Cancer Drugs Fund

Managed Access Agreement

Larotrectinib for treating NTRK fusion-positive advanced solid tumours [TA630]

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Cancer Drugs Fund – Data Collection Arrangement

Larotrectinib for treating NTRK fusion-positive solid tumours [TA630]

Company name: Bayer plc

Primary source of data collection:

- Pooled analysis from the ongoing clinical studies NAVIGATE (NCT02576431), SCOUT (NCT02637687) and LOXO-TRK-14001 (NCT02122913)
- Public Health England Systemic Anti-Cancer Therapy data
- Public Health England molecular data set
- Genomics England analysis

Secondary source of data collection:

- Bayer global non-interventional study (NIS)
- Access to EURACAN registry*

**EURACAN is the European Reference Network for adult rare solid cancers comprised of 66 sites across Europe. The EURACAN Genomic registry will be set up to collect genomic, clinical and safety data. Bayer will receive annual summary results (efficacy and safety) in counterpart of its support to the EURACAN registry.*

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1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the potential arrangements and responsibilities for further data collection for larotrectinib for treating NTRK fusion-positive solid tumours.

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 CDF guidance review are:

	Planned interim analysis	Final analysis
End of data collection (primary sources)	NAVIGATE: [redacted] PHE data sets: July 2022 Genomics England Analysis [redacted]	NAVIGATE: [redacted] PHE data sets: July 2023
Data available for development of company submission	[redacted]	[redacted]
Anticipated company submission to NICE	Q2 2023	September 2024

2.3 Bayer acknowledge their responsibility to adhere to the timelines presented in the document, and to notify NICE and NHS England and NHS Improvement of any delays within 14 days of becoming aware of any timing issues.

2.4 As the data collection involves substantial additional data from new and existing sources over an extended period the following will apply:

- An interim review of the data collected will be required. Bayer will be required to provide an evidence submission to enable this review to take place. Bayer's evidence submission will either be the dossier provided to the European Medicines Authority as part of the conditional marketing authorisation or a stand-alone document that includes all appropriate and relevant available evidence about the clinical effectiveness of the technology. NICE and NHS England and NHS Improvement and the company will review all available evidence and, and NICE and NHS England and NHS Improvement will decide whether further data collection is required to resolve the key uncertainties identified by committee, or the data is sufficient to initiate a NICE guidance review.

- The guidance review following the managed access period for this topic will be undertaken as a full technology appraisal. For further details of the technology appraisal process see NICE's guide to the processes of technology appraisal.

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

2.6 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 review of guidance follows the single technology appraisal 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 review. Further information is available on the NICE website.

2.8 The company must inform NICE and NHS England and NHS Improvement of any anticipated changes to the estimated dates for data collection at the earliest opportunity, and within 14 days of becoming aware of these new dates.

2.9 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHS England and Improvement.

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 Cancer Drugs Fund guidance review 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).

2.11 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 NHS England and Improvement, with details of the extension requested, including an explanation of the factors contributing to the request.
- It may be necessary for the company to take action 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 Public Health England to provide data over the extended period.

2.12 NICE and NHS England and NHS Improvement 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 will not report outcome data for an interim review.
- The primary sources 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 larotrectinib in the Cancer Drugs Fund include:

- application is made by the first cycle of systemic anti-cancer therapy by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy

- patient has a proven histological diagnosis of a malignant solid tumour (ie a carcinoma or sarcoma or melanoma or brain or spinal cord tumour) and does not have a leukaemia or lymphoma or myeloma
- patient has disease that is locally advanced or metastatic or would require surgical resection likely to result in severe morbidity
- patient has no satisfactory systemic therapy options. A satisfactory systemic treatment option is defined as one which is funded by NHS England for the disease and indication in question
- patient has a documented NTRK gene fusion in the tumour determined with a nucleic acid-based assay organised and validated by the regional Genomic Laboratory Hub
- patient has not previously received treatment with any tropomyosin receptor tyrosine kinase (TRK) inhibitor
- larotrectinib will be used as monotherapy
- patient has an ECOG performance status (PS) of 0 or 1 or 2
- a PET/CT/MR scan of measureable disease and the brain has been done prior to commencing larotrectinib and this must be repeated no later than 10 weeks after the start of treatment (if not indicated before 10 weeks on account of assessing risk of disease progression)
- patient has had a recent CT or MR scan of the brain and either has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting larotrectinib

- larotrectinib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or potentially curative surgery takes place
- Clinician is fully aware of the likely toxicities of larotrectinib as listed in its SPC
- a formal medical review as to whether treatment with larotrectinib should continue or not (on basis of being fit to continue treatment) will be scheduled to occur by the start of the second cycle (month) of treatment
- no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
- larotrectinib is to be otherwise used as set out in its Summary of Product Characteristics

3.2 **12 weeks** after initiation of larotrectinib the following eligibility criteria apply. If the eligibility criteria are not completed the dispensing Trust will not receive reimbursement for further larotrectinib use:

- The response assessment and (as appropriate) this application to continue treatment with larotrectinib is being made by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- a RECIST radiological assessment has been made of the index disease (and of any metastatic intra-cerebral or CNS disease, if applicable) at **10 weeks** after the start of larotrectinib.

- no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)

- larotrectinib is to be otherwise used as set out in its Summary of Product Characteristics

3.3 The estimated patient numbers per year for this technology are dependent on the implementation of genomic testing within England. The estimated patient numbers within the Cancer Drugs Fund are:

As estimated by the company	Estimated incident population in England of [redacted]. Clinical advice was that of those reaching 'last line' therapy, only [redacted]% of patients with advanced disease might be fit enough to proceed to treatment with larotrectinib.
As estimated by NICE Resource Impact Assessment team	[redacted]

4 Area(s) of clinical uncertainty

4.1 The committee identified the following key areas of clinical uncertainty. Please refer to the Final Appraisal Document for a full description of the clinical uncertainty:

- Prevalence and characterisation of NTRK gene fusions i.e. the gene fusions and the fusion partner, in each tumour site
- The potential prognostic importance of NTRK gene fusions

- The technology's position in the treatment pathway, in particular whether a proportion of people go on to receive subsequent therapies
- The diagnostic pathway is uncertain until NHS England and NHS Improvement establishes a national service for genomic testing of all advanced solid tumours
- Issues with the generalisability of the trial to NHS clinical practice
- The immaturity of the data does not allow a reliable estimation of the benefit on long-term survival
- Heterogeneity of response across tumour types
- The post-progression health utility state between larotrectinib and the comparator arm
- Whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	• Pooled analysis from the ongoing clinical studies NAVIGATE (NCT02576431), SCOUT (NCT02637687) and LOXO-TRK-14001 (NCT02122913) • Public Health England Systemic Anti-Cancer Therapy data • Public Health England molecular data set • Genomics England analysis
Secondary sources	• Bayer global non-interventional study (NIS) • Access to EURACAN registry*

Description of sources

5.1 **NAVIGATE (NCT02576431)** is an ongoing Phase II study with the primary objective of determining the overall response rate following

treatment with larotrectinib in subjects aged 12 years and older with an advanced cancer harbouring an NTRK gene fusion.

5.2 **SCOUT (NCT02637687)** was set up as a Phase 1/2 Study, with the primary objectives being to determine the safety and efficacy of oral larotrectinib in paediatric patients with advanced solid or primary central nervous system (CNS) tumors with NTRK gene fusion.

5.3 Patients were recruited sequentially as they presented to these trials and no solid tumour type was excluded from the larotrectinib trials.

5.4 Bayer will undertake additional data collection, in accordance with the conditional marketing authorisation granted by the EMA and FDA for larotrectinib, and the outputs from this will also be made available for the purposes of this DCA, including:

- As part of the NAVIGATE study - submit a prospective cohort of 75 patients, for which at least 1 year of follow-up is available, and perform an overall pooled analysis where the target population includes the ePAS2/SAS3 cohort (with the updated data) along with the prospective cohort.

- A commitment to enrol 200 additional patients in NAVIGATE and as part of the SCOUT study within a 36-month period post approval. Eighty patients will be recruited in the common tumour types and 120 in the other tumour types.

- Enrolling at least 9 and up to 20 patients in total in each of the identified common tumour type subgroups (i.e. lung, melanoma, colorectal cancer, non-secretory breast).

5.5 The data which will be available for the guidance review will be the pooled analysis of NAVIGATE, SCOUT and the Phase I study:

NCT02122913, in line with the regulatory submission and the original submission to NICE.

5.6 The **(ON-TRK) study (NCT04142437)** is a planned non-interventional study (NIS) as a result of post-marketing commitments made to EMA and FDA. The protocol is attached as a confidential appendix. UK treatment centres will be eligible to participate once larotrectinib is available via the CDF. ON-TRK stands for: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib. The purpose of this study is to describe, under real-world conditions, the safety and effectiveness of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrolment. The study aim is to enrol and collect data from up to 300 patients. Specific cohorts will be recruited: gastrointestinal, head and neck, lung, soft tissue sarcoma, primary central nervous system, melanoma, paediatrics, and others. The recruitment period will be 36 months; the end of the study for all cohorts but the paediatric cohort will happen after the final patient has been in the study for at least 24 months, or is no longer under observation owing to being lost to follow-up, withdrawal, or death. For the paediatric cohort, each patient will be followed up for at least 60 months from larotrectinib initiation unless the patient is discontinued due to lost to follow-up, withdrawal, or death. The international, non-interventional study design enables data to be collected from patients treated under local standard of care clinical practice; all decisions in terms of diagnostic procedures, treatments, management of the disease, and resource utilization are fully dependent on mutual agreement between the patient and the attending physician, without interference by the study initiator or study protocol. Data collection via SACT would not preclude interested UK centres participating in ON-TRK.

5.7 **EURACAN** is the European Reference Network for adult rare solid cancers comprised of 66 sites across Europe. The EURACAN Genomic registry will be set up to collect genomic, clinical and safety data. Bayer will receive annual summary results (efficacy and safety) in counterpart of its support to the EURACAN registry. We have limited further details at this time. There are some sites already in the EURACAN network and the first countries participating will be France and Germany., We anticipate that UK centres would be able to join the registry (clarification is being sought concerning the impact of EU exit) and data collection via SACT would not preclude this.

5.8 Bayer are in the process of commissioning a study using Genomics England data. The details of this study are still in the exploratory stages but should explore the prognostic value of NTRK gene fusions in cancer patients. The study is planned to report before the interim analysis in 2023.

5.9 NHS England and Improvement's Blueteq database captures the Cancer Drugs Fund population. NHS England and NHS Improvement shares Blueteq data with Public Health England for the Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

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

5.11 Public Health England will collect data, including via the SACT dataset, alongside the other primary sources of data collection.

6 Outcome data

Clinical trial

6.1 Through the ongoing pooled analysis of the NAVIGATE and SCOUT studies:

- Progression-free survival
- Overall survival
- Higher patient numbers and longer follow up may help address heterogeneity of response across tumour types
- Quality of Life and health utilities measures:
    - European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)
    - EuroQoL Five Dimension Questionnaire (EQ-5D)
    - For those <18 years of age: Pediatric Quality of Life Inventory-Core Module (PedsQL)

Other data, including SACT

6.2 Public Health England will collect the following outcomes through SACT and the molecular dataset 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
- Number and type of NTRK testing by tumour site
- Number of positive NTRK tests by tumour site
- Characterisation of NTRK gene fusions by tumour site

- Treatment duration
- Overall survival
- Subsequent treatments
- Baseline characteristics: age and gender

6.3 NHS England and NHS Improvement's Blueteq system will collect the following outcomes:

- Number of applications to start treatment
- Response at week 10
- Number of previous lines of therapy
- Baseline patient characteristics: performance status at the start of treatment, tumour site and histology, NTRK gene fusion type, and presence of CNS metastases

6.4 **Non-interventional study (ON-TRK)**

- Distribution of tumour sites in the real-world setting
- Information regarding systemic treatments received prior to larotrectinib.
- Information about the testing methodology
- Response rates
- Progression-free survival

Note: this is an international study rather than England specific. UK centres will be eligible to participate once larotrectinib is available via the CDF.

6.5 EURACAN

- Number of patients starting treatment by tumour site
- Progression-Free Survival

Note: this is a European-wide study rather than England specific. UK involvement has not been confirmed.

6.6 Genomics England Analysis

- The details of further data collection via Genomics England will be updated once details become available, not more than 6 months following the publication of the NICE Final Appraisal Document.

7 Data analysis plan

Clinical trials

7.1 There will be pre-planned annual updates of the pooled NAVIGATE, SCOUT and Phase I study: NCT02122913. The final analysis will be performed according to the protocol.

7.2 Annual reports are planned for the pooled analysis in [redacted] each year (based on the previous [redacted] cut off).

7.3 Database locks will be in [redacted] each year and the data will be available in [redacted] the following year.

Other data

7.4 At the end of the data collection period Public Health England will provide a final report for NHS England and NHS Improvement which provide analyses based on NHS England and NHS Improvement'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 review of guidance.

7.5 For the global NIS, interim reviews for safety and effectiveness will be performed [redacted]. Subsequent reviews will be performed [redacted] have met the same conditions.

7.6 Annual summary results will be obtained from the EURACAN registry.

8 Ownership of the data

8.1 For all clinical trial data listed above and the NIS, Bayer will be the owner.

8.2 EURACAN is the data owner of the EURACAN data reports. Bayer will be responsible for ensuring they have permission to share and reproduce aggregated, non-patient identifiable data and analysis as part of their submission for the guidance review.

8.3 The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data is facilitated by the Public Health England Office for Data Release. The company will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

8.4 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

Public Health England, have been established with NHS Trusts and NHS England and Improvement.

8.5 Blueteq's Cancer Drugs Fund system data is owned by NHS England and NHS Improvement, which is responsible for implementing Blueteq data collection and generally for the analysis of these data. NHS England and NHS Improvement shares Blueteq data with Public Health England for Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

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 Public Health England will produce a final report which includes analysis of data collected through SACT, molecular dataset and from NHS England and Improvement's Blueteq system. This report will be provided to NHS England and NHS Improvement and the company at the planned interim review and, if applicable, at the end of the managed access period. The final report will form part of NHS England and Improvement's submission to the Cancer Drugs Fund guidance review, and will therefore be publicly available at the conclusion of guidance review.

9.3 Public Health England will produce interim reports, which will be shared with NHS England and Improvement, 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 review.

9.4 Publications of any data from the Public Health England reports is not permitted until after the date of publication of the NICE committee

papers (on the NICE website) following the first NICE guidance review committee meeting.

9.5 The contribution of the all relevant individuals must be acknowledged in any publications regarding the Managed Access. Authors will need to contact the NICE Managed Access Team for a full list of group members.

10 Data protection

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

11 Equality considerations

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

☐ Yes ☒ No

12 Annex: List of supporting documents

IN CONFIDENCE: ON-TRK protocol: Prospective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib.

Commercial Access Agreement

Larotrectinib for treating NTRK fusion-positive advanced solid tumours [TA630]

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.