Managed Access Agreement

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Company name: Eli Lilly and Company Limited

Primary source of data collection: Ongoing clinical study, LIBRETTO-001 and LIBRETTO-431

Secondary source of data collection: NHSE routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

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NHSE Agreement Manager	Martine Bomb, Head of Data Projects
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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 selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer (ID4056) (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 2027

2.3 Eli Lilly and Company Limited 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 April 2027.

2.4 Eli Lilly and Company Limited 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 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 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 Eli Lilly and Company Limited 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 Eli Lilly and Company Limited 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 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 selpercatinib in the Cancer Drugs Fund include:

- The application for selpercatinib is being made by and the first cycle of systemic anti-cancer therapy with selpercatinib will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.
- The patient has locally advanced or metastatic non-small cell lung cancer.
- The patient has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer, of either:
    - non-squamous NSCLC, or
    - squamous NSCLC
- The patient's NSCLC has been shown to harbour a RET gene fusion as determined on a tumour tissue biopsy or a plasma specimen (liquid biopsy), or both.
- The patient's RET fusion partner has been determined to be in one of the categories as set out below:
    - KIF5B
    - CCDC6
    - NCOA4
    - RELCH
    - Another fusion partner
    - Unknown fusion partner

- The patient has NOT received any prior systemic therapy for this locally advanced or metastatic NSCLC indication.
- The patient has not previously received selpercatinib or any other TKI which targets the RET receptor unless the patient has received selpercatinib via a company early access scheme **and** the patient meets all the other criteria listed here.
- The patient has an ECOG performance status (PS) score of 0 or 1 or 2.
- The patient either has no known brain/CNS metastases or if the patient does have brain/CNS metastases then the patient is symptomatically stable before starting selpercatinib:
    - The patient has never had known brain/CNS metastases
    - The patient has had brain/CNS metastases treated before with surgery/radiotherapy and is currently symptomatically stable
    - The patient has brain secondaries which have not been treated with surgery/radiotherapy and is currently symptomatically stable
- Selpercatinib will be used as monotherapy.
- The clinician is aware of the following issues as regards the administration of selpercatinib as detailed in its Summary of Product Characteristics (SPC):
    - the dosage of selpercatinib is according to body weight
    - selpercatinib has reduced solubility at a higher pH and hence precautions are necessary with the co-administration of proton pump inhibitors or H2 antagonists
    - selpercatinib has clinically important interactions with CYP3A inhibitors or CYP3A inducers

- The patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment whichever is the sooner.
- A formal medical review as to how selpercatinib is being tolerated and whether treatment with selpercatinib should continue or not will be scheduled to occur at least by the start of the third 4-weekly cycle of treatment.
- When a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, I will complete a treatment break approval form to restart treatment, including as appropriate if the patient has had an extended break on account of Covid-19.
- Selpercatinib is to be otherwise used as set out in its Summary of Product Characteristics (SPC).

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

As estimated by the company	Year 1: [redacted] Year 2: [redacted] Year 3: [redacted]
As estimated by NICE Resource Impact Assessment team	Year 1: 99 Year 2: 130 Year 3: 130

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:

- The long-term progression-free survival estimates
- The long-term overall survival estimates
- The clinical efficacy compared with current clinical practice

5.2 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)	○ Phase 1/2 trial: LIBRETTO-001 ○ Phase 3 trial: LIBRETTO-431
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHSE's Blueteq data

Description of sources

6.1 LIBRETTO-001 (NCT03157128) is an ongoing multicentre, open-label, phase I/II study in patients with advanced solid tumours, with RET activation. Key eligibility criteria of the trial includes:

- Patients ≥12 years old
- locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal),

RET-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation)

- progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator, were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy
- and an ECOG ≤2 or LPS ≥40%.

The supplementary analysis set 1 (SAS1) for the systemic treatment-naïve RET-fusion positive NSCLC cohort is the population of interest for this data collection agreement.

LIBRETTO-431 (NCT04194944) is an ongoing multicenter, randomized, open-label, Phase 3 trial comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab as initial treatment of advanced or metastatic RET fusion-positive Non-Small Cell Lung Cancer. Key eligibility criteria of the trial includes:

- Histologically or cytologically confirmed, Stage IIIB-IIIC or Stage IV non-squamous NSCLC that is not suitable for radical surgery or radiation therapy.
- A RET gene fusion in tumour and/or blood from a qualified laboratory.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

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

(NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the 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 NDRS in NHSE will collect data, including via the SACT dataset, alongside the primary source of data collection.

7 Outcome data

Clinical trial

7.1 Progression free survival and overall survival are outcomes of interest and are reported outcomes from the LIBRETTO-001 trial. The data available in [redacted] will provide further evidence of progression free survival and overall survival in the trial population under consideration in the CDF.

7.2 Comparative progression free survival is the outcomes of interest and is reported from the LIBRETTO-431 trial. Progression free survival is the primary endpoint and a single interim efficacy analysis for PFS is planned when [redacted] are reached in the comparator arm for the ITT-pembrolizumab population will be available based on an interim analysis anticipated in [redacted]. Final analysis is planned when [redacted] are reached in the comparator arm for the ITT-

pembrolizumab population and these data are expected to be available in [redacted]. It is anticipated median OS data will be available in [redacted].

Other data, including SACT

7.3 NDRS in 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

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

- Number of applications to start treatment

8 Data analysis plan

Clinical trials

8.1 LIBRETTO-001 updated Non-Small Cell Lung Cancer (RET-fusion positive NSCLC) data is expected no later than [redacted]. Estimated study completion date is September 2024.

8.2 LIBRETTO-431 (RET-fusion positive NSCLC) data is expected no later than [redacted] based on median OS anticipated in [redacted]. Estimated study completion date is July 2027.

8.3 The company will use the new survival data to update the existing model presented in ID4056.

Other data

8.4 At the end of the data collection period NHSE will provide a final report 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, Eli Lilly and Company Limited will be the owner

9.2 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.

9.3 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.

9.4 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 NDRS 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 NDRS 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 NDRS 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 Eli Lilly and Company Limited, 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

Commercial Access Agreement

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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.