

Cancer Drugs Fund

Managed Access Agreement

**Tisagenlecleucel for treating relapsed or refractory
B-cell acute lymphoblastic leukaemia in people aged
up to 25 years [TA554]**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [TA554]

Company name: Novartis Pharmaceuticals Ltd

Primary source of data collection: Ongoing clinical trials: ELIANA, ENSIGN and B2101J

Secondary source of data collection: Bone marrow (stem cell) transplant register

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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 tisagenlecleucel for treating paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse [TA554]. A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee.

2 Commencement and period of agreement

- 2.1 This data collection arrangement shall take effect on publication of the managed access agreement. The data collection period is anticipated to conclude in June 2023 based on the pivotal ELIANA study. The final patient in this study will be followed up until this time point. The process for exiting

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the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

- 2.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the [addendum](#) to NICE's methods and processes when appraising cancer technologies.
- 2.3 If during the data collection period there is a change in the treatment landscape for paediatric and young adult patients with acute lymphoblastic leukaemia, a pragmatic decision will need to be made as to whether the current NICE scope would still be applicable.

3 Patient eligibility

- 3.1 Tisagenlecleucel therapy has been recommended for use within the Cancer Drugs Fund (CDF) as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years, only if the conditions in the managed access agreement are followed.
- 3.2 Key patient eligibility criteria for the use of tisagenlecleucel in the Cancer Drugs Fund for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years include:
- Application is made by leukapheresis and initiated by a consultant haematologist specifically trained and accredited in the use of systemic anti-cancer therapy and working in an accredited CAR T cell treatment centre **and** who is a member of the National CAR T Clinical Panel for acute lymphoblastic leukaemia **and** a member of the treating Trust's acute lymphoblastic leukaemia and CAR T cell multidisciplinary teams

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- Once the date of CAR T cell infusion is known, the patient must be reassessed to ensure they continue to meet key patient eligibility criteria
- Has relapsed or refractory acute lymphoblastic leukaemia, defined by one of the following criteria:
 - 2nd or more bone marrow relapse following conventional doses of chemotherapy/monoclonal antibody therapy, or
 - Any bone marrow relapse after allogeneic stem cell transplantation (SCT) and if so, a period of 4 months must have passed since time of transplant to planned time of tisagenlecleucel infusion, or
 - primary refractory disease i.e. not achieving a complete remission after 2 cycles of 1st line standard chemotherapy, or
 - secondary refractory disease i.e. not achieving a complete remission after 1 cycle of standard chemotherapy for relapsed disease, or
 - if Philadelphia positive acute lymphoblastic leukaemia, has disease that has failed standard therapy including 2 TKIs or patient is intolerant of TKIs or if TKIs are contraindicated, or
 - Relapsed disease and ineligible for allogeneic SCT due to comorbid disease (but still fit enough for CAR T cell therapy with tisagenlecleucel) or contraindicated to allogeneic SCT conditioning or lack of a suitable donor or prior SCT.
- Bone marrow with **both** flow cytometry detectable ALL **and** CD19 ALL positivity in the bone marrow.
 - Molecularly detectable minimal residual disease is not sufficient to comply with access to tisagenlecleucel
- Karnofsky (age ≥16 years) or a Lansky (<16 years) performance status of 50% or more

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- sufficient end organ function to tolerate treatment with tisagenlecleucel
- does **not** have an isolated extramedullary acute lymphoblastic leukaemia relapse, i.e. if the patient has extramedullary disease, then the patient must also have bone marrow disease
- Does not have active central nervous system involvement by acute lymphoblastic leukaemia
- No previous therapy with any genetically modified autologous T cell immunotherapy
- Prior to infusion a minimum of 4 doses of tocilizumab are available for use for this patient in the event of cytokine release syndrome
- Use of tisagenlecleucel has been formally given by the National acute lymphoblastic leukaemia CAR T cell Clinical Panel
 - following national approval, there has been local CAR T cell multidisciplinary team agreement that this patient continues to have the necessary fitness for treatment and fulfils all of the treatment criteria listed here
- Tisagenlecleucel will otherwise be used as set out in its Summary of Product Characteristics (SPC)

3.3 There are no additional patients that would form part of the data collection for the CDF, other than those starting treatment following the initiation of this agreement.

3.4 NHS England consider a phased implementation to the NHS will be necessary to deliver this treatment in a safe and equitable manner and to maximise clinical benefits for patients. Working collaboratively, NHS England and Novartis aim to mitigate risks associated with the introduction of this innovative and disruptive treatment by adopting cautious approach to treatment planning, particularly concerning the management of adverse events.

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- 3.5 A cautious approach is needed because the technology is associated with serious side effects such as cytokine release syndrome and acute neurological deterioration. These are rare conditions in existing care pathways and consequently experience in treating them is not extensive. For further information see 'Special warnings and precautions for use' of the [summary of product characteristics](#).
- 3.6 Providers require JACIE accreditation for Immune Effector Cell therapy, quality assurance from Novartis in line with their marketing authorisation and demonstrate that they meet the requirements of the NHS England service specification. A list of treatment centres that have successfully completed these assessments to be commissioned by NHS England to deliver tisagenlecleucel is available at: <https://www.england.nhs.uk/cancer/cdf/car-t-therapy/>.
- 3.7 It is estimated that there will be 25-30 new patients per year who will be eligible to have tisagenlecleucel. The number of patients who are expected to have treatment during the phased implementation cannot presently be estimated because this is highly dependent on the number of providers that receive JACIE accreditation, meet Novartis' quality assurance and NHS England's service specification standards. NHS England and Novartis anticipate being able to deliver services and treatment for the full eligible population by April 2020, and if it is able to deliver full capacity sooner, they will do so.
- 3.8 Given the phased implementation, NHS England has established a National CAR T Clinical Panel (NCCP) to prioritise patients for treatment as providers and manufacturers ramp up capacity across the country. This will include the scheduling of patients by taking into consideration patient need, available capacity and geographical access to ensure equity of access across the country. The NCCP is comprised of clinical experts, clinical leads from commissioned CAR T providers' and patient representation. For further

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details please refer to the documentation available at:

<https://www.england.nhs.uk/cancer/cdf/car-t-therapy/>.

- 3.9 The first meeting of the NCCP is scheduled for mid-November 2018, when the first patients will be prioritised for treatment as providers and manufacturers ramp up capacity across the country.

4 Area(s) of clinical uncertainty

- 4.1 Based on the NICE committee deliberations, the areas of most clinical uncertainty that are proposed to be addressed during the CDF data collection process are:

- Immaturity of data which does not fully support the curative nature of tisagenlecleucel
- Rate of subsequent stem cell transplant
- The number of people who would need treatment for B-cell aplasia with intravenous immunoglobulin, and the duration of this treatment.

5 Source(s) of data collection

Clinical trial

- 5.1 The primary source of data collection will be derived from the ongoing, international, multicenter, phase II, single-arm, open-label study- ELIANA (B2202). A final data cut and clinical study report is expected to be available in approximately June 2023. Further overall survival data will also be available from the ENSIGN and B2101J clinical trials to support the NICE re-appraisal.

Bone marrow (stem cell) transplant register

- 5.2 The UK bone marrow transplant registry is held at Guy's and St Thomas' and collects data on all bone marrow transplant in the UK. NHS England is exploring the possibility of gaining access to this data set. This could be used to determine the rate of subsequent stem cell transplants. NHS

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England will update NICE and the company on any progress relating to accessing this data source.

Other data

- 5.3 NHS England's Blueteq database captures the CDF population. NHS England will investigate opportunities to utilise data from the [British Society of Blood and Marrow Transplantation \(BSBMT\)](#) and from Medical Data Solutions and Services (MDSAS) for the CDF evaluation purposes.

6 Outcome data

Clinical trial

- 6.1 The following data will continue to be collected in the ELIANA trial. The data from this trial will help resolve the clinical uncertainty surrounding overall survival of patients treated with tisagenlecleucel and the proportion of patients who go on to have a stem cell transplant post tisagenlecleucel administration.

Key outcomes for data collection	• Overall survival
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Other data

- 6.2 Outcome data will not be collected for the relevant comparators

Bone marrow (stem cell) transplant register

- 6.3 The database can provide the proportion of patients who receive a stem cell transplant and the time of the transplant. However, it is anticipated that there may be difficulties in linking these data to other national data sets. This would mean that it may not be possible to identify those patients that have received tisagenlecleucel and the timing of the treatment. While these data sources will be explored further, it is anticipated that it may not be able to provide the outcomes required to resolve the clinical uncertainty.

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7 Data analysis plan

Clinical trials

- 7.1 The analysis will follow that of the existing ELIANA analysis plan and its associated trial protocol. The final analysis will follow the analysis plan outlined in the trial protocol.

The following data analysis has been planned for overall survival:

Overall survival (OS) is the time from date of first CTL019 infusion to the date of death due to any reason.

In case a patient is alive at the date of last contact on or before data cutoff, overall survival is censored at the date of last contact. No censoring will be done in case of SCT. Thus, patients should be followed-up for survival also in case of SCT.

Overall survival will be assessed in all patients in the Interim efficacy analysis set and the full analysis set. The distribution function of overall survival will be estimated using the Kaplan Meier (KM) method. The median overall survival along with 95% confidence intervals will be presented if appropriate.

Analysis for the further clinical trials, ENSIGN and B2101J, will follow the analysis plan outlined in the trial protocol.

No interim analyses from the ELIANA study are currently scheduled.

Other data

- 7.2 At a minimum, an annual report, will be provided by any other organisation collecting the data, and should be submitted to NHS England to check whether the data collection is on track, and to establish whether any additional action is needed]

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Bone marrow (stem cell) transplant register

- 7.3 NHS England will update NICE on any progress with the bone marrow transplant registry at a quarterly meeting. Any analytical and reporting requirements will be discussed if access to the data set is possible.

8 Ownership of the data

- 8.1 For all clinical trial data listed above, Novartis will be the owner.
- 8.2 Governance arrangements are not needed for the ongoing Novartis clinical trials.
- 8.3 Blueteq's CDF system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and generally for analysis of these data.
- 8.4 NHS England will explore implementation of a data sharing agreement with the Bone marrow (stem cell) transplant register for CDF evaluation purposes.

9 Publication

- 9.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.
- 9.2 NHS England will update NICE on any progress with the bone marrow transplant registry at a quarterly meeting. Any analytical and reporting requirements will be discussed if access to the data set is possible.

10 Data protection

- 10.1 The terms of clause 7 (data protection) of the managed access agreement, as apply between NHS England and Novartis , shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

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11 Equality considerations

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

☐ Yes ☒ No

Commercial Access Agreement

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