughout the data collection period.

3.3 A detailed description of the MAOG function will be available in a Terms of Reference document produced by NICE.

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4 Patient eligibility

4.1 Key patient eligibility criteria for the use of exa-cel in the Innovative Medicines Fund include:

- The patient is 16 years and older, being treated in an adult service, and the centre is commissioned to deliver this treatment OR the patient is 12 – 18 years old at the point of referral to the panel for approval, is being treated within a paediatric service, and the centre is commissioned to deliver treatment in this age group.
- The patient has sickle cell disease and has recurrent vaso-occlusive crises (VOCs) defined as at least 2 VOC's per year during the 2 previous years
 - To note: In the SmPC patients were eligible for the study if they had a history of at least 2 severe vaso-occlusive crisis events per year in the 2 years prior to screening, which were defined as:
 - an acute pain event
 - acute chest syndrome
 - priapism lasting at least 2 hours
 - splenic sequestration.
- The patient
 - has β^S/β^S , β^S/β^+ or β^S/β^0 genotype
 - is suitable for haematopoietic stem cell transplant

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- and for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell donor is not available
- The patient has not received a prior allogeneic or autologous successful haematopoietic stem cell transplant
- Approval for treatment has been obtained from the National Haemoglobinopathy Panel

4.2 The estimated patient numbers per year for this technology within the Innovative Medicines Fund are:

Table 2

As estimated by the company	[REDACTED]
As estimated by NICE Resource Impact Assessment team	[REDACTED]

5 Patient safety

5.1 Vertex and NHSE have responsibility to monitor the safety profile of the technology and must provide an overview of any new or updated safety concerns to NICE as part of routine updates. If any new safety concerns are confirmed, NICE and NHSE will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access agreement be suspended.

5.2 Vertex, and clinical MAOG members if applicable, have a responsibility to report any suspected unexpected serious adverse reactions (SUSARs) from CLIMB SCD-121 and CLIMB-131 to the MAOG. The MAOG will assess any SUSARs and if there are

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safety concerns will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access be suspended.

6 Area(s) of clinical uncertainty

6.1 The appraisal committee identified seven main areas of uncertainty (highlighted in bold), including occurrence of complications in the standard of care population, and whether new complications present for patients treated with exa-cel. Two areas of uncertainty identified by the committee affect whether the discount rate can be applied for this technology in this indication. All uncertainties are discussed below.

- Uncertainties related to application of non-reference discount rate (1.5% for costs & outcomes):

The appraisal committee accepted that it is plausible for exa-cel to qualify for the non-reference discount rate in the treatment of SCD in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) who have β^S/β^S , β^S/β^0 or β^S/β^+ , for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available, subject to resolving uncertainty in two main criteria:

- a) Returning patients to full or near-full health
- b) durability of the treatment effect of exa-cel (relapse rate)

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Data that could address these uncertainties, and additional areas described below, will be collected as part of the MAA. The Data Collection Arrangement (DCA) includes the clinical criteria that can be used to determine if the uncertainties that impact the discount rate are addressed. These have been included on the basis that the original appraisal committee accepted the plausibility of the non-reference case discount rate (1.5%) to be applicable to exa-cel in the treatment of SCD.

At the end of data collection, the future appraisal committee will decide on whether the data collected and presented in Vertex's submission, and guidance provided by NICE team and clinical experts, has adequately addressed the uncertainty in the optimistic scenario and the question of whether the non-reference rate discount rate (1.5%) will apply to costs and outcomes.

- **Returning patients to full or near-full health**

The following definition* from CLIMB-131 will be used in addition to other evidence provided to determine whether this uncertainty has been resolved:

*Note this is not an exhaustive list.

- $\geq 88\%$ of patients achieve:

HbF* $\geq 20\%$ for up to 12 months

and/or

- VF12: Freedom from any severe vaso-occlusive crises (see definition section 8.1) for at least 12 consecutive months

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and/or

- HF12 (see 8.1): Freedom from hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months

- **Durability of the treatment effect of exa-cel (relapse rate)**

The following definition* from CLIMB-131 will be used in addition to other evidence provided to determine whether this uncertainty has been resolved:

*Note this is not an exhaustive list.

Those patients achieving definition of near normal health, then show:

- Sustained HbF* $\geq 20\%$ for up to 36 months

and/or

- $\geq 90\%$ reduction in severe vaso-occlusive crises for up to 36 months

and/or

- $\geq 90\%$ reduction in hospitalisations due to severe vaso-occlusive crises for up to 36 months

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- **Baseline characteristics of patients treated with exa-cel (including age, gender, prior complications, annual VOC rate)**
- **Number of exa-cel treatment withdrawals**
- **Utility values for exa-cel and standard care**
- **The rates of complications for exa-cel and standard care**
- **Mortality and life expectancy for exa-cel and standard care**

6.2 Data collection could allow for updates to the model if appropriate. Vertex will consider this for re-appraisal.

6.3 The appraisal committee concluded that further data collection within the Innovative Medicines Fund could resolve these uncertainties. For the uncertainties written in full and further details of the appraisals committee’s discussion see section 3 of the Final Appraisal Document.

7 Sources of data collection

Primary and secondary sources of data collection

Table 3

Primary source(s)	<ul style="list-style-type: none"> ○ CLIMB-131 clinical trial
Secondary sources	<ul style="list-style-type: none"> ○ CLIMB SCD-121 ○ Post-Autorisation Safety Study (PASS) for exa-cel via EBMT registry ○ Vertex Connects™

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	<ul style="list-style-type: none"> ○ An update of the UK Burden of Illness Study (Udeze et al., 2024) – referred to as UK Bol Study ○ NHSE Prior Approval System data (Note NHSE currently uses the Blueteq® system)
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Description of sources

- 7.1 CLIMB-131 is a long-term follow-up study of people with SCD treated with autologous CRISPR-Cas9 modified haematopoietic stem cells. It includes people aged 12-35 years who received exa-cel in the parent study CLIMB SCD-121.
- 7.2 The PASS is a regulatory commitment to evaluate the long-term safety and effectiveness of patients with SCD treated with exa-cel. Data will be collected in the EBMT patient registry.
- 7.3 Vertex Connects™ is a secure order management portal used to facilitate steps throughout the exa-cel order management process for Authorised Treatment Centre (ATC) staff.
- 7.4 The UK Bol study (Udeze et al., 2024) became a key source of evidence to inform the standard of care arm within the economic analysis. During the period of managed access, the UK Bol will be reopened to explore the uncertainties identified within the NICE appraisal.
- 7.5 NHSE will collect Blueteq data, alongside the primary source of data collection.

8 Outcome data

Clinical trial

8.1 The following definitions are used from CLIMB-131:
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- VF12: freedom from any severe vaso-occlusive crises for at least 12 consecutive months
- HF12: freedom from hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months
- Severe vaso-occlusive crisis (VOC) events include any one of the following events:
 - Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions
 - Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
 - Priapism lasting >2 hours and requiring a visit to a medical facility
 - Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in haemoglobin concentration of ≥ 2 g/dL.

8.2 The following outcomes are measured in CLIMB-131: All are measured for 15 years post exa-cel infusion except for those marked otherwise.

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- New malignancies
- New or worsening haematologic disorders
- All-cause mortality
- Serious adverse events (SAEs) occurring up to 5 years after exa-cel infusion
- Exa-cel-related adverse events (AEs) and SAEs
- Hb concentration; total Hb and fetal haemoglobin (HbF)
- Proportion of alleles with intended genetic modification present in peripheral blood
- Change from baseline Patient Reported Outcomes (PROs)
- Proportion of patients who achieved VF12, and duration of VOC-freedom in patients who have achieved VF12
- Relative change from baseline in annualised rate of severe VOCs
- Proportion of patients with reduction in annualised rate of severe VOCs from baseline of at least 90%, 80%, 75%, and 50% post exa-cel infusion
- Proportion of patients who achieved HF12
 - Relative change from baseline in annualised rate of inpatient hospitalisations for severe VOCs
 - Relative reduction in annualised duration of inpatient hospitalisations for severe VOCs

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- Proportion of patients with sustained HbF $\geq 20\%$ for at least 3 months, 6 months, or 12 months
- Change from baseline in haemolysis markers:
 - Reticulocyte count (in absolute count and %)
 - Lactate dehydrogenase (LDH)
 - Haptoglobin
 - Total and indirect bilirubin
- Relative reduction from baseline in number of RBC units transfused for SCD-related indications
- Change from baseline in SCD-specific and pain PROs (5 years post exa-cel)

Other data

8.3

The PASS will utilise the EBMT registry. The EBMT requests from all member centres that all patients undergoing an HCT, treatment for aplastic anaemia, or any type of cellular therapy be registered in the EBMT Registry. The EBMT Registry Data Collection Forms aid the collection of all the data that is required to be submitted to the EBMT Registry and receives data from approx. 80% of EU European transplant centres. To ensure the data entered into the database is complete, correct, accurate, allowable, valid, and consistent, a number of data quality edit checks and reviews are implemented. There are six ATCs being established in England for the provision of exa-cel. These centres are all EBMT members and would therefore routinely submit data to the EBMT Registry. The PASS will collect the following outcomes:

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- Primary disease diagnosis
- Exposure, such as the date of the haematopoietic stem cell transplantation, and whether this was autologous with exa-cel or an allogeneic transplantation
- Safety outcomes, such as neutrophil recovery, platelet recovery, new malignancy, new or worsening haematologic disorder, mortality and mortality cause
- Effectiveness outcomes, such as severe VOC events, Red Blood Cell Transfusion (RBCT), haemoglobin measures, iron concentration measures, disease-related end-organ damage/dysfunction and iron overload management
- Additional variables, such as demographics, health status, mobilisation and conditioning regimen, transplant-related complication, and disease-related therapies are also recorded.

8.4 The PASS will act as a confirmatory study and validation of the data gathered in CLIMB-131. The PASS will report real world data, including that from the UK, with follow-up for up to 15 years. The number of RBCT and number of units transfused will be collected in the PASS for the 1-year preceding initiation of conditioning regime. Number of severe VOC events will be recorded pre- and post-transplant. Time from HSCT to most recent VOC event will be recorded.

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

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

8.5 Vertex Connects™ is a secure order management portal used to facilitate steps throughout the exa-cel order management process for ATC staff. Vertex Connects™ tracks all the constituent actions required for each step of the order process following patient identification and evaluation: pre-mobilisation; mobilisation & collection of cells; drug product manufacturing and quality; conditioning, administration and engraftment. This enables further data collection on the number of people who may start the treatment process of exa-cel but do not receive the infusion.

8.6 During the period of managed access, the UK BoI Study (Udeze et al., 2024) will be reopened to explore the uncertainties for the standard of care arm identified within the NICE appraisal, specifically to:

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- Generate additional evidence on rates and type of complications for severe SCD patients
- Incorporate feedback from the committee on including additional follow-up
- Estimate complication rates by age.
- age of death

8.7 The Bol study will use primary care records (Clinical Practice Research Datalink [CPRD]) linked with secondary care data (Hospital Episode Statistics [HES]) in a real world setting in England. The study period will be from 2008 up to the most recent data available at time of analysis (expected to be 2027) in advance of company submission. The complications within the scope of the analysis will be in line with those already included in the UK Bol Study (Udeze et al., 2024).

8.8 NHSE's Prior Approval System will collect the following outcomes:

- Number of applications to start treatment
- Baseline patient characteristics, including gender and age

9 Data analysis plan

Clinical trials

9.1 Primary endpoints of CLIMB-131 will be assessed up to 15 years after exa-cel infusion (unless otherwise):

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- New malignancies
- New or worsening haematologic disorders
- All-cause mortality
- All SAEs occurring up to 5 years after exa-cel infusion
- Exa-cel related AEs and SAEs

9.2 All secondary endpoints will be assessed up to 15 years from infusion of exa-cel with the exception of LIC, CIC, and PROs (including Pain Scales) which will be assessed for up to 5 years after infusion.

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- Total Hb and HbF concentrations will be summarised as continuous variables over time.
- Proportion of alleles with intended genetic modification present in peripheral blood will be summarised as a continuous variable over time.
- Change from baseline in PROs will be summarised as continuous variables over time in patients ≥ 18 years of age using:
 - EuroQol Questionnaire – 5 dimensions – 5 levels of severity (EQ-5D-5L)
 - Functional assessment of cancer therapy bone marrow transplant (FACT-BMT)
- Change from baseline in PROs will be summarised as continuous variables over time in patients < 18 years of age using:
 - EuroQol Questionnaire – 5 dimensions – youth (EQ-5D-Y; self-complete and proxy versions based on age)
 - Paediatric Quality of Life Inventory (PedsQL) Core (self-complete and proxy versions based on age)

9.3 The proportion of patients achieving VF12 will be provided, with one-sided P value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson Confidence Interval (CI).



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[REDACTED]

- 9.4 The proportion of patients who have not achieved VF12 in the parent study (CLIMB SCD-121) and long-term follow-up study (CLIMB-131) but have achieved at least 90%, 80%, 75%, 50% reduction from baseline in annualised rate of severe VOCs from Month 12 post exa-cel infusion will be provided.
- 9.5 The relative reduction from baseline in annualised rate of severe VOCs from Month 12 post exa-cel infusion will be summarised as a continuous variable for patients who have not achieved VF12.
- 9.6 The duration of severe VOC free will be summarised as a continuous variable for patients who have achieved VF12.
- 9.7 The relative reduction from baseline in annualised rate of inpatient hospitalisations for severe VOCs starting Month 12 post exa-cel infusion will be summarised as a continuous variable for patients who have not achieved HF12. Inpatient hospitalisation for severe VOCs after exa-cel infusion will also be plotted.
- 9.8 The relative reduction from baseline in annualised duration of inpatient hospitalisations for severe VOCs starting Month 12 post exa-cel infusion will be summarised as a continuous variable for patients who have not achieved HF12.

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- 9.9 The proportion of patients with sustained HbF $\geq 20\%$ at the time of analysis for at least 3 months, 6 months, or 12 months will be provided.
- 9.10 Reduction in volume of RBCT for SCD-related indications from baseline will be summarised as a continuous variable starting Month 12 post exa-cel infusion.
- 9.11 Change from baseline in haemolysis markers (reticulocytes/erythrocytes, lactate dehydrogenase [LDH], haptoglobin, total and indirect bilirubin) will be summarised as continuous variables over time.
- 9.12 Change in SCD-specific PROs from baseline in patients ≥ 18 years of age using Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) (patients from Study 121 only) will be summarised as a continuous variable over time.
- 9.13 Change in SCD-specific PROs from baseline in patients < 18 years of age using PedsQL SCD module (self-complete and proxy versions based on age) will be summarised as a continuous variable over time.
- 9.14 Change in Pain Scale PROs (based on age) from baseline using Numeric Rating Scale (NRS) 11-point, Wong Baker FACES Pain Scale, or FLACC Behavioral Pain Scale will be summarised as a continuous variable over time.
- 9.15 CLIMB-131: Subgroup analyses will be performed by age (at CLIMB SCD-121 screening), genotype, country of transplant, sex, race. All efficacy analyses will be performed on respective full analysis sets (FAS) populations unless specified otherwise.

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9.16 The following milestones have been pre-specified in the protocol. In addition to these milestones, data-cuts are planned on a yearly basis to inform monitoring of trial participants. Vertex will use data from the latest data-cut available by [REDACTED] to inform the MAA and the submission preparation. The latest data-cut available by [REDACTED] is expected to be between end of 2027 – early 2028.

Table 4

Milestone	Data included	Planned date
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
[REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]

*Not pre-specified in the protocol

Data collected in clinical practice

- 9.17 The PASS is a regulatory commitment to evaluate the long-term (up to 15 years) safety and effectiveness of patients with SCD treated with exa-cel. Data will be analysed by the EBMT registry at pre-specified time points over the study duration. The results of the interim and final analyses will be presented in interim and final study reports.
- 9.18 Vertex will develop a full protocol and statistical analysis plan to be reviewed by the relevant regulatory authorities. Once finalised, these can be shared with the Managed Access Oversight Group (MAOG).
- 9.19 The EBMT will be responsible for analysing the data collected within clinical practice and producing the corresponding reports, which will be delivered to Vertex. The reports produced will include anonymised, aggregated summary data. Progress reports and interim analysis reports according to Table 5 will be produced and shared with all members of the MAOG in advance of the NICE update of the guidance.
- 9.20 Descriptive statistics will be presented for all study outcomes:
- Continuous variables will be summarised using the following descriptive summary statistics, where appropriate: the number of observations, mean, standard

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deviation, 95% CI, median, minimum value, maximum value, and 25th and 75th percentile values.

- Categorical variables will be summarised using counts, percentages, and 95% CIs, as appropriate.
- Additional ad-hoc statistical analyses may be implemented, as needed – this may include modelling to adjust for differences in cohort characteristics in between-cohort analyses and/or time to event analyses for select outcomes.
- Subgroup analyses will be performed by age group, genotype and/or patient characteristics, as appropriate. Subgroup analyses by country of transplant may be performed if sufficient patient counts are available to preserve patient anonymity.

9.21 Safety and effectiveness analysis outcomes respectively will be evaluated at each time point of the post-transplant period. Analyses will be performed overall and in subgroups by patient age group, genotype and / or other category, as appropriate and if sufficient data are available. Additional analyses may be performed for outcomes deserving further investigation if sufficient data are available. Statistical testing may be performed comparing the frequencies or rates of outcomes from the SCD exa-cel and SCD Allo-HSCT cohorts if sufficient data are available.

- For the primary disease severity measures (number of severe VOC events), descriptive statistics for the number of events in the 1 year prior to the preparative regimen

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initiation and at each of the post-transplant follow-up periods will be reported.

- Proportions of patients who are severe VOC-free will also be reported at each timepoint of the post-transplant periods.
- Time VOC-free, from transplant date to the most recent event, will also be summarised.
- Hb measures (total Hb, % HbF) will be summarised as continuous variables for each timepoint of the post-transplant period, with a 95% CI, among patients with an observation.
- Iron concentration measures (serum ferritin, LIC, CIC) will be summarised as continuous variables for each timepoint of the post-transplant period, with a 95% CI, among patients with an observation. Absolute change from baseline may be calculated for patients with non-missing baseline and post-transplant years.
- New disease-related end-organ damage or dysfunction diagnoses will be summarised for each timepoint of the post-transplant period as the proportion of patients with a new diagnosis (i.e., categorical variables), with a 95% CI.
- Data collection will follow the existing registry transplant reporting routine including a baseline/transplant date report, follow-up at day 100, 6 month (if collected) and 1-

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year post-transplant assessments, then annual assessments thereafter.

- These data will be collated for study updates according to the progress report and interim analysis milestones in Table 5. Interim analyses are planned for completion after patient enrolment and then at respective intervals of 5-, 10-, and 15-years' follow-up.

9.22 Differences between database locks and availability dates are to allow for data cleaning, verification and analysis.

9.23 The EBMT will be responsible for analysing the data collected within clinical practice and producing the corresponding reports, which will be delivered to Vertex. The reports produced will include anonymised, aggregated summary data. The necessary controls will be put in place to ensure that patient confidentiality is not at risk. Progress reports and interim analysis reports according to Table 5 will be produced and shared with all members of the MAOG in advance of the NICE update of the guidance.

Table 5

Milestone	Data Included	Planned Date
Progress Report 1	Tentatively through 31/12/2024	Q4 2025
Progress Report 2	Tentatively through 31/12/2025	Q4 2026
Interim Analysis 1 / Progress Report 3	Tentatively through 31/12/2026 (anticipated end of enrollment period)	Q4 2027
Progress Report 4	Tentatively through 31/12/2027	Q4 2028
Progress Report 5	Tentatively through 31/12/2028	Q4 2029
Interim Analysis 2	Tentatively through 31/12/2032 (all enrolled patients anticipated to reach 5 years of follow-up)	Q4 2033
Interim Analysis 3	Tentatively through 31/12/2037 (all enrolled patients anticipated to reach 10 years of follow-up)	Q4 2038
Final Report	Tentatively through 31/12/2042 (all enrolled patients anticipated to reach 15 years of follow-up)	Q4 2043

9.24 Vertex will be responsible for the development of a detailed data analysis plan within 6 months following the commencement of this agreement, for review by the Managed Access Oversight Group (MAOG). Note this is expected to be no more than 9 months after the commencement of the MAA. This will detail the analyses that will be presented within the interim and final reports report, the methodologies used, and the schedule of delivery.

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- 9.25 As a minimum the number of patients starting treatment will be shared at each MAOG meeting to monitor the uptake in clinical practice.
- 9.26 At the end of the data collection period a final report will be produced and shared with all members of the MAOG in advance of the NICE update of the guidance.
- 9.27 Data collected in clinical practice is a secondary source of data. The availability of the final report will be aligned to the availability of data from the primary source, and data collection in clinical practice will end at a date that will allow for NHS trusts to upload data, data cleaning, data analysis, and report production.

10 Ownership of the data

- 10.1 For all clinical trial data listed above, Vertex will be the owner. For Vertex Connects™ and data obtained via Vertex Connects™, Vertex will be the owner. For the BoI Study update, Vertex will be the owner.
- 10.2 To ensure the data entered into the EBMT database for the PASS is complete, correct, accurate, allowable, valid, and consistent, a series of system-generated, automated and manual data quality edit checks will be implemented where applicable, as well as medical review by the EBMT medical officer.
- 10.3 Study specific data retrieval is a verified process carried out by the qualified data managers and enabled by qualified information technology specialists. After data are extracted for a study-specific need, the datasets undergo an analyses dataset preparation process, which includes data verification and study

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data file preparation by qualified and experienced EBMT personnel.

- 10.4 The study data file preparation takes place in order to enable data analytics on the EBMT Registry collected data, study statistical analyses, site management, and study management.
- 10.5 Vertex will be responsible for ensuring they have permission to share the reports resulting from the PASS (provided by EBMT), including non-patient identifiable data and analysis as part of their submission for the guidance update. EBMT will own this data, and details concerning what personal data EBMT collects from patients, how it is collected and stored and the purposes for which it is used can be found here: <https://www.ebmt.org/registry/ebmt-data-protection-privacy> .
- 10.6 The Prior Approval System (currently Blueteq®) Innovative Medicines Fund data is owned by NHSE. NHSE is responsible for implementing Prior Approval System data collection and generally for the analysis of these data. The lawfulness of this processing is covered under the data services for commissioners' direction. This gives NHSE statutory authority to process confidential patient information (without prior consent). Further information is available here: <https://www.england.nhs.uk/contact-us/privacy-notice/how-we-use-your-information/our-services/data-services-for-commissioners/>.

11 Publication

- 11.1 At the end of the data collection period a final report will be produced and shared with all members of the MAOG in advance

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of the NICE update of guidance. Data and analyses contained within the final report will be available to use as part of an evidence submission to NICE as part of the guidance update.

- 11.2 The final report will also form part of NHSE's submission to the guidance update. The final report will therefore be publicly available during the guidance update.
- 11.3 Publications regarding the implementation or managed access process are permitted as long as no data collected in clinical practice is included (e.g. patient leaflets, NICE presentations about operational aspects of MAAs).
- 11.4 Any draft abstracts or manuscripts related to this DCA must either:
- Be shared with the MAOG
 - Use data that has been shared with the MAOG prior to submission to conferences, journals or any other publicly available site.
- 11.5 The contribution of all relevant individuals must be acknowledged in any publications related to this DCA. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

12 Funding for data collection and analysis

- 12.1 Vertex will be required to pay direct and associated costs for:

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- Collection and entry of data into the specified databases.
- Database management – including data processing and quality assurance.
- All costs related to the production of interim and final analyses and reports.
- Costs associated with accessing and linking data to other sources (if applicable).
- Any other costs identified that are relevant to data collection and analysis associated with the uncertainties identified by the NICE appraisal committee.

12.2 Vertex is responsible for agreeing and documenting a separate agreement concerning the above direct and associated costs.

12.3 Vertex is required to provide the MAOG assurance that all separate agreements concerning the above direct and associated costs have been agreed. The relevant terms of these agreements should be presented to the MAOG for review within 9 months of the publication of the MAA

13 Data protection

13.1 Patient data collected as part of this Data Collection Arrangement will be managed in accordance with all applicable data protection legislation, including but not limited to the Data Protection Act 2018 and the UK General Data Protection Regulation.

13.2 The terms of the Managed Access Agreement relating to data protection, as apply between NHSE and Vertex, shall also apply

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between the parties to this Data Collection Arrangement in relation to the performance of their obligations under this Data Collection Arrangement.

14 Equality considerations

14.1 Do you think there are any equality issues raised in data collection?

Yes No

14.2 Vertex highlights patients in England with SCD are disproportionately represented in ethnic minority groups and lower socioeconomic communities which may impact willingness to be part of managed access. Due to health inequalities and negative experiences in hospitals patients often do not attend appointments; and the withdrawals of crizanlizumab and voxelotor have further reduced the already limited treatment options available. In the event of a managed access recommendation the NICE managed access team would proactively engage with patient groups during the managed access period to minimise any barriers to access due to data collection.

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Commercial Access Agreement

Exagamglogene autotemcel for treating sickle cell disease [TA1044]

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