Managed Access Agreement

Crizanlizumab for preventing sickle cell crises in sickle cell disease [ID1406]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Data Collection Arrangement

Crizanlizumab for preventing sickle cell crises in sickle cell disease

Company name: Novartis Pharmaceuticals UK Ltd (the company)

Primary source of data collection: STAND trial (NCT03814746)

Secondary source of data collection: National Haemoglobinopathy Registry (NHR)

NICE Agreement Manager	Brad Groves – Associate Director, Managed Access
NHS England and NHS Improvement Agreement Manager	Sharon Hodgson – National Programme of Care Manager
Novartis Agreement Manager	Heather Moses – Country Medical Director
National Haemoglobinopathy Registry Agreement Manager	Sally Cavanagh – Clinical Information Manager, NHSE&I Farrukh Shah – Chair, National Haemoglobinopathy Registry Steering Group

1 Purpose of data collection arrangement

The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for crizanlizumab for preventing sickle cell crises in sickle cell disease (TA743). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the NICE appraisal committee.

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 guidance review are:

End of data collection (primary source)	[redacted]
Data available for development of Company submission	[redacted]
Anticipated company submission to NICE for review	January 2025

2.3 The company anticipates the results from the additional data collected during the managed access period will be incorporated into an evidence submission and the updated economic model by January 2025.

2.4 The company acknowledges their responsibility to adhere as closely as possible to the timelines presented in this document.

2.5 NICE will, as far as is practicable, develop the scope and schedule a review into the NICE work programme to align with the estimated dates for the end of data collection. The review will use the NICE process and methods in place at the time the invitation to participate. For further details of the expected timelines for the NICE guidance review see the technology appraisal process guide.

2.6 As part of the MAA, the technology will continue to be available through managed access after the end of data collection and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the guidance review follows the timelines described in NICE's guide to the processes of technology appraisal.

2.7 The company is responsible for paying all associated charges for a guidance review. Further information is available on the NICE website.

2.8 The company must inform NICE and NHS England and NHS Improvement (NHSE&I) in writing of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.9 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE&I.

2.10 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:

- Where capacity allows, NICE will explore options to reschedule the guidance review 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).

2.11 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&I, 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.
- In the event of an extension, it may not be possible to amend the date of the final real-world data report, although NICE will explore options with NHR to provide data over the extended period.

2.12 The company acknowledges their responsibility to provide an evidence submission for a guidance review for this technology to NICE under all circumstances following a period of managed access.

2.13 NICE and NHSE&I may consider this Data Collection Agreement no longer valid, and withdraw the technology from the MAA 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 NICE committee.
- Amendments are made to the marketing authorisation.

3 Patient eligibility

3.1 Key patient eligibility criteria for the use of crizanlizumab during managed access include:

- Patient has a confirmed diagnosis of sickle cell disease.
- Patient is aged 16 and over and has had 2 or more confirmed sickle cell crises (vaso-occlusive crises) in the previous 12 months. A sickle cell crisis is as an acute painful episode that requires pain relief medication to manage at home or in hospital.
- Application for treatment is made by a Specialised Haemoglobinopathy Team having been discussed and approved by the Haemoglobinopathy Coordinating Centres Multi-Disciplinary Team prior to initiation of treatment.
- Crizanlizumab will be otherwise used as set out in its Summary of Product Characteristics (SmPC).

3.2 The estimated patient numbers per year for this technology within managed access are:

As estimated by the company	Year 1: 314 Year 2: 470 Year 3: 470
As estimated by NICE Resource Impact Assessment team	Year 1: 314 Year 2: 470 Year 3: 470

4 Area(s) of clinical uncertainty

4.1 The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:

1. long term clinical effectiveness of crizanlizumab, including after stopping treatment.
2. Whether patients with recurrent vaso-occlusive crisis (VOCs) have the same utility values outside of a VOC event that leads to hospitalisation.
3. Patient weight, gender mix, and concomitant hydroxycarbamide (HC/HU) use may not reflect clinical practice.
4. Concerns over the model structure.

4.2 The appraisal committee expect further data collection would allow for a new model to be presented at the guidance review.

4.3 The appraisal committee concluded that further data collection within managed access could resolve these clinical uncertainties. The committee were aware that data from the STAND trial is due to become available in 2023 and 2028. It agreed that 2023 was a reasonable timeframe for data

collection and would likely be sufficient to potentially resolve the clinical uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ STAND trial (NCT03814746)
Secondary sources	○ National Haemoglobinopathy Registry

Description of sources

5.1 The purpose of the ongoing phase III STAND trial (NCT03814746) is to assess the efficacy and safety of two doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) versus placebo in adolescent and adult SCD patients with history of vaso-occlusive crisis (VOC) leading to a healthcare visit. This multicentre, placebo-controlled, parallel, double blind clinical study in SCD patients 12 years of age and older started in July 2019 with a recruitment target of 240 participants. Patients will be randomised in a 1:1:1 ratio to receive either 5.0 mg/kg or 7.5 mg/kg crizanlizumab or placebo. Central randomisation will be stratified by concomitant HC/HU usage (yes/no) and baseline rate of VOCs leading to healthcare visit in 12 months prior to screening (2-4 VOCs vs ≥ 5 VOCs). The study is planned for one year, with an open label extension (5 years on investigational treatment).

5.2 The National Haemoglobinopathy Registry (NHR) is a confidential database of patients with red cell disorders living in the UK. Data is entered onto the NHR by a patient's healthcare team. The NHR is commissioned by NHSE&I and operated by Medical Data Solutions and Services (MDSAS) under a data processing contract.

6 Outcome data

Clinical trial

6.1 **Primary endpoint** - Annualised rate of VOC events leading to a healthcare visit in each treatment group over the first year post-randomisation

Secondary endpoints

- Annualised rate of all VOCs leading to a healthcare visit and treated at home over the first year post randomisation
- Annualised rate of VOCs managed at home over the first year post randomisation
- Duration of VOCs leading to healthcare visit over the first year post randomisation
- Number and percentage of subjects free from VOCs leading to a healthcare visit in each group over the first year post randomisation
- The time to first and second VOC calculated respectively as the time from date of randomisation until the first and the second VOC leading to a healthcare visit over the first year post randomisation
- Annualised rate of visits to clinic, Emergency room (ER) and hospitalisations, both overall and VOC-related over the first year post randomisation
- To assess SCD-related renal damage in each group - evolution of albuminuria and ACR over the first year post randomisation
- PK parameters after the first and fifth dose (e.g., AUC, Cmax, Tmax, half-life)
- PD parameters (P-selectin inhibition) after the first and fifth dose

- Exploratory endpoints

- To assess quality of life in each group

    - Change from baseline in the T-scores of each domain as measured by the ASCQ-Me (Adult Sickle Cell Quality of Life Measurement Information System) Short Forms for adults over the first year post randomisation
    - Number of work or school absences due to sickle cell pain crisis as measured by the Sickle Cell Pain Diary - Self report (SCPD-S)
    - Impact on activities of daily living due to sickle cell pain crisis as measured by the SCPD-S
    - Fatigue, sleep quality, emotional health due to sickle cell pain crisis as measured by the SCPD-S
- To assess SCD-related organ function/damage
    - Presence and evolution of leg ulcers
    - Evolution of cardiac function
- To assess the annualised rate of other acute pain crises managed at home
    - Annualised rate of other acute pain crises managed at home (based on documentation by health care provider following contact with subject) over the first year post randomisation
    - Annualised rate of other acute pain crises managed at home (based on documentation by health care provider following contact with subject) over the first year post randomisation
- Analysis of soluble biomarkers
    - P-selectin inhibition, efficacy and safety endpoints
    - Mutations in beta globin gene

Data from the phase III STAND trial will provide additional evidence on the efficacy and safety of crizanlizumab. Patients will be followed for up to 5 years to allow for assessment of longer-term efficacy and safety of treatment. The impact of crizanlizumab on prevention of both VOCs leading to a healthcare facility visit and those managed at home will be assessed as

well as the duration of VOCs. Additional quality of life assessments will be conducted compared with the phase II study using two SCD-specific QoL tools (Adult Sickle Cell Quality of Life Measurement information System [ASCQ-Me] and Sickle Cell Pain Diary – Self report [SCPD-S]).

Data collected in clinical practice

6.2 NHR will collect the following outcomes on patients treated with crizanlizumab through its registry unless it is determined by the Managed Access Oversight Group that no meaningful data will be captured during the period of data collection:

- Number of patients starting treatment
- Patient characteristics, including gender, age, frequency of VOCs in each financial year for duration of treatment, and weight
- Proportion of patients treated with HC/HU whilst on crizanlizumab
- Number of VOCs in the last financial year that lead to accident and emergency attendance or hospital admission
- Other mandatory data fields collected by NHR as part of its usual data collection. For further information please refer to the NHR dataset.

Table 1: Outline of assessments to be collected for patients

Assessment	Rationale	Frequency				Data collection responsibility	Data collection tool
		Baseline / Pre-treatment	3-monthly	6-monthly	Annually		
Age	Patient baseline characteristics	x				patient's healthcare team at the centre providing care	NHR
Gender		x					
Weight		x					
Received HC/HU in the past 12 months	To calculate proportion who receive HC/HU				x		
Number of VOCs in the last financial year that lead to accident and emergency attendance or hospital admission	To calculate annual VOC rate	x			x		

7 Data collection in clinical practice: responsibilities and outputs

7.1 NHR data is collected and entered by a patient's healthcare team at the treating centre.

7.2 NHSE&I, is the custodian of the NHR and the data controller of data use for secondary purposes. NHSE&I commissions Medical Data Solutions and Services Ltd (MDSAS Ltd) to provide the data platform for the collection of data into the NHR.

7.3 NHSE&I will be responsible for analysing the data and producing the corresponding reports, which will include anonymised summary data. NHSE&I will provide 6-monthly reports based on data collected by the NHR to be reviewed by the Managed Access Oversight Group. The data analysis plan will provide further detail on the schedule for delivery and the outcomes to be reported.

8 Data analysis plan

Clinical trials

8.1 The primary analysis will be conducted once all randomised subjects have reached one year of investigational treatment or discontinued within year 1 – estimated early 2023. Following the primary analysis, unblinding and change from placebo to crizanlizumab or to an alternative dose of crizanlizumab will be permitted for each individual subject. It is planned to observe subjects for 5 years on investigational treatment, however early termination of the study could be considered.

The study will be completed when all the randomised subjects have either completed or discontinued the study treatment and/or the 105 days follow-up period. Estimated study completion is 2027.

8.2 Database lock is estimated to be in [redacted], with data availability in [redacted].

Data collected in clinical practice

8.3 NHSE&I in partnership with NICE and the company will be responsible for the development of a data analysis plan within 6 months following the commencement of this agreement, for review by NICE's Managed Access Oversight Group. This will detail the methodologies used and analyses that will be produced for the interim and final reports.

8.4 At a minimum the number of patients starting treatment will be shared at each Managed Access Oversight Group Meeting to monitor the uptake in clinical practice. At the end of the data collection period a final report for the company and NHSE&I will be provided including analyses based on the NHR dataset. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with the company in advance of the planned review of guidance. The availability of the final report will be aligned to the availability of data from the primary source, (STAND trial). The end of NHR data collection will be approximately 8 months prior to the availability of the final report to allow for NHS trusts to upload data, data cleaning, and report production.

9 Ownership of the data

9.1 For all clinical trial data listed above, including the STAND trial data, the company will be the owner of all intellectual property rights in that data.

9.2 The data collected in clinical practice by NHR is derived from patient-level information collected by the NHS, as part of the care and support of haemoglobinopathies and rarer inherited anaemias. NHSE&I is the custodian of the NHR and commissions Medical Data Solutions and Services Ltd (MDSAS Ltd) to provide to provide the data platform for the collection of data into the NHR.

9.3 The company (Novartis) will not have access to the NHR patient data, but will receive reports using anonymised summary data, with appropriate governance controls in place.

9.4 NHR data is collected and entered by a patient's healthcare team. All necessary governance arrangements have been established and for collecting and processing these data the NHR relies on the following legal bases for the secondary use of data:

- For the purposes of preventative or occupational medicine and providing health and treatment management systems and services (Article 9(2)(h) of the GDPR)
- To ensure high standards of quality and safety of health care (Article 9(2)(i) of the GDPR)
- For the purposes of archiving in the public interest, and using data for scientific research purposes, and statistical analysis (Article 9(2)(j) of the GDPR)

10 Funding for data collection and analysis

10.1 The company will be required to pay direct and associated costs related to the collection and analysis of crizanlizumab data by NHR including, but not limited to:

- Amendment of the NHR dataset;
- 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.

10.2 The company and NHSE&I will be responsible for reaching and documenting a separate agreement concerning the costs of data collection and analysis.

10.3 The company will be required to provide NICE assurance that separate agreements concerning the resources required to operationalise data collection and analyses have been agreed with NHSE&I within 6 months of the publication of the MAA.

10.4 NHSE&I will be required to provide NICE assurance that the funding and resources required to deliver the data collection and analyses are in place for all patients receiving this technology through managed access.

10.5 The relevant terms of these agreements should be presented to the Managed Access Oversight Group for review within 6 months of the publication of the MAA.

11 Monitoring arrangements

11.1 NICE will convene a Managed Access Oversight Group with representation from NICE, the company, patient groups, clinicians, NHSE&I, and a representative of the NHR.

11.2 The Managed Access Oversight Group exists to oversee the operation of all aspects of the MAA and to address issues that may arise throughout the MAA term. The Managed Access Oversight Group is responsible for ensuring the data collection is on track and the analyses required for the NICE guidance review can be delivered. A detailed description of the

Managed Access Oversight Group function will be available in a Terms of Reference document produced by NICE.

11.3 The Managed Access Oversight Group will meet at 6 monthly intervals throughout the MAA period.

12 Patient Safety

12.1 The company, and clinical Managed Access Oversight Group members if applicable, have a responsibility to report any suspected unexpected serious adverse reactions (SUSARs) to the Managed Access Oversight Group. The Managed Access Oversight Group will assess any SUSARs and, if potential safety concerns are confirmed, 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 halted.

13 Publication

13.1 A final report which includes analysis of data collected through the NHR will be produced. This report will be provided to NHSE&I and the company at the end of the managed access period. The final report will be available to use as part of the evidence available for the company's submission to NICE as part of the guidance review will also form part of NHSE&I's submission to the guidance review. The final report will therefore be publicly available during the guidance review.

13.2 Interim reports will be produced, which will be shared with the Managed Access Oversight Group at regular intervals during the data collection period. These reports will be used to determine whether real-world data collection is proceeding as anticipated and will not form part of the guidance review.

13.3 The publication of any data from the NHR directly related to this Data Collection Agreement is not permitted without the permission of the

Managed Access Oversight Group until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance review committee meeting.

13.4 Any draft abstracts or manuscripts related to this Data Collection Agreement must be shared with the Managed Access Oversight Group prior to submission at conferences, in journals or any other publicly available site.

13.5 The contribution of all relevant individuals must be acknowledged in any publications regarding the data collection or analyses generated from the data collection arrangement. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

14 Data protection

14.1 Patient data collected as part of this Data Collection Agreement 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.

14.2 The terms of the Managed Access Agreement relating to data protection, as apply between NHSE&I and the company, shall also apply between the parties to this Data Collection Agreement in relation to the performance of their obligations under this Data Collection Agreement

15 Equality considerations

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

☐ Yes ☒ No

15.2 It was highlighted during scoping and during the development of this Data Collection Agreement that sickle cell disease predominantly affects patients from African or African-Caribbean family origin and that some people who

receive treatment with crizanlizumab may be less willing to have their data included within the NHR for the purposes of a MAA.

15.3 The MAA will not change the rights on how an individual may access, amend, erase and move their personal data, withdraw their consent and object to or complain about the data that the NHR holds about them. Therefore, a MAA will not make it more difficult for a specific group to access the technology in practice. Further detail on an individual's rights is available on the NHR website.

Commercial Access Agreement

Crizanlizumab for preventing sickle cell crises in sickle cell disease [ID1406]

The contents of this document have been redacted as they are confidential