Cancer Drugs Fund

Managed Access Agreement

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [ID1684]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [ID1684]

Company name: Gilead Sciences Ltd

Primary source of data collection: ZUMA-7 clinical trial and NHS England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set and Blueteq

Secondary source of data collection: None

NICE Agreement Manager	Thomas Strong, Associate Director, Managed Access
NHSE Agreement Manager	Prof Peter Clark, CDF Clinical Lead
NHSE Agreement Manager	Martine Bomb, Head of Data Projects
Gilead Agreement Manager	Debbie Flanagan, Director

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 axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy (ID1684) (to be updated with TA number after final guidance has been published). A positive recommendation within the context of a managed access agreement (MAA) 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.

2.2 Estimated dates for data collection, reporting and submission for a guidance update are:

End of data collection (primary source)	[redacted]
Data available for development of company submission	[redacted]
Anticipated company submission to NICE for a guidance update	April 2028

2.3 Gilead anticipate the results from the additional data collected during the Cancer Drugs Fund period will be incorporated into an evidence submission and the updated economic model by anticipated April 2028.

2.4 Gilead 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.

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 entered into the managed access agreement.

2.7 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund 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 update follows the standard timelines.

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

2.9 The company must inform NICE and NHS England (NHSE) in writing of any anticipated changes to the estimated dates for data collection 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:

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

2.13 Gilead acknowledge their responsibility to provide an evidence submission for this technology to NICE under all circumstances following a period of managed access.

2.14 In the event that Gilead do not make a submission to NICE for the purpose of updating the guidance, NICE and NHSE will require the company 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 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 agreement no longer valid, and withdraw the technology from the Cancer Drugs 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. Patient eligibility

3.1 Key patient eligibility criteria for the use of axicabtagene ciloleucel in the Cancer Drugs Fund include:

The first part of the Blueteq form is for the approval of leucapheresis and manufacture of CAR-T cells. This includes the following eligibility criteria:

- the application is being made by and that leucapheresis for and treatment with axicabtagene ciloleucel-modified CAR-T cells will be initiated by a consultant haematologist or medical oncologist 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 DLBCL and high-grade B-cell lymphoma (HGBCL) and a member of the treating Trust's DLBCL and HGBCL CAR-T cell multidisciplinary team.

- the patient is an adult (age 18 years or over) on the date of approval for axicabtagene ciloleucel by the National CAR-T Clinical Panel for DLBCL and HGBCL.

- the patient has a confirmed histological diagnosis of DLBCL or HGBCL:

    - Diffuse large B-cell lymphoma (DLBCL) NOS (including ABC and GCB types) or

    - High grade B-cell lymphoma (HGBCL) with or without MYC and BCL2 (double hit) and BCL6 (triple hit) re-arrangements or

    - Transformed follicular lymphoma (TFL) to DLBCL or

  - T cell/histiocyte-rich large B-cell lymphoma or
  - Primary cutaneous DLBCL of leg type or
  - HHV8 positive DLBCL
  - DLBCL associated with chronic inflammation or
  - EB virus positive DLBCL

    Note: Patients with Burkitt lymphoma or primary mediastinal B cell lymphoma or primary CNS lymphoma or Richter's transformation to DLBCL are not eligible for treatment with axicabtagene ciloleucel in this indication.

- the histological diagnosis of DLBCL or HGBCL or transformed lymphoma to DLBCL has been either made by or reviewed and confirmed by a designated lymphoma stem cell transplant centre.
- prior to consideration of CAR-T cell therapy the patient's disease has been re-biopsied unless either the patient had outright progressive disease on standard 1st line chemo-immunotherapy or a biopsy is unsafe in which case the patient must have progressive disease at previously known sites of active disease. In such situations the original diagnostic biopsy review is acceptable.
  - All patients with transformed follicular lymphoma to DLBCL who fulfil the criteria below must have a re-biopsy and have confirmation of DLBCL histology prior to consideration of CAR-T cell therapy, either:

  - no biopsy necessary as the patient had outright progressive disease during 1st line chemo-immunotherapy or
  - re-biopsy has confirmed DLBCL or HGBCL or
  - re-biopsy has confirmed transformed follicular lymphoma to DLBCL or
  - re-biopsy is unsafe for the patient and the patient has progressive disease at previously known sites of active disease and the previous histology was DLBCL or HGBCL.

- the patient fulfils one of the following clinical scenarios relating to these definitions of relapsed or refractory lymphoma as applied to the failure of 1st line standard chemo-immunotherapy:
  - Refractory disease is defined as progressive disease as the best response to 1st line standard chemo-immunotherapy or stable disease as the best response after at least 4 cycles of 1st line standard chemo-immunotherapy or a partial response as the best response after at least 6 cycles of 1st line standard chemo-immunotherapy with biopsy-proven residual disease or a partial response with biopsy-proven progressive disease within 12 months or less from completion of treatment.
  - Relapsed disease is defined as disease that was in complete remission following 1st line standard chemo-immunotherapy and has been followed by a biopsy-proven disease relapse within 12 months or less from completion of treatment.

Progressive disease should be defined radiologically as per RECIST version 1.1 and be based on CT or MR scans and aided if necessary, after discussion at the National CAR T Clinical Panel, with the use of Lugano lymphoma response criteria.

Clinicians will be required for each patient to tick one of the following 5 definitions of response to 1st line chemoimmunotherapy;

- progressive disease after at least 2 cycles of chemo-immunotherapy as the best response to 1st line standard chemo-immunotherapy OR
- stable disease as the best response after at least 4 cycles of 1st line standard chemo-immunotherapy with biopsy-proven residual disease OR
- a partial response as the best response after at least 6 cycles of 1st line standard chemo-immunotherapy with biopsy-proven residual disease OR
- a partial response to 1st line standard chemo-immunotherapy with biopsy-proven progressive disease within 12 months or less from completion of treatment OR
- a complete response to 1st line standard chemo-immunotherapy with biopsy-proven disease relapse within 12 months or less from completion of treatment.

- the patient has been previously treated with a full dose 1st line anthracycline-containing standard regimen for his/her lymphoma or

with the Marietta protocol if presenting with CNS involvement. Note: acceptable anthracycline-containing regimens include R-CHOP, Pola-R-CHP, R-CODOX-M/R-IVAC, DA-EPOC-R and the Marietta protocol.

- that the patient has been previously treated with a regimen containing an anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease.

- on the date that the patient was confirmed as having refractory or relapsed disease according to the above definitions, the patient had only received 1st line of therapy for the DLBCL or HGBCL or TFL to DLBCL. Note: it is recognised that some patients at the time of the demonstration of refractory or relapsed disease have very rapidly progressive disease and thus have to commence urgent 2nd line treatment. It is therefore acceptable for patients to have received a maximum of 2 cycles of standard 2nd line chemotherapy with one of the following regimens ('anticipatory bridging therapy'): R-GDP, R-GemCarbo, R-ESHAP, R-ICE, R-IVE, R-BendaPola and the Marietta protocol.

  The applicant confirms whether the rate of disease progression as outlined above required urgent 2nd line salvage chemotherapy ('anticipatory bridging therapy') in this patient:

  - no urgent chemotherapy required prior to this application or

  - a maximum of 2 cycles of one of the above standard salvage chemotherapy regimens have been given prior to this application on grounds of urgent need and all other treatment criteria on this form are fulfilled

- in the absence of the availability of axicabtagene ciloleucel for this 2nd line indication the patient would have been fit and intended for both standard 2nd line salvage chemotherapy and potential stem cell transplantation. Note: Second line treatment regimens which are appropriate include: R-GDP, R-GemCarbo, R-ESHAP, R-ICE, R-IVE, R-BendaPola and the Marietta protocol.

- the patient has not previously been treated with an anti-CD19 antibody-drug conjugate.

- there is no current suspicion of CNS involvement by the lymphoma.

- the patient has an ECOG performance score of 0 or 1.

- the patient has sufficient end organ function to tolerate treatment with CAR-T cell therapy.

- the patient has either had no previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy or the patient has been treated with doses of genetically modified autologous or allogeneic T cell immunotherapy within an abandoned dosing cohort in a first in human dose-escalation phase I clinical trial.

- prior to infusion 2 doses of tocilizumab are available for use in this patient in the event of the development of cytokine release syndrome.

- axicabtagene ciloleucel-modified CAR-T cell therapy will otherwise be used as set out in its Summary of Product Characteristics (SPC).

- approval for the use of axicabtagene ciloleucel has been formally given by the National DLBCL/HGBCL CAR-T cell Clinical Panel.

- following national approval for use of axicabtagene ciloleucel 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.

The second part of the Blueteq form is to document the date of infusion of CAR-T cell therapy and for registration of this infusion with NHSE so that the treating Trust is reimbursed for the cost of axicabtagene ciloleucel. This includes the following eligibility criteria:

- this application for continuation is being made by and treatment with axicabtagene ciloleucel-modified CAR-T cells will be initiated by a consultant haematologist/medical oncologist 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 DLBCL and HGBCL and a member of the treating Trust's DLBCL and HGBCL and CAR-T cell multidisciplinary teams.
- the patient has an ECOG performance score of 0 or 1 or 2.
- the applicant confirms whether the patient has required bridging therapy in between leucapheresis and CAR-T cell infusion, and indicates what type(s) of bridging therapy has been required:
    - no bridging therapy at all or
    - corticosteroids only or
    - chemo(immuno)therapy only or
    - radiotherapy only or

  - corticosteroids and chemo(immuno)therapy or
  - corticosteroids and radiotherapy or
  - chemo(immuno)therapy and radiotherapy ± corticosteroids

- the applicant confirms the nature of any imaging procedure performed to assess response to bridging therapy below:
  - no bridging therapy and so no radiological assessment performed or
  - PET-CT scan performed or
  - CT or MR scan performed or
  - had bridging therapy but no radiological assessment performed

- Note: a PET-CT scan is the most informative imaging for patients having bridging therapy and is therefore highly desirable in this situation but NHSE recognises that this is not always possible.

  the applicant confirms the response assessment to bridging therapy below:
  - no bridging therapy and so no radiological assessment performed or
  - complete response (CR) or complete metabolic response (CMR) or
  - partial response (PR) or partial metabolic response (PMR) or

  - stable disease (SD) or
  - progressive disease (PD) or
  - had bridging therapy but no radiological assessment performed

- the applicant confirms the primary reason for the decision to employ bridging therapy if used:
  - no bridging therapy used at all or
  - the need to relieve local symptoms or
  - the need to relieve systemic symptoms or
  - the need to relieve both local and systemic symptoms or
  - the belief that toxicity and long-term outcomes will be better with bridging therapy
- The applicant confirms the time gap between the date of leucapheresis and start of bridging therapy.
- the patient has sufficient end organ function to tolerate treatment with CAR-T cell therapy.
- prior to infusion 2 doses of tocilizumab are available for use in this patient in the event of the development of cytokine release syndrome.
- axicabtagene ciloleucel-modified CAR-T cell therapy will otherwise be used as set out in its Summary of Product Characteristics (SPC).
- following national approval for use of axicabtagene ciloleucel there has been local CAR-T cell multidisciplinary team agreement that this

patient continues to have the necessary fitness for infusion and fulfils all of the treatment criteria listed here.

3.2 The estimated patient numbers per year for this technology within the Cancer Drugs Fund are:

As estimated by the company	Estimated patient numbers taken from UK market research: Year 1: [redacted] Year 2: [redacted] Year 3: [redacted]
As estimated by NICE Resource Impact Assessment team	Original estimate: Year 1: 135 Year 2: 216 Year 3: 286 Reduced market share estimate: Year 1: 108 Year 2: 162 Year 3: 216

4. Patient safety

4.1 The company and NHSE have the responsibility to monitor the safety profile of the technology and must provide an overview of any new or updated safety concerns to NICE. 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. Area(s) of clinical uncertainty

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

- Long-term overall survival in people treated with axicabtagene ciloleucel compared with standard care including:
    - The crossover adjustment required to adjust for the use of third-line CAR T-cell therapy in ZUMA-7.
    - The distribution used to extrapolate overall survival for people treated with axicabtagene ciloleucel in ZUMA-7.
- Generalisability of the results from ZUMA-7 to NHS practice because bridging chemotherapy was not permitted.

5.2 The committee expect further data collection will allow for a new model to be presented when the guidance is updated.

5.3 The committee concluded that further data collection within the Cancer Drugs Fund could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

6. Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ ZUMA-7 clinical trial data ○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHSE's Blueteq data
Secondary sources	○ None

Description of sources

6.1 ZUMA-7 is an international randomised Phase 3 trial comparing axicabtagene ciloleucel versus standard of care (high dose chemotherapy with autologous stem-cell transplantation if the disease is responsive to salvage chemoimmunotherapy) as a second line treatment in patients with early relapsed or refractory large-B cell lymphoma.

6.2 NHSE's Blueteq database captures the Cancer Drugs Fund population. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHSE, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHSE.

6.3 The Systemic Anti-Cancer Therapy (SACT) dataset is a mandated dataset as part of the Health and Social Care Information Standards. NHSE is responsible for the collection, collation, quality-assurance and analysis of this dataset.

6.4 Both the ongoing ZUMA-7 clinical trial data and NHSE routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set and Blueteq will be the primary source of data.

7. Outcome data

Clinical trial

7.1 The outcome data that will be collected during the data collection arrangement:

- Outcome 1 – Overall survival. Data from ZUMA-7 are expected up to 6 or 7 years of follow-up. This will help to resolve uncertainty around survival in the second-line setting.
- Outcome 2 – Subsequent stem cell transplant and whether autologous or allogeneic.

Other data, including SACT

7.2 NHSE will collect the following outcomes through SACT unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection:

- Number of patients starting treatment
- Baseline patient characteristics, including gender, age and performance status
- Treatment duration
- Overall survival

7.3 NHSE's Blueteq system will collect the following outcomes:

- Number of applications to receive treatment
- The number of patients that receive bridging chemotherapy prior to infusion
- Primary reason for bridging chemotherapy

- Response assessment to bridging therapy
- Time to bridging therapy
- Number of patients treated that are primary refractory versus number of patients treated who have relapsed within 12 months of first-line treatment
- Subsequent stem cell transplant and whether autologous or allogeneic.

8. Data analysis plan

Clinical trials

8.1 The minimum time frame for data collection in ZUMA-7 is determined by OS events. The primary OS analysis is planned when [redacted] death 'events' have been observed OR no later than [redacted] years after first patient enrolment, whichever comes first (per ZUMA-7 protocol). The final analysis will follow the analysis plan outlined in the trial protocol. An interim analysis of OS had already been triggered at time of primary EFS analysis (per Locke et al 2022). Further read-outs and availability of data from the primary OS analysis of ZUMA-7 will be shared during the CDF data collection period. Database lock for 5-year data is anticipated to occur by [redacted] and data are anticipated to be made available by [redacted]. Database lock for 7-year data is anticipated to occur by [redacted], with data made available by [redacted].

Other data

8.2 At the end of the data collection period NHSE will provide a final report which will provide analyses based on NHSE's Blueteq data and routinely collected population-wide data, including that collected via SACT. 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 guidance update. Where SACT is a secondary source of data, availability of the final SACT report will be aligned to the availability of data from the primary source. The end of SACT data collection will be 8 months prior to the availability of the final SACT report to allow for NHS trusts to upload SACT data, data cleaning, and report production. For this data collection period, the final SACT report is required by February 2028.

9. Ownership of the data

9.1 For all clinical trial data listed above, Kite Pharma, Inc (an affiliate of Gilead) will be the owner.

9.2 Gilead will be responsible for ensuring they have permission to share the clinical study report, including non-patient identifiable data and analysis as part of their submission for the guidance update.

9.3 This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which is part of NHSE. The company will not have access to the NHSE patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

9.4 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by NHSE, have been established with NHS Trusts.

9.5 Blueteq's Cancer Drugs Fund system data is owned by NHSE. NHSE is responsible for implementing Blueteq data collection and generally for

the analysis of these data. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHSE, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care. The lawfulness of NHSE's processing is covered under article 6(1)(c) of the UK GDPR – processing is necessary for compliance with a legal obligation to which the controller is subject (the NDRS Directions).

10. Publication

10.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

10.2 NHSE will produce a final report which includes analysis of data collected through SACT and from NHSE's Blueteq system. This report will be provided to NHSE and the company at the end of the managed access period. The final report will form part of NHSE's submission to the guidance update, and will therefore be publicly available at the conclusion of the guidance update.

10.3 NHSE will produce interim reports, which will be shared with NICE and the company 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 update.

10.4 Publications of any data from the NHSE reports is not permitted until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance update committee meeting.

10.5 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.

11. Data protection

11.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHSE and Gilead, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement.

12. Equality considerations

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

☐ Yes ☒ No