Cancer Drugs Fund

Managed Access Agreement

Entrectinib for treating NTRK fusion-positive solid tumours [TA644]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Entrectinib for treating NTRK fusion-positive solid tumours [TA644]

Company name: Roche Products Ltd

Primary sources of data collection:

- Ongoing entrectinib trial STARTRK-2
- Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set and molecular data set,
- Flatiron real-world data and Foundation Medicine genomic database,

Secondary sources of data collection:

- Ongoing entrectinib trial STARTRK-NG
- Intergroup non-interventional study (NIS) sponsored by European Thoracic Oncology Platform (ETOP).

NICE Agreement Manager	Brad Groves, Associate Director, Managed Access
NHS England and NHS Improvement Agreement Manager	Peter Clark, CDF Clinical Lead
Public Health England Agreement Manager	Rebecca Smittenaar, Analytical Lead
Roche Agreement Manager	[redacted], Head of Health Economics & Strategic Pricing

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 entrectinib 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)	STARTRK-2: [redacted] Flatiron interim report: [redacted] PHE data sets: Q1 2023	STARTRK-2: [redacted] Flatiron final report: [redacted] PHE data sets: July 2026
Data available for development of company submission	[redacted]	[redacted]
Anticipated company submission to NICE	December 2023	September 2027

2.3 Roche 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. Roche will be required to provide an evidence submission to enable this review to take place. Roche's evidence submission will be either 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 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 entrectinib 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 an appropriate nucleic acid-based assay(s)
- patient has not previously received treatment with any tropomyosin receptor tyrosine kinase (TRK) inhibitor
- entrectinib 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 entrectinib 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 entrectinib
- entrectinib 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 entrectinib as listed in its Summary of Product Characteristics (SPC)
- a formal medical review as to whether treatment with entrectinib 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)
- entrectinib is to be otherwise used as set out in its SPC

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

- the response assessment and (as appropriate) this application to continue treatment with entrectinib 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 entrectinib.
- 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)
- entrectinib is to be otherwise used as set out in its SPC

3.3 Roche UK closed an entrectinib compassionate use programme in May 2020 for patients who have a confirmed NTRK fusion positive

locally advanced or metastatic solid tumour, which was opened in November 2018. As of May 2020 no people in England have received entrectinib outside of a clinical trial for the indication in question.

3.4 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	[redacted]
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 and tumour type proportions in the UK population 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 and patient identification 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 trials to NHS clinical practice
- The comparative effectiveness of entrectinib versus best supportive care
- The pre-progression health utility state between entrectinib and the comparator arm
- Long term efficacy and safety of entrectinib
- Heterogeneity of response, including efficacy and safety, across existing and unknown tumour types
- 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)	• Ongoing entrectinib STARTRK-2 trial • PHE's Systemic Anti-Cancer Therapy (SACT) dataset • PHE's Molecular dataset • NHS England's Blueteq data • United States: Flatiron real-world data and Foundation Medicine genomic database

Secondary sources	• Europe: Intergroup non-interventional study (NIS) sponsored by European Thoracic Oncology Platform (ETOP) • Ongoing entrectinib STARTRK-NG trial

Description of sources

5.1 Ongoing entrectinib trial programme – STARTRK-2 and STARTRK-NG.

5.2 Flatiron real-world data and Foundation Medicine genomic database: United States-based combined clinico-genomic database comprising aggregated real-world clinical outcomes (Flatiron element) and tumour genomic profiling (Foundation Medicine element).

5.3 Intergroup non-interventional study (NIS) sponsored by ETOP: cohort study covering NTRK fusion-positive lung cancer, breast cancer and sarcoma cohorts (with potential for additional tumour types to be subsequently added). Retrospective and prospective cohorts.

5.4 NHS England and NHS 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.

5.5 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.

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

6 Outcome data

Clinical trial

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of response (DOR)
- Intra-cranial PFS (IC-PFS)
- Time to CNS progression
- Intra-cranial ORR (IC-ORR)
- Intra-cranial duration of response (IC-DOR)
- Safety and tolerability

Patient recruitment and follow-up is ongoing in the existing clinical trial programme (STARTRK-2 and STARTRK-NG). This will consequently resolve uncertainty over long term survival outcomes, and reduce uncertainty relating to efficacy in both existing and unknown tumour types by increasing the numbers of patients in these groups.

Other data, including SACT

6.1 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

6.2 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

6.3 Flatiron real-world data and Foundation Medicine genomic database: United States-based combined clinic-genomic database comprising aggregated real-world clinical outcomes (Flatiron element) and tumour genomic profiling (Foundation Medicine element)

- Patient demographics, including:
    - Performance status
    - Histology
    - Stage

- Metastatic sites

- Genomic test information
- Real-world response
- Real-world progression
- Time on treatment

This initiative aims to describe the natural history (clinical characteristics, molecular data, standard of care treatment and clinical outcome) of NTRK fusion-positive tumours through retrospective analysis of real-world data

Roche are currently investigating the feasibility of identifying a matched NTRK fusion-negative cohort, to provide a comparator cohort for entrectinib-treated patients.

6.4 Intergroup non-interventional study (NIS) sponsored by ETOP: Cohort study covering NTRK fusion-positive lung cancer, breast cancer and sarcoma cohorts (with potential for additional tumour types).

The NIS study aims to describe the natural history (clinical characteristics, molecular data, standard of care treatment and clinical outcome) of NTRK fusion-positive tumours through retrospective and prospective analysis of real-world data for these patients. If feasible this study may also provide a comparator cohort for certain tumour types represented in the entrectinib clinical trial population. The full details of this study will be released when details of the trial are publicly available.

[redacted]

[redacted]

7 Data analysis plan

Clinical trials

7.1 STARTRK-2: minimum time frame for data collection driven by post-marketing regulatory commitments – time needed to enrol additional patients and ensure minimum 12 months' follow-up.

7.2 STARTRK-NG: minimum time frame for data collection driven by post-marketing regulatory commitments – time needed to recruit additional patients and to assess long term effect on growth and development.

7.3 Updates are planned in line with annual reports to be submitted to the EMA for annual renewal of Conditional Marketing Authorisation.

7.4 STARTRK-2:

- Final database lock: [redacted]
- Interim database locks: [redacted]

STARTRK-NG:

- Final database lock: [redacted]
- Interim database locks: [redacted]

Other data

7.5 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.

7.6 Flatiron real-world data and Foundation Medicine genomic database: It is anticipated that an interim report will be available by [redacted] and the final report by [redacted].

7.7 Intergroup non-interventional study (NIS) sponsored by ETOP: [redacted]

8 Ownership of the data

8.1 For all clinical trial (STARTRK-2 and STARTRK-NG) data listed above, and data derived from the Flatiron real-world data and Foundation Medicine genomic databases, Roche will be the owner. For the ETOP NIS, ETOP will own the data.

8.2 For data where Roche are not the data owners, Roche 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 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 data collection 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 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 Roche, 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

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.