Cancer Drugs Fund

Managed Access Agreement

Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (TA893)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (TA893)

Company name: Gilead Sciences Ltd

Primary source of data collection: Ongoing ZUMA-3 clinical trial data

Secondary source of data collection: NHS England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set, and Blueteq

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 Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (TA893). 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	February 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 February 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 Brexucabtagene autoleucel 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 brexucabtagene autoleucel-modified CAR-T cells will be 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 adult acute lymphoblastic leukaemia **and** a member of the treating Trust's adult acute lymphoblastic leukaemia and CAR-T cell multidisciplinary teams.

- The patient has relapsed or refractory B lineage acute lymphoblastic leukaemia (ALL):

    - Philadelphia chromosome **negative** ALL or,

    - Philadelphia chromosome **positive** ALL either previously treated with at least 2 tyrosine kinase inhibitors (TKIs) or the patient has failed at least 1 second or third generation TKI or the patient is unsuitable or intolerant to TKI therapy

  Note: patients with Burkitt leukaemia/lymphoma or with chronic myeloid leukaemia lymphoid blast crisis are not eligible for treatment with brexucabtagene autoleucel.

- The patient fulfils **one** of the following clinical scenarios relating to the definition of relapsed or refractory ALL.

    - the patient has primary refractory disease i.e. did not achieve a complete remission after 2 cycles of standard chemotherapy for newly diagnosed ALL or,

- the patient has a bone marrow relapse after allogeneic stem cell transplantation in 1st remission and is at least 3 months since allogeneic SCT with no active Graft versus Host Disease (GVHD) requiring systemic therapy or,
- the patient has a bone marrow relapse after allogeneic stem cell transplantation in 2nd remission and is at least 3 months since allogeneic SCT with no GvHD requiring systemic therapy or,
- the patient is in 1st bone marrow relapse following a remission lasting 12 months or less (not had SCT) or,
- the patient is refractory to or has relapsed after 2nd or more line chemotherapy/monoclonal antibody (not had SCT) or,
- relapsed disease and ineligible for allogeneic SCT due to comorbid disease (**but still fit enough for CAR-T cell therapy with brexucabtagene autoleucel**) or contraindicated to allogeneic SCT conditioning or lack of a suitable donor.

- The patient at the time of demonstration of such refractory/relapsed disease and thus consideration for potential treatment with brexucabtagene autoleucel has a bone marrow with CD19+ B-ALL demonstrable by flow cytometry. (Measurable residual disease by molecular methods is insufficient to comply with access to brexucabtagene autoleucel.)
- The patient does **not** have an **isolated** extramedullary ALL relapse i.e. if the patient has extramedullary disease, then the patient must also have bone marrow disease as set out above in criterion 4.

- At the time of this application for treatment with brexucabtagene autoleucel the patient does **not** have active CNS involvement by ALL whether this be CNS2 with neurological changes or CNS3.

- The consultant will confirm whether the patient has been previously treated with blinatumomab or not. If there has been previous therapy with blinatumomab, there must be CD19 expression on the lymphoblasts (bone marrow or blood) after the most recent line of treatment.

- The consultant will confirm whether the patient has been previously treated with inotuzumab or not.

- 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.

    - No previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy or,

    - Previously 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.

- The patient has an ECOG performance status of 0 or 1.

- The patient has sufficient end organ function to tolerate treatment with brexucabtagene autoleucel.

- The patient is aged 26 years or more on the date of approval for brexucabtagene autoleucel by the National CAR-T Adult ALL Clinical Panel.

- The consultant will confirm whether the current intent is for the patient to receive bridging therapy prior to the conditioning chemotherapy before CAR-T infusion.

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

- Brexucabtagene autoleucel-modified CAR-T cells will otherwise be used as set out in its Summary of Product Characteristics (SPC).

- Approval for the use of brexucabtagene autoleucel has been formally given by the National adult acute lymphoblastic leukaemia CAR-T cell Clinical Panel.

- Following national approval for use of brexucabtagene autoleucel there has been local CAR-T cell multidisciplinary team agreement that this patient continues to have the necessary fitness for treatment and fulfils all 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:

- Whether the patient has been treated with bridging therapy in between leucapheresis and CAR-T cell infusion:

    - no bridging therapy at all, or

- corticosteroids only, or
- TKI therapy with or without steroids, or
- systemic cytotoxic chemotherapy with or without steroids, or
- systemic cytotoxic chemotherapy plus TKI with or without steroids, or
- inotuzumab with or without steroids, or
- other.

- The patient has an ECOG performance status of 0 or 1 or 2.
- The patient has sufficient end organ function to tolerate treatment with brexucabtagene autoleucel.
- Prior to infusion a minimum of 2 doses of tocilizumab are available for use in this patient in the event of the development of cytokine release syndrome.

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 sourced from market research. Current practice: 0 Year 1: [redacted] Year 2: [redacted] Year 3: [redacted]

As estimated by NICE Resource Impact Assessment team	Number of patients expected by year: Year 1: 31 Year 2: 57 Year 3: 75

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:

- Relapse-free survival and cure assumption.
- Overall survival.

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)	○ Ongoing ZUMA-3 clinical trial data
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHSE's Blueteq data

Description of sources

6.1 ZUMA-3 is a Phase 2 international multi-centre single-arm, open label study evaluating the efficacy and safety of the CAR-T brexucabtagene autoleucel in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL).

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 The ongoing ZUMA-3 clinical trial data will be the primary source of data collection and NHSE will collect data, including via the SACT dataset, alongside the primary source of data collection.

7 Outcome data

Clinical trial

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

- Outcome 1 – 5-year clinical trial data and RWE from SACT will support the relapse free survival and cure assumption
- Outcome 2 – Longer term overall survival from clinical trial

The data capture should resolve the uncertainties highlighted in section 5.1 as these are related to longer term overall survival data.

Other data, including SACT

7.2 NHS England 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

8 Data analysis plan

Clinical trials

8.1 The minimum time frame for data collection was decided as follows: primary data cut-off occurred in [redacted]. Expected subsequent [redacted] data cut-offs to review [redacted] have occurred ([redacted] data cut-off occurred in [redacted] and [redacted] data cut off in [redacted]). Another analysis on the [redacted] data cut is planned and an anticipated data cut in [redacted] and a data cut in [redacted]. The final analysis [redacted].

8.2 At the end of the data collection period NHS England will provide a final report for NHSE which 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.

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 NHS England. 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 x☐ No

Commercial Access Agreement

Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over

(TA893)

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

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.